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Neurophysiology of human touch and eye gaze in therapeutic relationships and healing: a scoping review

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ABSTRACT

Objective: The primary objective of this scoping review was to examine and map the range of neurophysiological impacts of human touch and eye gaze, and consider their potential relevance to the therapeutic relationship and to healing.

Introduction: Clinicians, and many patients and their relatives, have no doubt as to the efficacy of a positive therapeutic relationship; however, much evidence is based on self-reporting by the patient or observation by the researcher. There has been little formal exploration into what is happening in the body to elicit efficacious reactions in patients. There is, however, a growing body of work on the neurophysiological impact of human interaction. Physical touch and face-to-face interaction are two central elements of this interaction that produce neurophysiological effects on the body.

Inclusion criteria: This scoping review considered studies that included cognitively intact human subjects in any setting. This review investigated the neurophysiology of human interaction including touch and eye gaze. It considered studies that have examined, in a variety of settings, the neurophysiological impacts of touch and eye gaze. Quantitative studies were included as the aim was to examine objective measures of neurophysiological changes as a result of human touch and gaze.

Methods: An extensive search of multiple databases was undertaken to identify published research in the English language with no date restriction. Data extraction was undertaken using an extraction tool developed specifically for the scoping review objectives.

Results: The results of the review are presented in narrative form supported by tables and concept maps. Sixty-four studies were included and the majority were related to touch with various types of massage predominating. Only seven studies investigated gaze with three of these utilizing both touch and gaze. Interventions were delivered by a variety of providers including nurses, significant others and masseuses. The main neurophysiological measures were cortisol, oxytocin and noradrenaline.

Conclusions: The aim of this review was to map the neurophysiological impact of human touch and gaze. Although our interest was in studies that might have implications for the therapeutic relationship, we accepted studies that explored phenomena outside of the context of a nurse-patient relationship. This allowed exploration of the boundary of what might be relevant in any therapeutic relationship. Indeed, only a small number of studies included in the review involved clinicians (all nurses) and patients. There was sufficient consistency in trends evident across many studies in regard to the beneficial impact of touch and eye gaze to warrant further investigation in the clinical setting. There is a balance between tightly controlled studies conducted in an artificial (laboratory) setting and/or using artificial stimuli and those of a more pragmatic nature that are contextually closer to the reality of providing nursing care. The latter should be encouraged.

Keywords Gaze; healing; neurophysiological; therapeutic relationship; touch

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Introduction

The purpose of the review was to examine the connection between two distinct research fields. The first field is aligned to the social sciences and examines the importance of human interaction and positive therapeutic relationships for healing and the delivery of fundamental care.[1] The second research field is aligned to the natural sciences, and investigates the neurophysiological impact of touch and eye gaze during human interaction. Although arising from different research domains, both bodies of work are strongly connected, with touch and gaze being key elements of human interaction that have the potential to influence therapeutic relationships, healing and patients' experiences of fundamental care delivery. The connection of these bodies of work is further emphasized by the shared variables of trust and positivity as relevant mediators of the impact of human interaction.

Fundamental care refers to the essential elements of care that every patient requires regardless of their clinical condition or the setting in which they are receiving care. These elements of care can be physical (e.g. nutrition, hydration, elimination and hygiene), psychosocial (e.g. respect, dignity, privacy and cultural safety) or relational in nature (e.g. empathy and compassion).[1] Given the growing evidence that these fundamentals are being poorly executed globally, there is increasing emphasis on how they can best be delivered in clinical practice.[2-10] Research is beginning to acknowledge that a positive, trusting nurse-patient relationship is integral to the delivery of high-quality, person-centered fundamental care.[1,11] However, the specific neurophysiological mechanisms through which this positive relationship impacts patient care and experiences is largely unknown and unexplored.

In addition to work on fundamental care, there is a large body of work on the importance of an empathic, therapeutic relationship for healing, patient health, resilience and hope.[12-14] This therapeutic relationship might involve multiple ''actors'', given that patients can interact with multiple health professionals in any healthcare episode. Specific studies focusing on the therapeutic relationship include studies on connectedness,[15] social influences on healing and stress,[16,17] meta-analyses of noncontact healing studies[18] and reviews of the effect of interpersonal touch on patients[19,20] and specific cells.[21]

There are also studies and literature reviews on the role of trust in health professional (particularly nurse)-patient relationships[22,23] and the impact of increasing technological interaction on this therapeutic relationship.[24,25] These studies demonstrate the increased capacity for hope displayed by the patient when there is a high trust relationship and personal interaction between the patient and nurse/medical practitioner.[26,27] The observed interactions and interconnections that are considered to be relevant for improving the healing capacity of patients in these circumstances include the display of genuine empathy, compassion, direct eye contact and physical touch.

Whilst clinicians, and many patients and relatives, are in no doubt as to the efficacy of a positive therapeutic relationship, much evidence is based on self-reporting by the patient or observation by the researcher.[23,24] There is, however, a growing body of work on the neurophysiological impact of human interaction. Physical touch and face-to-face interaction, entailing eye gaze and retinal eye lock, are two types of contact that produce neurophysiological effects on the body.[20,28,29]

There are a growing number of studies investigating the neurophysiological impact of physical touch. Such studies have examined the cortical dynamics of both discriminative (discrimination of stimuli) and affective (pleasant, gentle stroking) touch,[30-34] and the way in which the brain registers (codes) affective touch.[35-38] The neurophysiological response to touch includes the release of specific chemicals and neurotransmitters that lead to neuroendocrine effects; vagal stimulation; reduction of stress, pain and depression; and enhancement of immunity.[20,39-42] Affective touch also appears to lessen allostatic load (i.e. stress) in critically ill patients,[20] due to the positive effects on pathophysiological processes aggravated by stress, such as immune and neuroendocrine derangements and inflammation.[28,39] There is recent evidence of an interoceptive effect of affective touch that aids rehabilitation through alterations to the insular cortex and limbic system.[43]

Affective touch is transmitted primarily through stimulation of the nerve's unmyelinated C-fibers, the impact of which is beneficial to healing.[29] Affective touch is represented in areas of the brain that are closely related to the perception of emotion and empathy, and this affective-emotional pathway runs

in part through the spinomesencephalic tract, engaging the amygdala, insula and anterior cingulate cortex.[29] Resultant neurophysiological reactions can mediate the perception of touch, and are shown to be beneficial to the healing process, as well as having a positive effect on a patient's capacity for pain management[29,44] and a number of physiological outcomes, including changes to autonomic innervation through repetition of affective stimulation.[20]

One of the most powerful human interactions is face-to-face contact involving eye gaze. The interaction between trusted individuals creates a *neural duet* between brains due to the reciprocal firing of the brain's social networking areas, with a powerful effect on the level of trust and empathy as well as a positive attitudinal shift.[45] Face-to-face contact involves the activation of mirror and spindle neurons.[33,46-48] When interacting with trusted others a number of chemicals are released including oxytocin and vasopressin,[49,50] both of which help to lower the physiological stress response and aid growth and wound healing.[51] Social interaction becomes an interactive process of positive feedback whereby increased levels of oxytocin in turn encourage even greater levels of gaze to the eye region of human faces.[50] This dynamic further increases the level of trust and empathy between the interacting parties.

When there is sufficient trust and positivity, a positive feedback effect can occur, which stimulates the parasympathetic nervous system and releases immune system chemicals that enable neuroplasticity and neurogenesis to occur.[52,53] These same chemicals are involved in immune system strength and changes to hormonal responses triggered by stress, pain signalling and integration. Each of these are directly related to healing and resilience through such mechanisms as modulating the interplay of lymphocytes that produce antibodies[54] and triggering hormone and neuropeptide changes that mediate emotions.[13,55]

Eye gaze and retinal eye lock between an anxious person and a trusted ''other'' has a direct effect on the synchronization of the right brain hemispheres[56,57] and the quietening of the sympathetic nervous system and amygdala,[58] increasing the ability to deal with trauma. Thus, it enables the caregiver or trusted ''other'' to ''soothe''.[49,58] This ''eye contact effect'' modulates activity in structures in the social brain network,[59] aiding communicative intention and affective arousal. There is growing evidence of the link between these neurophysiological reactions and a decreased level of morbidity and mortality through such changes as an increased capacity for hope,[13,60] the capacity to reframe vulnerability and deal with trauma,[61,62] and neurophysiological reactions related to the placebo effect.[63]

In summary, touch and face-to-face interaction with trusted others have a number of neurophysiological effects that are relevant to the therapeutic relationship. These neurophysiological effects are impacted by the quality of the relationship shared by the individuals. Trust and empathy, in particular, appear to be mediators given they have a profound effect on the body's generation and/or secretion of beneficial chemicals, such as serotonin.

This review maps the research literature on interventions that directly or indirectly replicate aspects of a therapeutic relationship using touch and/or eye gaze. This research literature arguably complements the existing body of research, indicating that therapeutic relationships can have a positive impact on patients, particularly in relation to the delivery of fundamental care. Research evaluating objective neurophysiological measures might provide further insight as to why and how this positive impact occurs.

A search of the Cochrane Library, the *JBI Database of Systematic Reviews and Implementation Reports* (JBISRIR) and PubMed revealed a very large number of systematic reviews primarily concerned with the effects of massage and other forms of touch. Typically these reviews were condition specific such as the impact on lower back pain[64] or prevention of pressure ulcers.[65] These, and many other systematic reviews, typically examined clinical outcomes and not neurophysiological outcomes. One Cochrane systematic review did consider neurophysiological outcomes but was narrowly focused on massage for mental and physical health in infants under the age of six months.[66] One scoping review was identified that mapped massage studies that measured neurophysiological impacts, but only in relation to blood pressure.[67]

The objectives, inclusion criteria and methods of analysis for this review were specified in advance and documented in a protocol.[68]

Review question/objective

The specific review question for this review was: what are the neurophysiological impacts of human touch and eye gaze that have the potential to influence healing and the therapeutic relationships?

The objective of this scoping review was to examine and map the range of neurophysiological impacts of human touch and eye gaze, and explore possible links to and implications for the therapeutic relationship and healing. Touch and gaze are two central components of human interaction. Understanding the neurophysiological impact of touch and gaze might provide insights in to how these components of interaction can be used to enhance relationships in a therapeutic context. Our intention was not to only include studies that overtly stated a link between touch or gaze and the impact on the therapeutic relationship and healing. This would have been too restrictive. Our objective was to look broadly at studies that measured the neurophysiological impact of touch and gaze and consider: the contexts in which these occurred; who received the touch or gaze and who provided it; what were the variants of touch and gaze; and what was being measured. In keeping with the purpose of a scoping review, this information allowed us to explore and map this emerging research field.

Inclusion criteria

Participants

This scoping review considered studies that included cognitively intact human subjects of any age. Patients who were heavily sedated or unconscious were excluded.

Concept

This scoping review investigated a number of areas related to the neurophysiology of human interaction (e.g. touch, eye gaze) and their potential connection to building a useful therapeutic relationship. The concept/s examined included:

- Neurophysiology of touch
- Neurophysiology of eye gaze
- Neurophysiological impacts on healing
- Neurophysiology of care
- Therapeutic relationship.

Specifically, we considered who received the touch or gaze and who provided it; what the variants of touch and gaze were; and what outcomes were being measured.

Context

This scoping review considered studies that examined, in either clinical or laboratory settings, the neurophysiological impacts of touch and eye gaze, and which have potential links to the therapeutic relationship. Clinical settings included acute care, long-term care and community care, including the home.

Types of studies

This scoping review considered both experimental and quasi-experimental study designs including: randomized controlled trials, non-randomized controlled trials, before and after studies and interrupted time-series studies. In addition, analytical observational studies including but not limited to prospective and retrospective cohort studies and case-control studies were considered for inclusion. Only quantitative studies were included as the aim was to examine objective measures of neurophysiological changes as a result of human touch and gaze.

Methods

This scoping review adopted the methodology for Joanna Briggs Institute (JBI) scoping reviews as described in the JBI Reviewers' Manual.[69,70]

Search strategy

A three-step search strategy was utilized for this review. An initial limited search of Scopus, PubMed and CINAHL was undertaken, followed by an analysis of the text words contained in the title and abstract, and of the index terms used to describe the articles. A second search using all identified keywords and index terms was then undertaken across all included databases. Thirdly, the reference list of all identified reports and articles were searched for additional studies. Only published studies in English were considered for inclusion in this review. The decision not to search for unpublished papers was due to the large amount of results from searching the databases of published studies, making additional imprecise searches in the gray literature impractical. There were no date restrictions.

The databases searched included: CINAHL, PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, PsycINFO and Web of Science. Results of all searches are provided in Appendix I.

Initial keywords used were: gaze, healing, neurophysiological, therapeutic relationship, touch.

Study selection

All searches were imported into Endnote X8 (Clarivate Analytics, PA, USA) and all title and abstracts were reviewed by two reviewers independently. Full-text of studies were then retrieved and reviewed by two reviewers independently. All discrepancies in selection were resolved through discussion.

Extraction of results

Data were extracted from papers included in the scoping review by two independent reviewers using the data extraction tool specified in the review protocol.[68] The data extracted included specific details about the populations, concept, context and study methods of significance to the scoping review question and specific objectives. Any disagreements that arose between the reviewers were resolved through discussion.

Data mapping

The extracted data are presented in both diagrammatic and tabular form as per scoping review guidelines, including mind-maps of the various aspects of the study and how they interrelate. A narrative summary accompanies the tabulated and diagrammatic results.

Results

Description of studies

The initial search of all databases was conducted on 12–13 November 2015 and updated in February 2017. The search strategy was deliberately sensitive and therefore resulted in a large number of studies identified. Database searches identified 18,734 records. Other sources, primarily reference lists of included studies, provided a further 46 records. After removal of duplicates and screening of title and abstracts, 86 studies were retrieved in full text and 22 were then excluded based on inclusion criteria (See Appendix II). A total of 64 studies have been included in the review. The PRISMA flowchart in Figure 1 describes the flow of decisions for inclusion of studies.

Characteristics of included studies

Of the 64 studies included in the review (Table 1), most (61%) were set in the clinical environment,[72-110] with the vast majority of studies conducted in the US (39%),[42,79,80,83-90,93,95,97,98,104,106,108,111-117] Sweden (13%),[75,77,78,99,100,102,110,118] Japan (9%),[82,91,109,119-121] South Korea[96,122-124] and the UK (6% each).[72,103,107,125] Nearly half of the studies were randomized controlled trials,[42,73,74,77,78,80,84-90,95,98,99,101,105-108,112,115,116,120,123,124,126-128] and there were slightly fewer studies involving patients (45%)[72-75,77-80,82,84-87,89,90,92,95-99,101,103,106-108,110,113,129] as opposed to healthy participants. The largest group of patients were those with cancer.[77-79,95,101,106,107] Fifty-seven studies (89%) investigated "touch" as an intervention,[42,72-93,95-124,126,127,130,131] four (6%) investigated the effect of "gaze",[125,129,132,133] two (3%) investigated "touch and gaze" combined[94,128] and one study (2%) investigated touch and gaze with the addition of vocalization and facial expression.[134] It should be noted, that although our aim was to identify studies that addressed the neurophysiological impact of touch and gaze in relation to healing there were no studies identified that addressed this directly.

The detailed characteristics of all included studies are provided in Appendix III.

Review findings

Interventions and intervention sub-types

Figure 2 maps the included studies showing the numbers of studies investigating each of the intervention types, and for each of the intervention sub-types. The sub-types were derived iteratively as part of the mapping process.

For studies of touch, the most prominent sub-type was "massage" (46 studies, 81% of touch studies),[42,72-75,77-79,81,82,84-92,95-101,105-110,113,115,116,118-124,126,127,130,131] followed by "skin to skin" (also known as "kangaroo care") (5 studies, 9%),[76,80,93,103,104] "warm affective touch/holding" (5 studies, 9%)[83,102,111,112,114] and "Reiki touch" (1 study, 2%).[117]

In the "skin to skin" care studies most involved preterm infants,[80,93,103,104] with only one study involving full-term infants;[76] all with the mother providing the contact. The studies of "warm affective touch/holding" included mother and infant dyads[83,102] or couples in a relationship.[111,112,114] The "Reiki touch" study involved healthy participants with a trained Reiki practitioner.[117] Characteristics of the massage studies are provided in more detail later.

For studies of gaze, one intervention sub-type ("direct and averted") was represented by two studies,[129,132] others sub-types ("direct, averted and closed" and "still face")[125,133] were investigated in

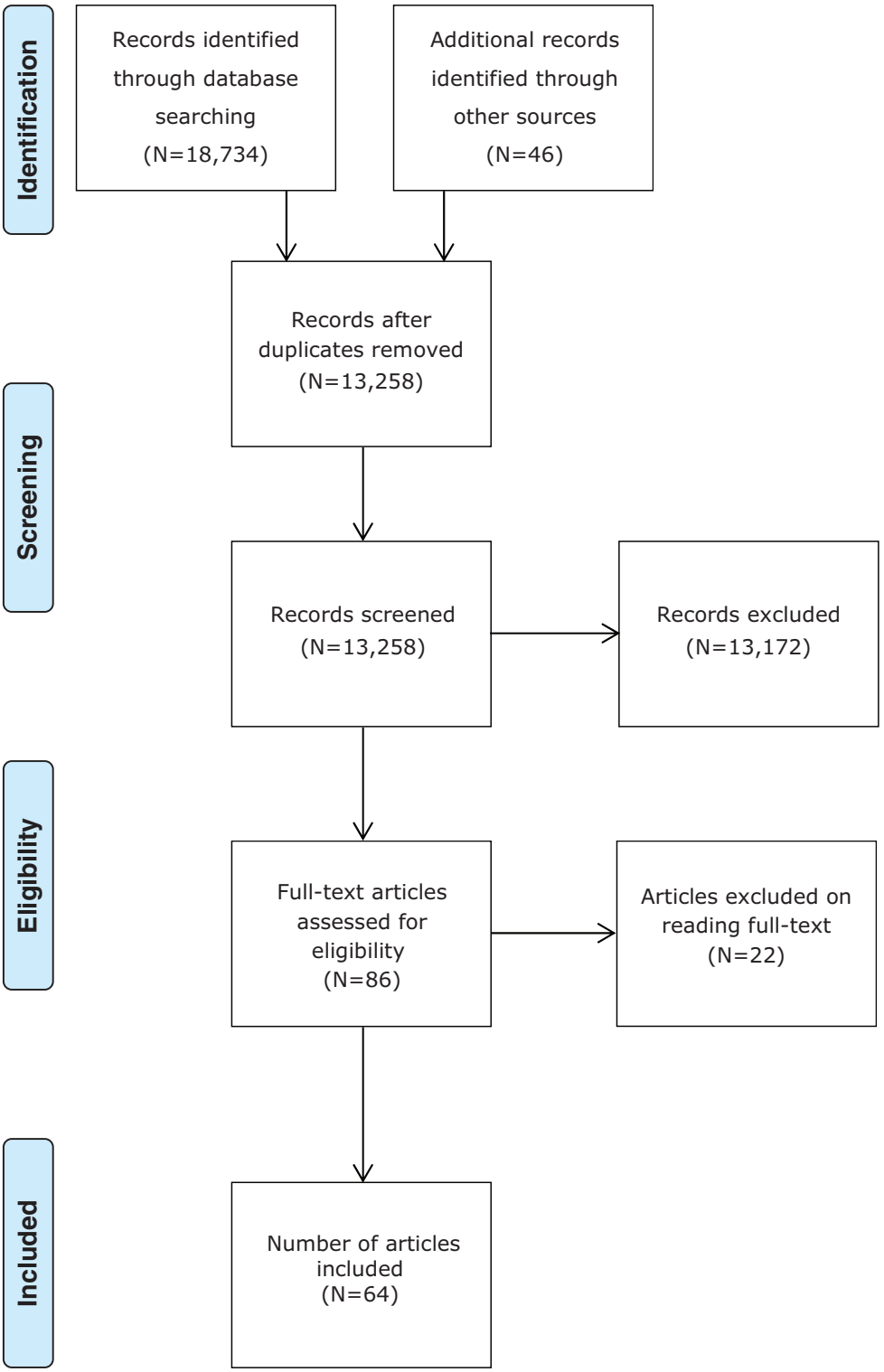

Figure 1: PRISMA flowchart for the scoping review process[71]

Table 1: Overview of included studies

Category	Variable	n	%
Setting	Clinical (including acute, long term community and home care)	39	61
	Laboratory	25	39
	USA	25	39
	Sweden	8	13
	Japan	6	9
	South Korea	4	6
	UK	4	6
	Israel	3	5
	Australia	2	3
Country	Finland	2	3
	Germany	2	3
	Iran	2	3
	Brazil	1	2
	Canada	1	2
	Switzerland	1	2
	Taiwan	1	2
	Thailand	1	2
	Turkey	1	2
	Randomized Controlled Trials	31	48
	Non-randomized controlled trials	17	27
Study design	Pre-test post-test	7	11
	Case-Series	7	11
	Other	2	3
Population	Healthy	35	55
	Patients	29	45
	Touch	57	89
Intervention	Gaze	4	6
	Touch and gaze	2	3
	Touch, gaze, vocalisation, facial expression	1	2

one study each. One study involved mothers and infants.[125] The other three studies involved women and men viewing the gaze of either the researcher,[129] or of live models.[132,133] For the two studies of touch and gaze (combined), the intervention sub-types were "free play"[94] and "still face and touch".[128] Both studies involved parents and their children. One study focused on the combined intervention of "touch, gaze, vocalisation and facial expression", and examined the intervention sub-type of "social interaction". This study

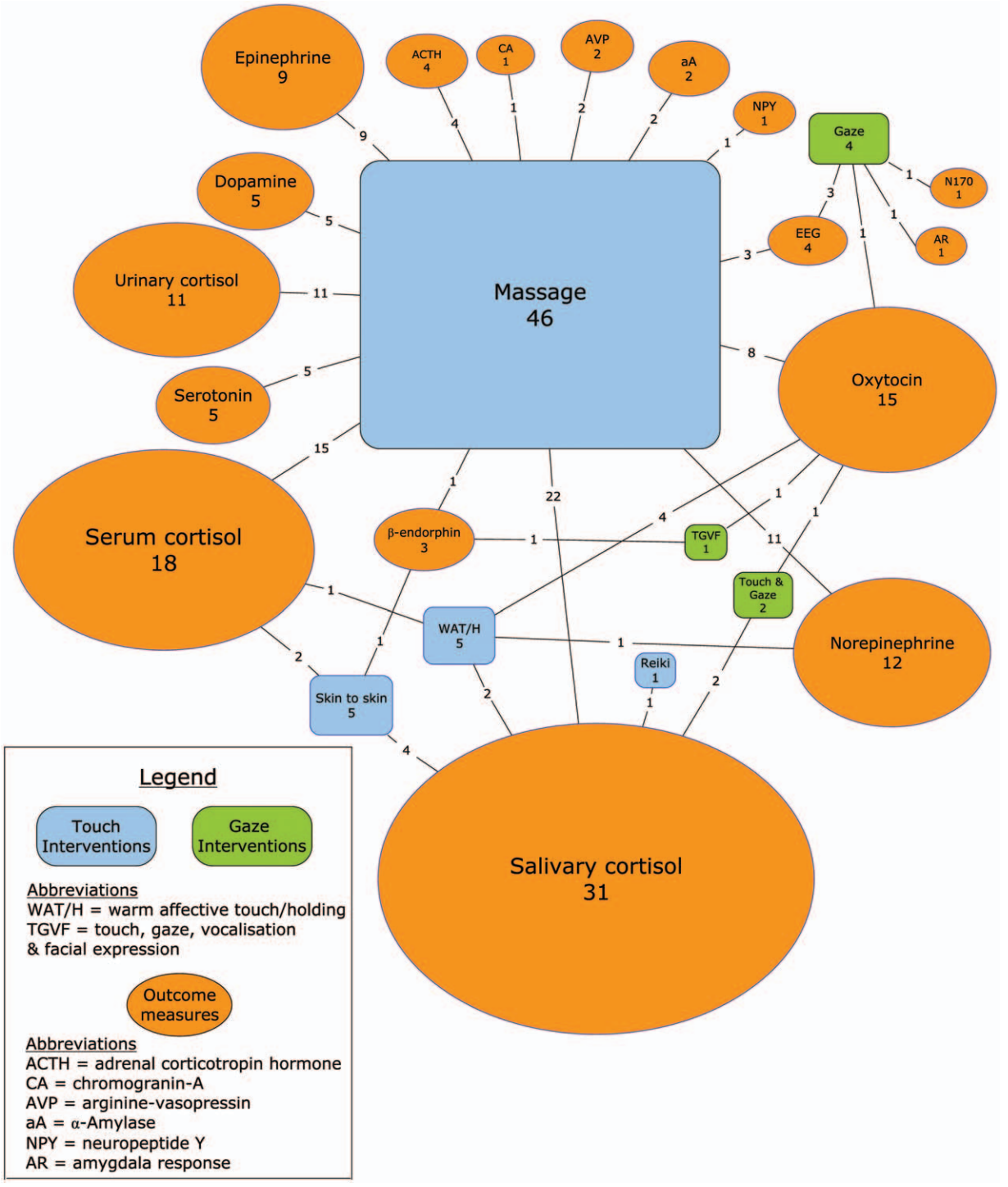

Figure 2: Mapping of intervention types and outcome measures (values correspond to the number of studies as does the relative size of each component of the figure)

included a variety of participants including couples and parents with children.[134]

Figure 3 presents a detailed analysis of the key characteristics of "massage", the most frequently measured intervention sub-type. Many studies failed to provide various details of these characteristics; therefore, the totals for some characteristics in Figure 3 are less than 46.

Six aspects of massage apparent from the literature are presented:

(i) Body area: The different amounts/locations of the body being massaged, including: full body (n = 28);[42,73-75,78,79,81,82,84-87,90,91,95,97-99,106,108,110,113,116,119,120,124,126,131] back (n = 4);[89,115,118,121] back, neck and head (n = 2);[101,105] limbs (n = 3);[77,92,100] neck and shoulders (n = 1);[127] scalp (n = 1);[123] trunk (n = 1);[96] upper body and limbs (n = 3);[72,88,109] acupressure points (n = 2);[122,130] and self-selected (n = 1).[107]

(ii) Type: The style of massage being provided, ranging from gentle/tactile (n = 9),[72,75,77,78,98,100,109,110] and Swedish (n = 7),[88,90,101,108,115,118,131] to other forms such as anma

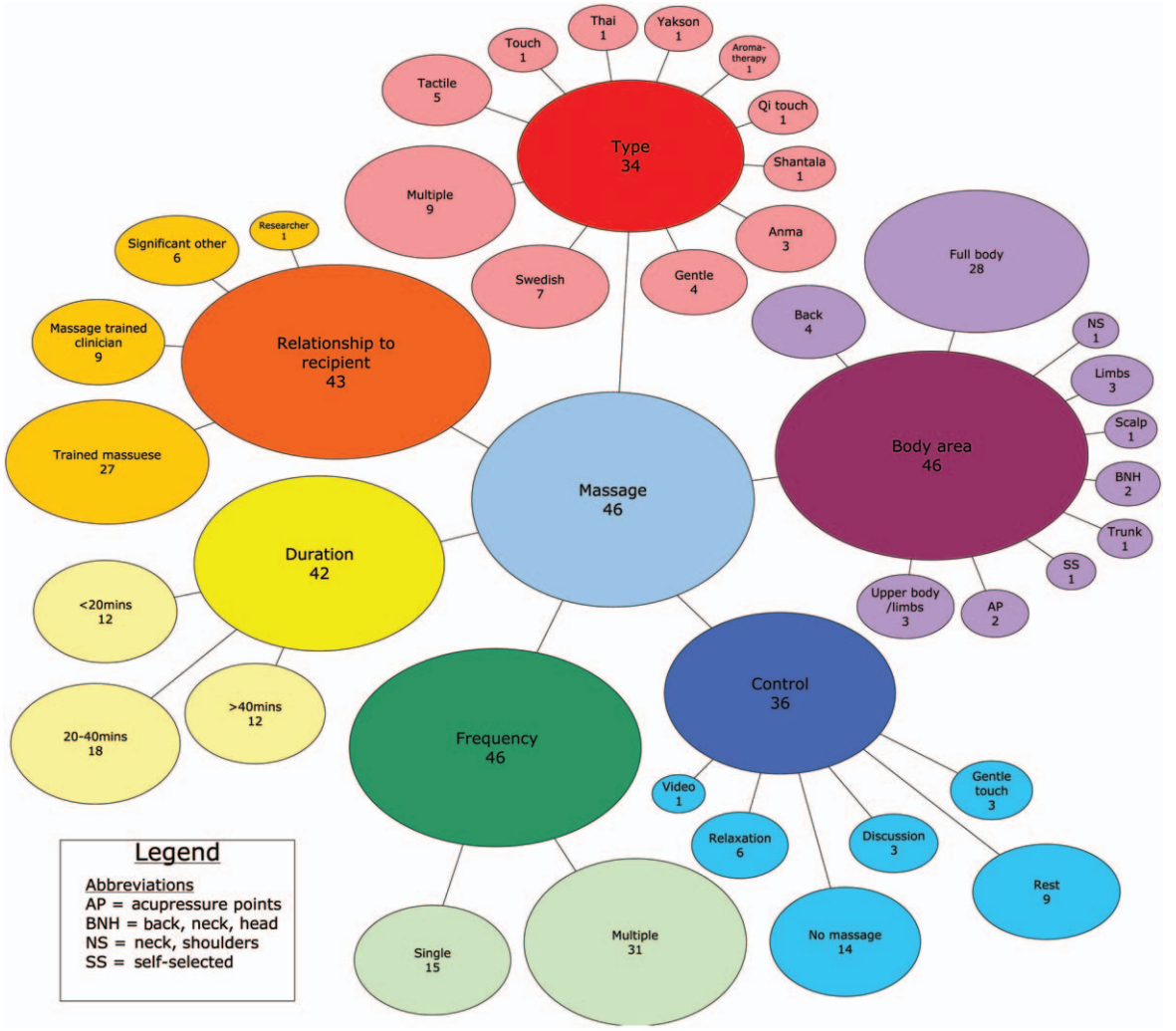

Figure 3: Mapping of "massage" intervention study characteristics (values correspond to the number of studies as does the relative size of each component of the figure)

(n = 3),[82,119,120] shantala,[81] Thai[126] and Yakson.[96] Nine studies used multiple types of massage,[42,73,74,95,105-107,113,116] and a further 12 did not specify the type of massage used.[79,84-87,89,91,92,121,123,127,130]

(iii) Relationship to provider (where stated): The provider was either a trained masseuse (n = 27) or researcher/research assistant (n = 1) that had no existing relationship with the recipient;[42,75,78,79,81,86-90,92,95,101,106,108,110,113,115,116,118-120,122-124,126,130,131] a trained clinician involved in the subject's care (all nurses: n = 9);[72,74,77,96,97,99,100,105,107] or a significant other (a person in a relationship with the receiver) (n = 6).[73,84,85,91,109,127]

(iv) Duration: The duration of the massage, ranging from less than 20 minutes (n = 12),[81,87,88,91,96,98,105,115,121,123,127,130] 20–40 minutes (n = 18)[72,77,79,82,85,86,89,90,92,95,99,101,107,109,118,120,124] to greater than 40 minutes (n = 12).[42,73-75,78,97,100,108,113,116,126,131]

(v) Frequency: Whether the massage was conducted once (n = 14)[42,72-74,99,100,107,115,118,120,122,126,127,130] or multiple times (n = 31).[75,77-79,81,82,84-92,95-98,101,105,106,108-110,113,116,119,123,124,131]

(vi) Control: If a control group was used, the most frequently occurring comparator was no massage (n = 14),[72,73,84,91,92,95,97,98,105,109,113,123,124,131] followed by rest (n = 9)[82,99-101,106,115,118,119,126] and then relaxation (n = 6).[79,85,86,88,90,110] A small number of studies used gentle touch (n = 3)[42,96,116] and attentive discussion (n = 3).[77,78,127] One study used video viewing.[89] Due to study design, three studies had no comparator.[75,81,121]

Outcomes

Figure 2 also presents the outcomes measured for all of the included studies. The most common outcome measure was cortisol accounting for 83% (n = 53) of studies. This included salivary cortisol in 48% (n = 31),[42,76-78,80-84,86,88-94,100,104,106,112,113,116,117,119-121,124,126,128] serum cortisol in 28% (n = 18)[42,72-75,80,97,99,101,103,105,107,111,116,122-124,131] and urinary cortisol in 17% (n = 11) of studies.[79,85-87,89,95,96,98,108,110,113] It should be noted that in a number of studies, two sources of cortisol were sampled. None of the studies with gaze as a sole intervention measured cortisol. Oxytocin was measured in 23% (n = 15) of studies and this was mostly serum oxytocin.[42,75,77,94,102,109,111,112,114-116,118,125,127,134] The next most frequent group of outcome measures were the catecholamines: dopamine, epinephrine (adrenaline) and norepinephrine (noradrenaline) in 19% (n = 12) of studies.[72,79,85,87,89,95,96,98,110,111,113,123] Serotonin was measured in only 8% (n = 5) of studies.[79,85,87,95,101] Neural activity including EEG, amygdala response and N170, a component of event related potential (stimulus in response to viewing faces), were measured in a small number of studies involving gaze[129,132] and massage.[88,124,130]

It should be noted that the inclusion criteria also addressed studies in regard to the neurophysiology of healing, care and the therapeutic relationship. Although many included studies made inferences about the potential for the various neurophysiological measures and we have explored this potential, no studies were identified that directly measured the neurophysiological impact on these concepts. This issue is elaborated in the following discussion.

Discussion

As this is a scoping review, the included studies have not been subjected to critical appraisal. There is therefore no attempt to address the effectiveness of the interventions.

The impetus for this review was the growing body of work on the neurophysiological impact of touch and eye gaze during direct human interaction and the benefits of a positive, trusting therapeutic relationship as the central element in the delivery of high-quality, person-centered fundamental care.[11,135] This review, therefore, aimed to identify research that evaluated neurophysiological measures as a response to touch and gaze, given they are essential elements of establishing and maintaining therapeutic relationships. We considered the nature of the interventions in terms of what intervention was delivered, who administered the intervention and who received it.

Although we identified a large body of research, arguably only a small number of studies measured relevant neurophysiological responses and were contextually specific to what could be described as the development and maintenance of a clinician-patient relationship. These studies involved patients and clinicians (all nurses) in the clinical setting.[72,74,77,96,97,99,100,105,107] However,

to restrict the review to these studies alone would have prevented exploration of a number of aspects of touch and gaze. For example, the effect of gaze was not addressed in any of the studies involving nurses.

The scoping review methodology allows, even encourages, the exploration of the boundaries of a concept. We would assert that therapeutic relationships are not restricted to a nurse and patient. These relationships can and often do include relatives of patients, with nurses often including them in therapeutic activities. In the case of infants, this would include encouraging mothers to have skin-to-skin contact. We established our boundary at the point where objective measurement of direct human to human touch and gaze occurred. Regarding the types of touch and the inclusion of massage, there is a continuum from light or gentle affective touch to firm even forceful touch of deep tissue massage. There is no natural cut-off point within this range. We recognize that gentle affective touch would occur when a nurse is giving comfort to a patient. At the other end of the spectrum nurses will touch patients more firmly when technical care is provided and it is this boundary which we aimed to explore.

The actions of nurses when caring for patients involve a great deal of touch.[136,137] This includes touch that would be intended to comfort (gentle touch) and, as part of an intervention, technical or instrumental touch.[138] In considering touch in the context of nursing practice, a bed-bound patient requiring washing by a nurse might also be provided with gentle massage, which would closely approximate some studies in the current review where a back massage was the intervention. There were a small number of included studies involving holding; warm, affective touch; and skin-to-skin contact, and once again these studies would contextually relate to the use of touch by nurses to comfort a patient.[76,80,83,93,102-104,111,112,114] Other aspects related to touch that were reflected in the studies included the skill level of the masseur/therapeutic provider and the relationship they had to the person receiving touch.

Trust is considered foundational in any therapeutic relationship.[23,135] A trusting relationship is considered to be ''dynamic and ongoing'',[23(p506)] suggesting that those who form this relationship are known to each other and have multiple interactions. The majority of studies had massage provided by a trained masseuse, with the next largest group massaged by a significant other, most often a spouse or life partner, and half as many again from a trained clinician. Whilst only four studies reported clinicians providing touch on more than three occasions,[77,96,97,105] the trust engendered by an ongoing relationship with a nurse or other type of clinician during therapy (either in a hospital or undergoing regular treatment) might offer potential benefits in regard to the therapeutic relationship and patient recovery/healing.

In the present review, the decision was made to only include studies with ''live'' gaze, and not the presentation of photos or videos, due to the body of evidence indicating a difference in the neurophysiological reaction to ''live'' gaze as opposed to gaze that is intermediated by technology (i.e. interaction over a screen, images of faces).[132,133] As a result, only seven studies addressing gaze (with or without touch) were included.[94,125,128,129,132,134] These studies measured both the effect of direct and averted gaze. This is relevant for the nurse-patient relationship as a more intense physiological response from the stimulus of direct gaze might result in a greater level of cognitive social network engagement which could lead to interpersonal neural synchronization and an increase in empathy.[133] It might also result in an increase in neuro-chemicals that strengthen the endocrine system and modulate the stress response. However, no studies that involved gaze between a patient and nurse were identified in the search.

The majority of included studies measured a single intervention, either touch or gaze. In the studies that involved touch, it is reasonable to assume that those providing touch might be making eye contact with the subjects; however, only a small number of studies noted the potential for, or effect of, direct eye gaze as a mediating factor on results. This appears to be due to the lack of awareness of the potential neurophysiological impact of direct eye gaze and therefore, the lack of recognition of its role in moderating or mediating outcomes. Only three studies explicitly involved interventions of both touch and gaze.[94,128,134] Notably one recent study included an intervention involving the *synchrony codes* of touch, gaze, vocalization and facial expression, and its ''pragmatic'' design meant it was one of the few studies to attempt to control for the reality of the complexity of human-to-human interaction.[134]

A number of different population groups received interventions. Approximately half of the studies

involved the intervention being administered to patients with a variety of medical conditions; the largest group being people with cancer.[77-79,95,101,106,107] Many studies aimed to use touch to reduce anxiety and stress, which is common in patient population groups. A few of the studies focusing on healthy individuals used a range of mechanisms to induce stress in the subjects before or after the intervention process, which included touch, gaze and proximity to a trusted or significant other.[99,114,127] A number of these studies reported results that can potentially inform how to mediate stress via the therapeutic relationship.

The environment in which the intervention was provided was also a consideration in a number of the studies. Approximately half of the studies were undertaken in a non-clinical environment where conditions could be well-controlled in terms of stimuli not directly related to the human-to-human interaction, such as light and noise. Although the studies undertaken in a clinical setting might be considered more relevant, there was no direct attempt to control for such environmental stimuli.

For the majority of studies (n = 53), the major impact marker tested was cortisol,[42,72-101,103-108,110-113,116,117,119-124,126-128,131] with 15 studies measuring oxytocin.[42,75,77,94,102,109,111,112,114-116,118,125,127,134] Cortisol levels were measured in serum, saliva and/or urine. In the nine studies that involved patients with nurses providing (gentle) touch, cortisol levels were measured as an indicator of stress.[72,74,77,96,97,99,100,105,107] In many cases, the purpose of touch therapy was to reduce stress in patients, and in some it was to explore beneficial neurophysiological effects (including immunological), particularly when the patient was undergoing treatment. Direct eye gaze was also indicated as a de-stressor in the studies that examined at it as an intervention.[94,125,128,129,132-134] This highlights the potential for touch and eye gaze, as part of the nurse-patient relationship, to positively impact patients, as supported by findings showing an integrative role of the oxytocinergic system in supporting social affiliation, and an associated rise in immune biomarkers.[134]

Cortisol was shown to be a complex indicator, as a number of variables are involved, including relationship, gender, age, baseline/resting level, type of touch, type of cortisol (salivary, plasma and urinary) and collection method. For example, massage involving firm pressure (such as Swedish massage) was reported to increase cortisol (due to pressure sensors in the skin); yet, it had other beneficial physiological impacts such as stimulation of oxytocin and immune system function. In many of the studies that had oxytocin as an outcome measure, it was used as an indicator of bonding and/or synchrony. Though not part of this review's objectives, there was a consistent link reported between raised oxytocin and an increase in immunological activity, and this warrants further research in terms of the potentially beneficial outcomes from direct interaction with the clinician. It also raises the potential of using oxytocin as a measure of the development of a therapeutic relationship; however, in the studies with nurses, only one measured oxytocin levels and the rationale was that it was an anxiolytic.[77]

A small number of studies measured neurological changes including amygdala and other neural activity, changes in nervous system activity and vagal tone, and the presence of various neurochemicals/transmitters in response to study interventions.[128-130,132,133] The reported results were consistent with the body of research work regarding the beneficial neurophysiological effects of direct human interaction.[30-41]

Nursing interventions are often complex with many confounders. Qualitative research investigating touch as part of nurse-patient interaction reports that gentle touch can result in comfort or distress depending on a range of contextual issues, such as the gender of the nurse, the environment in which the touch is administered, and the simple but important act of explaining what is happening before the touch is administered.[136,138] Looking for objective evidence about the impact of a good therapeutic relationship is challenging, confounded by the iterative and synergistic neurophysiological nature of direct interaction on both parties.[99] The majority of studies that we identified aimed to measure the impact of a single intervention, most commonly massage, often ignoring the additional moderation/mediation of direct eye gaze. The interventions were rarely within the context of the nurse-patient relationship.

Limitations

One potential limitation of this review is that we focused specifically on touch and gaze as central elements of human interaction, including as part of a therapeutic relationship, in studies that

quantifiably measured neurophysiological outcomes of such interaction. Human interaction is much more complex than touch and gaze, as shown in those studies that included related aspects such as social synchrony, convergence of biomarkers during bonding and affiliation, and the interplay of such things as allostasis and trust. There are also many studies that explore the neurophysiological impact of other aspects of human interaction, either inclusive or exclusive of touch and gaze, using qualitative methodologies. Such studies, when robust, should also inform this area of research as the complex interplay cannot be measured by quantitative measures alone.

Regarding gaze, the decision was made to only include ''live'' faces and this restricted the literature we accessed. A further limitation is that, due to the complexity of cultural differences in regard to direct gaze and touch, this review has not included cultural difference as a criterion. This was compounded by only including English language studies. Future research in this area would be valuable in terms of informing nurses and other clinicians on the complex mediating effects.

Finally, it should be noted that we did not search for unpublished literature. In preparation for this review we deemed a comprehensive search for unpublished papers impractical. As this is a scoping review without critical appraisal we make no specific judgments of effect which would be an issue in relation to publication bias.

Conclusion

The aim of this review was to identify studies that evaluated two important elements of human interaction, touch and gaze, and their impact on a range of neurophysiological measures. An important consideration was the relevance of the studies in regard to the nurse-patient relationship, interpreted through the wider lens of the therapeutic relationship. Although small in number, there were studies that did involve nurses and patients, but most did not address the complexity of human interaction as would be seen in the clinical setting. However, there was sufficient consistency in trends evident across many studies regarding the beneficial impact of touch and eye gaze to warrant investigation in the clinical setting. There is a balance here between studies that are tightly controlled and those of a more pragmatic nature that are contextually closer to the reality of providing nursing care. The latter should be encouraged.

Recommendations for research

Given the growing evidence that fundamental care is being poorly executed globally,[2-10] there is increasing emphasis on understanding how such care can be delivered effectively and safely and on elucidating the positive impact for patients when such care is delivered well. Fundamental care involves multiple opportunities for touch (as part of routine activities, such as bathing, or intended to comfort) and gaze, and is positively influenced by a trusting nurse-patient relationship. Systematic reviews of effectiveness could help to elucidate the specific neurophysiological mechanisms though which nurses' routine work and fundamental care result in positive care experiences for patients and improved patient healing. These reviews would range from those considering the neurophysiological effect of massage as a standalone intervention, likely to include a large number of studies, to a review on the effectiveness of comforting touch by nurses, likely to include only a small number of studies. There is also potential for reviews in a number of other areas including neural engagement and synchronization and immunological change.

In regard to primary research, most of the included studies were designed to control for a single stimulus. Very few studies were conducted in the clinical setting with the multiple stimuli that would represent the reality and complexity of nurse-patient interaction. However, these studies demonstrated the feasibility of this type of pragmatic research. Studies in which nurses are the providers of the intervention should be undertaken in the clinical area, to further explore the impact of the relationship between patient and nurse, and it would be relevant to further explore such an impact on both parties, as informed by studies regarding the reciprocal nature of the neurophysiological impacts of direct human interaction. The study by Ulmer-Yaniv *et al.*[134] provides a methodological example of quantifying multiple convergent elements and outcomes of human interaction. Other studies have also used video and accompanying software to code interactions between individuals in both the clinical and simulated environments, also demonstrating feasibility of this approach.[139,140] In the early 1990 s, Estabrooks and Morse used a grounded theory approach to

investigate how intensive care nurses learn to touch.[136] This raises the potential of using both neurophysiological measures and technological intermediation and/or imaging as interventions or aids to teach nurses how to use touch and gaze in order to develop therapeutic relationships.

This review has research implications for the positive use of massage, and for differentiating the type of massage dependent on the required therapeutic outcome desired, as well as controlling for duration, timing, frequency, expertise, relationship and amount of body.

A research area that is currently under-developed is the inclusion of direct eye gaze as a contributing variable in both research studies and practice. Whilst there were only a small number of studies directly related to the role of eye gaze, in a therapeutic context there was evidence that the opportunity for, and effect of, eye gaze is also a potential mediator for a positive interactive outcome, and may have an additive effect when touching is also involved.

The increase in technology in health care requires decisions to be made about the level of human or technological intervention in the care of patients. However, there is currently very little research evidence to guide these choices to maximize benefits to patients, clinicians and the medical institution involved. Recognizing the therapeutic impact of touch and gaze may redefine the way nurses choose to interact with their patients and the future delivery of health care.

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Appendix I: Search strategies

All searches conducted in February 2017

Source	Query	Results
CINAHL	(touch or massage or gaze or retinal or eye) AND (oxytocin or vasopressin or cortisol or dopamine or serotonin or amygdala)	259
Cochrane (CENTRAL)	(touch or massage or gaze or retinal or eye) AND (oxytocin or vasopressin or cortisol or dopamine or serotonin or amygdala)	634
PubMed	((oxytocin[Title/Abstract] OR cortisol[Title/Abstract] OR dopamine[Title/Abstract] OR serotonin[Title/Abstract] OR vasopressin[Title/Abstract] OR amygdala[Title/Abstract])) AND ((touch[Title/Abstract] OR massage[Title/Abstract] OR gaze[Title/Abstract] OR retinal[Title/Abstract] OR eye[Title/Abstract])	3932
JBISRIR	(touch OR massage OR gaze OR retinal OR eye) AND (oxytocin OR vasopressin OR cortisol OR dopamine OR serotonin OR amygdala)	36
Web of Science	(touch or massage or gaze or retinal or eye) AND (oxytocin or vasopressin or cortisol or dopamine or serotonin or amygdala)	5276
Scopus	(touch or massage or gaze or retinal or eye) AND (oxytocin or vasopressin or cortisol or dopamine or serotonin or amygdala)	6959
PsycINFO	((touch or massage or gaze or retinal or eye).mp. [mp = title, abstract, heading word, table of contents, key concepts, original title, tests & measures]) AND ((oxytocin or cortisol or dopamine or serotonin or vasopressin or amygdala).mp. [mp = title, abstract, heading word, table of contents, key concepts, original title, tests & measures])	1638

Note that MeSH (Medical Subject Headings) were not used in any of the searches.

Appendix II: Excluded studies based on eligibility criteria

Busch M, Visser A, Eybrechts M, van Komen R, Oen I, Olff M, *et al.* The implementation and evaluation of therapeutic touch in burn patients: an instructive experience of conducting a scientific study within a non-academic nursing setting. Patient Educ Couns. 2012;89(3):439–46.

Reason for exclusion: No skin-to-skin contact

Chatel-Goldman J, Congedo M, Jutten C, Schwartz JL. Touch increases autonomic coupling between romantic partners. Front Behav Neurosci. 2014;8:95.

Reason for exclusion: No reporting of neurophysiological measures

Currin J, Meister EA. A hospital-based intervention using massage to reduce distress among oncology patients. Cancer Nurs. 2008;31(3):214–21.

Reason for exclusion: No reporting of neurophysiological measures

Gordon I, Voos AC, Bennett RH, Bolling DZ, Pelphrey KA, Kaiser MD. Brain mechanisms for processing affective touch. Hum Brain Mapp. 2013;34(4):914–22.

Reason for exclusion: No skin-to-skin contact

Groer M, Mozingo J, Droppleman P, Davis M, Jolly ML, Boynton M, *et al.* Measures of salivary secretory immunoglobulin A and state anxiety after a nursing back rub. Appl Nurs Res. 1994;7(1):2–6.

Reason for exclusion: No reporting of neurophysiological measures

Helminen TM, Kaasinen SM, Hietanen JK. Eye contact and arousal: the effects of stimulus duration. Biol Psychol. 2011;88(1):124–30.

Reason for exclusion: Only measured skin conductance response

Henricson M, Berglund AL, Maatta S, Ekman R, Segesten K. The outcome of tactile touch on oxytocin in intensive care patients: a randomised controlled trial. J Clin Nurs. 2008;17(19):2624–33.

Reason for exclusion: Patients semi-conscious or unconscious

Hodgson NA, Lafferty D. Reflexology versus Swedish Massage to Reduce Physiologic Stress and Pain and Improve Mood in Nursing Home Residents with Cancer: A Pilot Trial. Evid Based Complement Alternat Med. 2012;2012:456897.

Reason for exclusion: Some participants not capable of providing consent so surrogate was used

Kanitz JL, Reif M, Rihs C, Krause I, Seifert G. A randomised, controlled, single-blinded study on the impact of a single rhythmical massage (anthroposophic medicine) on well-being and salivary cortisol in healthy adults. Complement Ther Med. 2015;23(5):685–92.

Reason for exclusion: No detailed reporting of salivary cortisol

Kujala MV, Carlson S, Hari R. Engagement of amygdala in third-person view of face-to-face interaction. Hum Brain Mapp. 2012;33(8):1753–62.

Reason for exclusion: Subject not directly involved in interaction but observing others

Lee MS, Rim YH, Kang CW. Effects of external qi-therapy on emotions, electroencephalograms, and plasma cortisol. Int J Neurosci. 2004;114(11):1493–502.

Reason for exclusion: No skin-to-skin contact

Lee YH, Park BN, Kim SH. The effects of heat and massage application on autonomic nervous system. Yonsei Med J. 2011;52(6):982–9.

Reason for exclusion: No skin-to-skin contact

Listing M, Krohn M, Kim I, Reisshauer A, Peters E, Liezmann C, *et al.* The Influence of Classical Massage Therapy on Stress Perception, Mood Disturbances, Body Image, Cortisol and Oxytocin Levels 2011. 389- p.

Reason for exclusion: Conference paper unable to access full-text

Okvat HA, Oz MC, Ting W, Namerow PB. Massage therapy for patients undergoing cardiac catheterization. Altern Ther Health Med. 2002;8(3):68–70, 2, 4–5.

Reason for exclusion: Cortisol only raised in discussion

Peled-Avron L, Wagner S, Perry A, Shamay-Tsoory S. Get in touch: the role of oxytocin in social touch2013. S90-S p.

Reason for exclusion: Conference paper unable to access full-text

Pierno AC, Becchio C, Turella L, Tubaldi F, Castiello U. Observing social interactions: the effect of gaze. Soc Neurosci. 2008;3(1):51–9.

Reason for exclusion: Not live faces

Ponkanen LM, Hietanen JK, Peltola MJ, Kauppinen PK, Haapalainen A, Leppanen JM. Facing a real person: an event-related potential study. Neuroreport. 2008;19(4):497–501.

Reason for exclusion: Unable to access full-text

Rapaport M, L. Hale K, Koury M, Shubov A, J. Bresee C. The role of oxytoncin, vasopressin and cortisol in the beneficial effects of massage therapy 2008. 1S-S p.

Reason for exclusion: Conference paper unable to access full-text

Sato W, Kochiyama T, Uono S, Toichi M. Neural mechanisms underlying conscious and unconscious ***attentional*** shifts triggered by eye gaze. Neuroimage. 2016;124(Pt A):118–26.

Reason for exclusion: Not live faces

Sato W, Kochiyama T, Uono S, Yoshikawa S. Amygdala integrates emotional expression and gaze direction in response to dynamic facial expressions. Neuroimage. 2010;50(4):1658–65.

Reason for exclusion: Not live faces

Sato W, Yoshikawa S, Kochiyama T, Matsumura M. The amygdala processes the emotional significance of facial expressions: an fMRI investigation using the interaction between expression and face direction. Neuroimage. 2004;22(2):1006–13.

Reason for exclusion: Not live faces

Sauer A, Mothes-Lasch M, Miltner WH, Straube T. Effects of gaze direction, head orientation and valence of facial expression on amygdala activity. Soc Cogn Affect Neurosci. 2014;9(8):1246–52.

Reason for exclusion: Not live faces

Appendix III: Characteristics of included studies

Citation	Study aims	Setting	Study Type	Population (N=)	Intervention	Outcomes	Key findings
Acolet *et al.* (1993)[72]	To assess the biochemical and clinical response to massage in preterm infants	UK, Clinical	Non-RCT	Stable pre-term infants (16)	Gentle massage of the trunk and limbs using arachis oil for approximately 20 minutes (only one massage) Provider: massage trained clinician (nurse) Comparator(s) Control (no massage)	Cortisol (plasma) Epinephrine Norepinephrine	Cortisol concentrations were consistently reduced after massage. No significant difference detected between the change in cortisol concentration in the group receiving massage and in the control group.
Adib-Hajbaghery, Rajabi-Beheshtabad & Abasi (2013)[73]	To evaluate the effect of whole body massage performed by a patient's companion on the level of blood cortisol among patients admitted in the CCU	Iran, Clinical	RCT	Male patients in CCU (60)	60-min. whole body massage. Techniques used included static massage, superficial stretching technique, stretching massage, lymph vacuuming technique, latitudinal rubbing technique, and myofacial releasing technique, accompanied with effleurage using almond oil. Provider: patient's companion Comparator(s) Control (no massage, routine care)	Cortisol (plasma)	In the group massaged by the patients' companions, the mean of blood cortisol was 323.6 ± 162.6 nanomoles, which decreased to 268.4 ± 141.1 after the intervention ($P < 0.102$). The mean of blood cortisol in the control group did not change significantly.
Adib-Hajbaghery, Rajabi-Beheshtabad, Ardjmand (2015)[74]	To compare the effect of massage applied by a nurse specialist and patients' relatives on blood cortisol level among patients admitted in CCU	Iran, Clinical	RCT	Male patients in CCU (90)	One 60-minute, whole body massage. The techniques used were static massage, superficial stretching technique, stretching massage, lymph vacuuming technique, latitudinal rubbing technique and myofascial releasing technique, which were accompanied with effleurage of almond oil. Provider: massage trained clinician (nurse) Comparator(s) (1) One session of 60-minute, whole body massage by patients' relatives (2) Control (no massage, routine care)	Cortisol (plasma)	In the nurse group, the median blood cortisol level was decreased after the intervention ($P < 0.007$). The median blood cortisol level for the patients' relatives and control group did not change significantly. There was no significant difference between the cortisol level in the three groups either before or after the intervention.
Andersson, Wändell & Törnkvist (2004)[75]	To investigate how TM, short term and over time, affects blood glucose, stress hormones and well-being in women with type 2 diabetes mellitus	Sweden, Clinical	Pre-test post-test	Women with Type 2 diabetes (11)	Whole-body massage for 60 minutes 1/week for 10 weeks. Tactile massage (TM): pain-free but deliberate, gentle and superficial massage of the skin without manipulation of the underlying muscles. Odourless vegetable oil. Quiet music is played during the massage. Three measurement times: before massage, one week after and twelve weeks after. Provider: trained masseuse	Cortisol (plasma) Oxytocin (plasma)	No statistically significant differences were found regarding oxytocin, however, the oxytocin measurements did show tendencies to decline over time, with the lowest value measured on occasion 3. The S-cortisol value on occasion 2 showed a statistically significant reduction ($p < 0.05$).
Bennett *et al.* (2016)[126]	To examine the acute effects of TTM on cortisol level, blood pressure, heart rate and stress perception in academic stress	Thailand, Lab	RCT	Physiotherapy students with self-perceived stress score equal to or greater than 3 on a 5-point scale (rated by 1 = not stressed at all and 5 = extremely stressed) (36)	Whole body TTM was applied to participants in the TTM group for 90 minutes. Provider: trained masseuse Comparator(s) Participants were awake resting in the supine position for 90 minutes	Salivary cortisol collected between 10:00 and 12:00 and then after the procedure	No evidence to indicate that single TTM could decrease saliva cortisol when compared with rest in the supine position.

(*Continued*)

Citation	Study aims	Setting	Study Type	Population (N=)	Intervention	Outcomes	Key findings
Bigelow *et al.* (2012)[76]	To investigate the effect of mother/infant SSC on mothers' postpartum depressive symptoms during the first 3 postpartum months and their physiological stress during the first postpartum month	Canada, Home Visits	Non-RCT	Mothers and their full-term infants (90)	Mothers in the SSC group provided approximately 5 hours per day of SSC with their infants in the infants' first week and then more than 2 hours per day until the infants were age one month. Saliva samples were taken from the mothers when the infants were one week and one month. Provider: mothers Comparator(s) Control (mothers provided little or no SSC)	Cortisol (salivary)	Mean values for salivary cortisol for the one-week visit were .340 μg/dL (SD = .163) for the SSC group and .278 μg/dL (SD = .128) for the control group. The mean values for the one-month visit were .234 μg/dL (SD = .095) for the SSC group and .244 μg/dL (SD = .161) for the control group. Over their infants' first month, mothers in the SSC group had a greater reduction in their salivary cortisol than mothers in the control group.
Billhult *et al.* (2008)[77]	To examine the effect of repeated effleurage massage treatments compared with a visit control group on circulating lymphocytes, levels of cortisol in saliva and oxytocin in plasma as well as degree anxiety, depression and quality of life, in women with breast cancer	Sweden, Clinical	RCT	Women with breast cancer undergoing radiation therapy (22)	Effleurage massage therapy (20 minutes of effleurage on ten occasions), directly after the scheduled radiation. The patients could choose between massage on either both feet/lower legs or both hands/lower arms. Cold-pressed vegetable oil was used, and the limb was wrapped in a towel after the massage. Provider: massage trained clinician (nurse) Comparator(s) The control group was given the same amount of attention as the massage group but did not receive massage.	Cortisol (salivary) Oxytocin (plasma) Lymphocytes	No significant changes between groups were detected on cortisol and oxytocin concentrations.
Billhult *et al.* (2009)[78]	To examine the short-term effects of light pressure effleurage on circulating lymphocytes, salivary cortisol levels, heart rate and blood pressure in patients with breast cancer	Sweden, Clinical	RCT	Women with breast cancer undergoing radiation therapy (30)	A single 45 min. full-body light pressure effleurage massage. Cold-pressed vegetable oil was used. The effleurage technique used was strokes with both hands, palms and fingers, using light pressure (in average 0.0090 kg/cm2). Provider: massage trained clinician (nurse) Comparator(s) The control group was given the same amount of attention as the massage group but did not receive massage.	Cortisol (salivary) Lymphocytes	No significant differences were seen between groups in changed cortisol levels.
Boylan (2005)[79]	In a pilot study massage resulted in women with breast cancer reporting reduced anxiety, depression and anger, increased urinary dopamine and serotonin, increased natural killer {NK) cells and lymphocytes. Thus, this study was designed to determine whether it was indeed massage, or just simple relaxation, that provided the benefits in the pilot study.	USA, Clinical	Non-RCT	Women diagnosed in the previous 3 years with early stage (I-III) breast cancer. Women were not admitted into the study until 3 months post-surgery and/or had completed their last radiation and/or chemotherapy session. (58)	The massage sessions (3 x 30 minutes each week for 5 weeks). The therapists were instructed to restrict any talking during the sessions to only questions concerning pressure and tender points. The massage was a full body massage. Provider: trained masseuse Comparator(s) (1) Relaxation group practised progressive muscle relaxation, 3 sessions each week for 5 weeks. (2) Control group only seen at the start and the end of the 5 weeks study.	Cortisol (urinary) Serotonin (urinary) Epinephrine (urinary) Norepinephrine (urinary) Dopamine (urinary)	There were large variances in the urine results. Positive changes (increases) were beneficial for dopamine and serotonin. Only the increases in dopamine and serotonin in the massage group were statistically significant.

(*Continued*)

Citation	Study aims	Setting	Study Type	Population (N =)	Intervention	Outcomes	Key findings
Chang *et al.* (2012)[130]	To investigate a subject's EEG performance under massage treatment applied by hand and treatment applied by mechanical devices	Taiwan, Lab	Non-RCT	Healthy volunteers, mainly college students (24)	Hand massage. Three minute circular massage for each of 4 acupoints in the mid shoulder area. Provider: trained masseuse Comparator(s) The same as the intervention but subjects massaged themselves with a mechanical device.	Neural activity (EEG)	There are was a comparison around EEG coherence during massage sessions between the hands-on group and mechanical massage group. The coherence value is higher when channel pair distance is greater. This is valid for both groups. Second, the coherence value of the hands-on group is averagely higher than that of the same channel pairs for the mechanical massage group. The hands-on group's coherence does not change significantly during the massage session, but the mechanical massage group's coherence becomes lower, especially with regard to alpha and beta rhythms. Massage by hand seems to maintain EEG channel coherence, while massage by mechanical may interrupt the original brain interaction between different brain regions. For left-right symmetry coherence, P3-P4 pair is the lowest coherence value pairs for both groups. Similar with around coherence, there were more significant variations on theta, alpha, and beta rhythms for mechanical massage than for hands-on massage, and there was a significant massage stage-type interaction on beta rhythm.
Cong, Ludington-Hoe & Walsh (2011)[80]	This study tested KC effects on bio-behavioral responses to heel stick in preterm infants (30–32 weeks' gestational age, 2–9 days old) measured by Premature Infant Pain Profile and salivary and serum cortisol. The paper reports two pilot studies.	USA, Clinical	RCT	Male and female preterm infants at 30–32 weeks' GA and 2–9 days' postnatal age (28)	Study 1 KC for 80 minutes, after 60 minutes baseline data was collected and then KC continued for 20 minutes Study 2 KC for 30 minutes, after 10 minutes baseline data was collected and then KC continued for 20 minutes Provider: mother Comparator(s) Control group: Infants remained in the Incubator for the procedure. They were left undisturbed for the same time as the KC.	Cortisol (salivary and serum)	30 minutes of KC before and throughout heel stick appeared to be effective in reducing bio-behavioural pain responses and cortisol levels in preterm infants. Changes in these outcomes were not seen for 80 minute KC.
de Cássia Fogaça *et al.* (2005)[81]	To evaluate the levels of salivary cortisol before and after Shantala massage therapy on healthy infants	Brazil, Clinical	Pre-test post-test	Healthy infants aged 4–6 months (9)	Infants received two standard 15 minute Shantala massages on two consecutive days and then after a one week interval in the morning and the afternoon Provider: researcher	Cortisol (salivary)	Cortisol levels increased after the two consecutive days and were still raised after one week. The differences were only statistically significant for the afternoon measures.

(*Continued*)

Citation	Study aims	Setting	Study Type	Population (N =)	Intervention	Outcomes	Key findings
Ditzen *et al.* (2007)[127]	The authors hypothesized that standardized physical partner contact (neck and shoulder massage) results in attenuated responses of the hypothalamic–pituitary–adrenal axis and the autonomic nervous system to acute psychosocial stress in women.	Switzerland, Lab	RCT	Healthy, heterosexual women, aged 20–37 years, who had been married or cohabiting with a significant other for at least 12 months (67)	Standardized physical contact (i.e., instructed neck and shoulder massage, no conversation) for 10 minutes from spouse 5 minutes prior to Trier Social Stress Test (5 minute public speaking task and then 5 minute mental arithmetic task in front of a panel). Provider: spouse Comparator(s) (1) Social support (i.e., only verbal support from spouse) for 10 minutes from spouse 5 minutes prior to Trier Social Stress Test (2) No spousal support (left alone) for 10 minutes 5 minutes prior to Trier Social Stress Test	Cortisol (salivary) Oxytocin (plasma)	Women with positive physical partner contact before stress exhibited significantly lower cortisol and heart rate responses to stress but no different plasma oxytocin levels compared to women who received social support or no social interaction. Verbal social support alone was not associated with reduced stress responsiveness.
Donoyama, Munakata & Shibasaki (2010)[119]	To use scientifically valid parameters to determine the effect of Anma therapy on both the body and mind	Japan, Lab	Non-RCT	Fifteen healthy female volunteers in their fifth decade (15)	40-minute Anma therapy session after a 15 minute rest and assessment. Standard therapy of kneading, stroking and pressing, with comfortable intensity over whole body. Five sessions over 2 and a half consecutive weeks. Comparator(s) same as for the Anma therapy group, but participants rested for 40 minutes instead.	Cortisol (salivary)	Salivary cortisol concentration was reduced only marginally after Anma therapy sessions.
Donoyama & Shibasaki (2010)[120]	To examine how differences in massage practitioners' proficiency impacted clients physically and psychologically, as measured by cortisol, pain (visual analogue score), anxiety (State-Trait Anxiety Inventory)	Japan, Lab	RCT	Females in the fifth decade of life with chronic muscle stiffness around the neck and shoulders. (8)	40 minutes Anma Therapy (whole body through clothing, using kneading, stroking and pressing). Provider: trained masseuse Comparator(s) (1) Intervention administered by 1st year student of massage and acupuncture (2) Intervention administered by 2nd year student (3): Rest on massage table	Cortisol (salivary)	For concentration levels of salivary cortisol, post-intervention values were significantly lower than those obtained pre-intervention; however, there were no significant differences among the four interventions.
Donoyama, Shoji & Munikata (2005)[82]	To determine the effect of Anma therapy on both the body and mind. Impact on Cortisol s-IgA, Pain (visual analogue score), anxiety (State-Trait Anxiety Inventory).	Japan, Clinical	Non-RCT	Intervention = 3 patients, 51–74 years with a variety of diagnosis Non-intervention = 3 'healthy' college students, 22–43 years with a musculoskeletal (MS) injury (6)	15 minute rest followed by 40 minutes Anma Therapy (whole body through clothing, using kneading, stroking and pressing), twice a week for 2 and half weeks. Five sessions in total. Provider: not stated Comparator(s) Same as for intervention group except Anma was replaced with resting on the bed for the same period.	Cortisol (salivary)	Marginal decreases for cortisol in Anma group. Results were considered inconclusive due to study design, particularly differences between groups and small sample size.

(*Continued*)

Citation	Study aims	Setting	Study Type	Population (N=)	Intervention	Outcomes	Key findings
Elverson *et al.* (2012)[83]	To explore relationships between selected social regulation behaviors (holding and feeding) and the transitional newborn infant's cortisol response during the first 6 hours after birth.	USA, Clinical	Correlational study	Mothers and their term transitional newborn infants (46 dyads)	Behaviors of 46 mothers and their term transitional newborn infants were measured with the Index of Mother-Infant Separation. For each infant, eight unique random times for Index of Mother–Infant Separation observations during each of the 6 hours after birth (total of 48 observations) were undertaken. The first saliva sample was collected at 15 to 45 minutes of age, except after cesarean births when saliva was collected as soon as possible after the mother and infant returned to the labor–delivery–recovery room (n = 10, 22% of sample, oldest was 82 minutes of age). Subsequent saliva samples were obtained at 2 hours (±15 minutes) and 6.5 hours (±15 minutes) after birth. In addition, saliva samples were collected before the bath (after admission to the nursery) and 20 to 30 minutes after the beginning of the initial bath.	Cortisol (salivary)	A higher percentage of observations in which mother was holding infant was related to lower infant total cortisol during the first 6 hours after birth.
Feldman, Singer & Zagoory (2010)[128]	To measure the effects of touch on infant stress reactivity during simulated maternal deprivation	Israel, Lab	RCT	Mothers and their infants (53 dyads)	Fifty-three dyads were tested in two paradigms: still-face (SF) and still-face with maternal touch (SF+T). Maternal and infant cortisol levels were sampled at baseline, reactivity, and recovery and mother's and infant's cardiac vagal tone were measured during the free play, still-face, and reunion episodes of the procedure.	Cortisol (salivary) Vagal tone (Vna) Oxytocin (serum)	Cortisol reactivity was higher among infants in the SF condition. In the recovery phase, cortisol decreased for infants in the SF+T, and it markedly increased for those in the SF. Vagal tone showed a greater suppression when SF was not accompanied by maternal touch. In reunion phase, Vna in touch condition recovered to free play level, but in no-touch, remained same as SF. Touch synchrony during free play was associated with higher infant vagal tone, not cortisol. Touch myssynchrony – maternal tactile stimulation while the infant gaze averts – correlated with higher maternal and infant cortisol and higher gaze aversion, and lower infant Vna during free play.
Field *et al.* (1992)[89]	To examine the independent effects of massage on the behaviors of children and adolescents hospitalized for depression or adjustment disorders	USA, Clinical	RCT	Children and adolescents hospitalized for depression or adjustment disorders (72)	52 subjects received a 30 minute back massage per day for 5 days. Provider: psychology students Comparator(s) 20 subjects received a videotape viewing for the equivalent time	Cortisol (saliva), Cortisol (urine), norepinephrine, epinephrine and dopamine	In the short term, to 30 minutes follow-up there was a decrease in salivary cortisol only. Salivary cortisol did not change over the 5 day period but both urinary cortisol and urine norepinephrine did decrease over the 5 day period.

(*Continued*)

Citation	Study aims	Setting	Study Type	Population (N=)	Intervention	Outcomes	Key findings
Field & Grizzle (1996)[86]	To compare the effects of massage and relaxation therapies on anxiety and depression in a sample of depressed adolescent mothers	USA, Clinical	RCT	Depressed adolescent mothers who had recently given birth at a large inner-city hospital and were recruited from the hospital's maternity ward (32)	The massage therapy subjects (N=16) received a 30-minute massage per day on two consecutive days per week for five consecutive weeks (10 massages). Provider: trained masseuse Comparator(s) The relaxation therapy subjects (N=16) spent the same amount of time in relaxation therapy as the massage therapy subjects spent in MT. The first 15 minutes consisted of yoga exercises. The second 15-minute segment consisted of progressive muscle relaxation.	Cortisol (salivary and urinary)	Lower salivary cortisol levels after massage therapy (no effect for the relaxation group); and lower urine cortisol levels on the last day versus the first day of massage therapy (no effect for the relaxation group). Only the massage therapy group showed lower stress hormone (cortisol) levels after their sessions. In addition, only the massage therapy group experienced a reduction in depression and in stress (as manifested by their lower urinary cortisol levels) across the course of the study.
Field *et al.* (2009)[84]	To assess the effects of pregnancy massage by significant others on prenatal measures as well as perinatal outcomes	USA, Clinical	RCT	Depressed women recruited between 16 and 20 weeks gestation from two ultrasound clinics. Primarily low socioeconomic status. 20% met criteria for major depressive disorder. (129)	Massage group received 2 moderate pressure massages per week for a period of 12 weeks. Provider: significant others who were taught the massage by a massage therapist and were given DVDs for at-home coaching in the massage procedure. Comparator(s) Control group: standard treatment	Newborn cortisol (salivary) Maternal cortisol (salivary)	Massage group neonates had lower cortisol levels. The massage group mothers had lower cortisol levels (M=128.6 versus 2328.8, F=4.17,p=.05). Newborns of the massaged mothers also had lower cortisol levels than the newborns of the control mothers.
Field *et al.* (2004)[85]	To assess a more cost-effective form of massage therapy, namely having the "significant other" instead of a massage therapist provide the massage	USA, Clinical	RCT	Depressed pregnant women 8–24 weeks gestation recruited from obstetric and gynaecology clinics. Of middle socio-economic status (112)	Two 20-minute massages per week over 16 weeks. Provider: Trained massage therapists taught the massage to the "significant others" of the women. Comparator(s) (1) Progressive muscle relaxation comparison group (2) Standard prenatal care only group (3) Group of 28 non-depressed women	Cortisol (urinary) Catecholamines (norepinephrine, epinephrine, dopamine) (urinary) Serotonin (urinary)	A group by first/last day interaction effect showed that the massage therapy group experienced the following effects: i) increased serotonin levels; ii) decreased cortisol levels; iii) increased dopamine levels; and iv) decreased norepinephrine levels.
Field, Grizzle *et al.* (1996)[87]	To evaluate the potential benefits of massage therapy for healthy infants who were born to depressed mothers	USA, Clinical	RCT	40 full-term I-to-3-month old infants born to depressed adolescent mothers (40)	Massage-therapy infants were provided a 15 minute massage midway between morning feedings 2 days per week for 6 weeks. The therapist placed a small amount of mineral baby oil on the palms of her warm hands and placed her hands on the infant's chest then worked on six regions of the infant's body. Provider: researcher Comparator(s) The rocking group: During this condition, the infant was held in a cradled position by the researcher and rocked in a rocking chair.	Cortisol (salivary and urinary) Norepinephrine (Urinary) Epinephrine (urinary) Serotonin (urinary)	Salivary cortisol levels decreased in the massage group during the massage unlike the rocking group infants whose cortisol levels remained the same. Over time (comparing day 1 and day 12), the massage group experienced decreases in urinary catecholamine and cortisol levels and increased serotonin levels. Increased soothability and decreased stress levels, as suggested by lower cortisol and catecholamine levels, may have contributed to the infants' enhanced responsivity.

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Citation	Study aims	Setting	Study Type	Population (N=)	Intervention	Outcomes	Key findings
Field, Ironson *et al.* (1996)[88]	To investigate the effects of massage on alertness as measured by EEG and by speed and accuracy of performance on math computations. In addition, anxiety, depression and cortisol levels were expected to decrease.	USA, Clinical	RCT	Medical faculty and staff members (80% females, M age = 26). (50)	Chair massage: 15 minutes a day, 2 days a week for 5 weeks, and the sessions were scheduled at noon each day. Standard Swedish massage procedure (kneading of muscles) was used. Provider: trained masseuse Comparator(s) Relaxation control group: The subjects were asked to relax by tightening and relaxing the same body parts as those that were massaged for the massage therapy group (and in the same sequence).	Cortisol (salivary) Neural activity (EEG)	Salivary cortisol levels were lower following the massage but not the control sessions but only on the first day (a repeated measures by group interaction effect revealed a decrease in salivary cortisol levels on the first day for the massage group and an increase on the last day for the relaxation control group). No effect on cortisol was observed after 5 weeks of massage.
Field *et al.* (1998)[90]	Massage therapy was expected to reduce stress hormones in patients with burns injuries before debridement	USA, Clinical	RCT	Patients with burn injuries at a Burn Center (28)	Standard care and a 20 minute massage once a day for 1 week. Massage took place just before debridement. Massage was delivered in a supine then prone position. Provider: trained masseuse Comparator(s) Usual care plus 20 minutes of sitting and relaxing.	Cortisol (salivary)	On both days the salivary cortisol levels decreased after massage in the massage group but there was no difference in the control group. Salivary cortisol (measured before the massage) was lower after the 5 day period than before.
Fujita *et al.* (2006)[91]	To evaluate the effects of baby massage on mothers' mood status and salivary cortisol level within 3 months after delivery	Japan, Clinical	Non-RCT	Mothers who had just given birth (39)	Baby massage (stroke and/or massage each area of the babies' body; legs, belly, chest, arms, and back). At least 10 minutes/day until 3 months after delivery. Provider: mother Comparator(s) Control group (no massage)	Cortisol (salivary)	No significant differences in salivary cortisol levels between groups, however, salivary cortisol did increase in the control group and decrease in the massage group over time.
Garner *et al.* (2008)[92]	To examine the effectiveness of a relaxation massage therapy programme in reducing stress, anxiety and aggression on a young adult psychiatric inpatient unit.	Australia, Clinical	Non-RCT	Young adult psychiatric inpatients aged 15–25 years (32)	MT consisted of a 20 minute massage therapy session offered daily to patients during their period of hospitalization. Natural massage balm containing no essential oils or scent, was applied to forearms and hands. Measures were taken at baseline and follow-up (after conclusion of 7 weeks) and just before and immediately following both the first and last massage sessions. Provider: trained masseuse Comparator(s) Treatment as usual	Cortisol (salivary)	No differences in cortisol levels between groups overtime. There were some immediate effects of massage on cortisol. Following the 20 minute massage therapy session there was a significant reduction in saliva cortisol levels at both the initial and final massage therapy session.

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Citation	Study aims	Setting	Study Type	Population (N =)	Intervention	Outcomes	Key findings
Gitau *et al.* (2002)[93]	To determine the effects of a 20 minute intervention of maternal skin-to-skin contact, massage, or a control period, on stress (as measured by salivary cortisol) of pre-term babies	USA, Clinical	Non-RCT	Clinically stable preterm babies no longer requiring intensive care support and within 4 weeks of birth in a low dependency unit (40)	20 minute skin-to-skin over 2 consecutive days. The mother was seated on a standard rocking chair, tilted at an angle of approximately 60°. Provider: mother Comparator(s) (1) 20 minute massage consisted of gentle massage of the trunk and limbs using rachis oil. Massage was carried out at a particular time of day, independent of the state of the baby. (2) Control group	Cortisol (salivary)	Control: No significant change in cortisol over time Massage group: no significant change overall Skin-to-skin contact: there was a reduction in saliva cortisol, and the overall reduction for the whole group was highly significant.
Gordon *et al.* (2010)[94]	To determine impact of oxytocin (OT) and salivary cortisol (CT) on triadic synchrony.	Israel, Home	Correlational study	Cohabitating parents and their healthy firstborn infant (37)	Families were visited at home twice during the evening hours (4–8 PM). Interactions were videotaped between each parent and the child. On the second home visit, families were videotaped in a free-play triadic interaction. Parents were instructed that the two of them play together with the infant as they normally do and no specific position or toys were required.	Triadic synchrony: Moments of coordination between physical proximity and affectionate touch between the parents as well as between parent and infant while both parent and child are synchronizing their social gaze	Among mothers, OT was an independent positive predictor and cortisol (CT) was an independent negative predictor of triadic synchrony. For fathers, only OT independently predicted triadic synchrony and no relations were found between paternal CT and synchrony in the family triad, indicating that higher paternal OT predicted higher levels of triadic synchrony
Grewen *et al.* (2005)[111]	To examine whether the magnitude of plasma oxytocin (OT), norepinephrine (NE), cortisol, and blood pressure (BP) responses before and after a brief episode of warm contact (WC) with a spouse/partner may be related to the strength of perceived partner support.	USA, Lab	Pre-test post-test	Healthy couples living with their current spouse or monogamous partner for at least 1 year (76)	Baseline: Partners were seated in comfortable chairs in separate rooms. Warm contact: Couples were seated on a loveseat in a quiet room and instructed to sit close together, holding hands if they felt comfortable doing so. They were asked to talk about a time they had spent together that made them feel closer as a couple (2 minutes). They then watched a 5-minute segment of a romantic video they had previously seen. They then were instructed to talk for 2 minutes about a time when they felt close as a couple. At the end of this session, partners stood for a 20-second hug. Provider: partner Postcontact: Subjects were moved to separate chambers to rest quietly alone for 10 minutes.	Oxytocin (plasma) Cortisol (plasma) Norepinephrine (plasma)	Cortisol levels were lower after WC than before it in both men and women. However, there were no differences in cortisol between subjects reporting high versus low partner support. Individuals reporting high versus low partner support exhibited greater OT across the protocol (between subjects). There were significantly greater mean OT levels in the high versus low partner support groups at all measurement times. The link between greater partner support and higher OT values was observed in men and women at baseline and was present after WC with partner in women (postcontact rest alone minute 4). When baseline OT was examined by partner support quartiles, a consistent pattern of increasing OT with increasing partner support was seen. Although there were no links between greater partner support and lower diastolic blood pressure, heart rate, NE, or cortisol, correlations of higher OT with lower systolic blood pressure, diastolic blood pressure, and NE were obtained. These associations were seen in women but not men.

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Citation	Study aims	Setting	Study Type	Population (N=)	Intervention	Outcomes	Key findings
Hernandez-Reif *et al.* (2004)[95]	To examine massage therapy for women with breast cancer for i) improving mood and biological measures associated with mood enhancement (serotonin, dopamine), ii) reducing stress and stress hormone levels, and iii) boosting immune measures	USA, Clinical	RCT	Women with Stage 1 or 2 breast cancer diagnosis within the past 3 years and at least 3 months post-surgery, chemotherapy, and/or radiation therapy (34)	Received 15 massages during the study period (three massages each week for 5 weeks). Each massage was 30 minutes long and consisted of Swedish, trager, and acupressure techniques. The massages were conducted in a quiet and private room on a massage table. Provider: trained masseuse Comparator(s) Control group: standard medical care alone.	Norepinephrine (urinary) Epinephrine (urinary) Cortisol (urinary) Dopamine (urinary) Urinary 5-Hydroxyindoleacetic acid (a metabolite of serotonin)	Cortisol stress hormone, norepinephrine, and epinephrine levels did not decrease following massage therapy. However, for the massage therapy group there was an increase in (1) dopamine, and (2) serotonin levels, from the first to the last day. The control group showed a significant increase in norepinephrine.
Hietanen *et al.* (2008)[132]	We aimed to determine whether seeing another person's direct vs. averted gaze has an influence on the observer's neural approach-avoidance responses. We also examined whether it would make a difference if the participants were looking at the face of a real person or a picture.	Finland, Lab	Non-RCT	Adults with normal or corrected-to-normal vision (20)	Participants viewed a face/gaze stimulus and a control object (a radio) in four different conditions factorially manipulating the gaze/object direction (direct and averted) and the stimulus–presentation mode (picture and live). The pictures were presented on a computer monitor, whereas the live stimuli were presented through a liquid crystal shutter. Provider: researchers Comparator(s) Two small, portable radios (presented in picture and live)	EEG activity (power in the alpha band) Skin conductance responses	Measurements of hemispheric asymmetry in the frontal EEG activity indicated that another person's direct gaze elicited a relative left-sided frontal EEG activation (indicative of a tendency to approach), whereas averted gaze activated right-sided asymmetry (indicative of avoidance). Skin conductance responses were larger to faces than to control objects and to direct relative to averted gaze. Gaze direction also influenced subjective ratings of emotional arousal and valence. However, all these effects were observed only when participants were facing a real person, not when looking at a picture of a face.
Holt-Lundstad, Birmingham & Light (2008)[112]	To investigate the impact of warm touch enhancement on plasma oxytocin, 24-hour ambulatory blood pressure, and salivary cortisol and alpha amylase	USA, Lab	RCT	Healthy married couples (68)	Couples underwent one session of training in listening-touch based on the types of touch used in Rosen Method Bodywork and one training session in head, neck, and shoulder massage. The intervention couples then practiced these warm touch techniques for 30 minutes $\geq$3 times per week for 4 weeks. Provider: partners Comparator(s) Behaviour monitoring control group: Subjects were told not to change anything about their normal behaviour with their spouse and to simply keep a diary of their physical affection and mood.	Oxytocin (plasma and salivary) Cortisol (salivary) Alpha amylase	There was no main effect of the intervention on salivary cortisol, or plasma OT, however, there was a significant effect of the intervention for salivary OT obtained at home during the month of treatment/monitoring. Even as early as intervention week 1, salivary OT levels were significantly higher in the intervention group than the control group. Both men and women in the intervention condition continued to have higher OT levels than those in the monitoring control condition during the final week. This effect remained significant after adjusting for pre-treatment plasma OT and even after adjusting for their higher week 1 OT levels, indicating that further significant albeit modest increases in OT activity occurred with greater exposure to the warm touch intervention. After controlling for pre-treatment levels, post-treatment alpha amylase was significantly lower among husbands and wives in the intervention group than those in the control group.

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Citation	Study aims	Setting	Study Type	Population (N=)	Intervention	Outcomes	Key findings
Im & Kim (2009)[96]	To test the effect of Yakson and Gentle Human Touch (GHT) on preterm infants' stress and behaviours compared to usual nursing care	South Korea, Clinical	Non-RCT	Pre-term infants with a gestational age of 26–34 weeks at birth (59)	Yakson: 15 minutes twice a day for 15 days. Yakson consists of three 5-minute phases: resting the hand on the infant, gentle caressing, and resting the hand again. Provider: massage trained clinicians (nurse) Comparator(s) (1) GHT: 15 minutes twice a day for 15 days. GHT consists of hand resting for 15 minutes. (2) Control group: usual care.	Cortisol (urinary) Norepinephrine (urinary)	Following the intervention period, infants in the Yakson and GHT groups had significantly lower stress hormone levels compared to the control group infants. No significant difference was found in stress hormone levels between Yakson and GHT group infants.
Ironson *et al.* (1996)[113]	To examine the effects of daily massage for one month on the immune function of HIV+ and HIV- gay men	USA, Lab	Mixed design including pre-test post-test and crossover for part of the sample	HIV+ and HIV- gay men with no AIDS-defining symptoms. If on Antiretroviral therapy, had to have been on them for at least 3 months. (29)	45 minute daily massage. Provider: trained masseuse Comparator(s) Control (no massage)	Cortisol (urinary and salivary) Norepinephrine (urinary) Epinephrine (urinary)	There was a significant decrease in urinary cortisol, during the massage period and a marginally significant increase during the control period. For catecholamines during the massage period, the change was not significant.
Jung *et al.* (2006)[122]	To evaluate differences in the effects of Qi therapy without touching or with touching on anxiety, mood, neurohormones, and cellular immune function	South Korea, Lab	RCT	Men aged 20–35 years (women were not included because of their hormonal variations) (24)	Qi no touching (QTN): The subjects received QTN for 10 minutes according to the procedures described in the standard sequence. The Qi master's hand is moved about 3–10 cm from the body in a pattern from the head to the toes. When a subject arrived for the experiment, he was taken to the experimental room and seated on a bed. After 5 minutes rest (Pre), the subject received Qi. Qi therapy was followed by 10 minutes of rest (Post I). Provider: trained masseuse Comparator(s) Qi touching (QTT): Administered by the same Qi master, who pressed several important acupoints with effort or intention to insert Qi through them.	Cortisol (plasma)	No significant differences between the effects of Qi therapy with and without touching. There were significant effects on anxiety, alertness, depression, fatigue, tension, cortisol levels, and NK cell cytotoxicity for both QTN and QTT, and on neutrophil function for QTN only. These findings suggest that there are few differences between the effects of QTN and QTT.
Kim *et al.* (2014)[125]	To examine the relationship between maternal oxytocin response and mother-to-infant gaze during periods of infant non-distress as well as distress. Two patterns of maternal gaze, maternal gaze toward and gaze shifts away from the infant, were micro-coded while mothers interacted with their 7-month-old infants during a modified still-face procedure.	USA, Lab	Pre-test post test	Non-clinical sample of first-time mothers (50)	The Modified Still Face Procedure (MSFP) is a three-phase procedure, during which the mother interacts freely with the infant in Phases 1 and 3, but is instructed to maintain a neutral 'still face' during Phase 2, suddenly depriving the infant of maternal contingency and inducing stress in the infant. The MSFP thereby offers an opportunity to examine the mother's behavior in the absence and presence of signals of infant distress.	Oxytocin (plasma)	The mother's oxytocin response was positively associated with the duration of time her gaze was directed toward her infant, while negatively associated with the frequency with which her gaze shifted away from her infant. Importantly, these associations were more pronounced under conditions of infant distress than non-distress. Mothers who showed low/average oxytocin response demonstrated a significant decrease in their infant gaze during periods of infant distress, while such change was not observed in mothers with high oxytocin response.

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Citation	Study aims	Setting	Study Type	Population (N=)	Intervention	Outcomes	Key findings
Kim, Kim & Ko (2016)[123]	A scalp massage was conducted on female office workers divided into a 15 minute group and 25 minute group and its effect on stress hormone, blood pressure and heart rate was analyzed in order to provide a theoretical rationale to apply scalp massage as stress therapy	South Korea, Lab	RCT	Female office workers, aged between 20–49 years (34)	Scalp massage was performed for 15 minutes/session for experimental group (I) Provider: trained masseuse Comparator(s) (1) 25 minutes/session for experimental group (II), twice a week, for a total of 20 times over 10 weeks in both groups. (2) Control group: no massage	Epinephrine (plasma) Norepinephrine (plasma) Cortisol (plasma)	In this study, 15-minute and 25-minute scalp massages had a significant effect on norepinephrine and cortisol while the 25-minute scalp massage had a significant effect on epinephrine. This suggests that a scalp massage decreases the activation of the sympathetic nerve while increasing the activation of the parasympathetic nerve, resulting in a decrease in the secretion of norepinephrine and cortisol, or in other words, stabilization of hormone levels.
Kramer *et al.* (1975)[97]	To ascertain whether touch, in the form of extra tactile stimulation, would result in more rapid physical and social development and a greater degree of social development of the premature infant	USA, Clinical	Non-RCT	Premature infants with a gestational age of 38 weeks or less (14)	Extra tactile stimulation: gentle, non-rhythmic stroking of the greatest possible area of skin surface of the infant's body by the nurse's hand for a total of 48 minutes a day and for a minimum of two weeks while the infant was confined to an isolette (the 48 minutes was additional to other tactile stimulation provided in the usual course of premature infant care) Provider: massage trained clinician (nurse) Comparator(s) Control group: no extra tactile stimulation	Cortisol (plasma)	Plasma cortisol levels revealed no significant difference between the two groups. An inspection of the means and standard deviations, however, indicated that they were going in the right direction (i.e., a decrease in cortisol in the extra tactile stimulation group).
Kuhn *et al.* (1991)[98]	To investigate the neuroendocrine response in preterm infants to a pattern of tactile-kinesthetic stimulation that facilitates their growth and development	USA, Clinical	RCT	Preterm infants (mean gestational age 30 weeks, mean birth weight 1176 gm) (40)	Tactile-kinesthetic stimulation for three 15-minute periods at the start of 3 consecutive hours each day for 10 days. Stimulation was conducted at the end of a sleep cycle, when infants were awake but in a state of quiet rest. The stimulation session comprised of three standardized 5-minute phases. The first and third phases were tactile stimulation; the second phase was kinesthetic stimulation. For tactile stimulation, the infant was placed in the prone position. The infant was stroked with the flats of the fingers of both hands for five 1-minute segments over each region of the body. For kinesthetic stimulation, the infant was placed in a supine position. Each five 1-minute segment consisted of six passive flexion-extension motions lasting approximately 10 seconds each. Each 1-minute segment involved a different body part. Provider: not stated Comparator(s) Normal nursery care	Dopamine (urinary) Norepinephrine (urinary) Epinephrine (urinary) Cortisol (urinary and plasma)	Urine norepinephrine and epinephrine values increased significantly only in the stimulated babies. Urine dopamine and cortisol values increased in both groups, and serum growth hormone decreased in both groups.

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Citation	Study aims	Setting	Study Type	Population (N=)	Intervention	Outcomes	Key findings
Light, Grewen & Amico (2005)[114]	To examine the relationships between self-reported frequency of partner hugs, plasma OT and BP levels in premenopausal women before and after warm contact with their husbands/partners ending with hugs. Tested whether OT activity may be a partial mediator of the expected relationships between greater Partner Hugs and lower cardiovascular responses.	USA, Lab	Pre-test post-test	Premenopausal women aged 20–49-years old (59)	Baseline: Women were seated alone in a room separated from their partners. Warm contact: Couples were seated on a love-seat in a quiet room and instructed to sit close together, holding hands if they felt comfortable doing so. They were asked to talk about a time they had spent together that made them feel closer as a couple (2 minutes). Next they watched a 5-minute segment of a romantic video they had previously seen. They then were instructed to talk again for 2 minutes about a time during which they felt especially close as a couple. Couples were left alone, unmonitored and unobserved except when the experimenter entered the room to give instructions. At the end of this session partners stood for a 20 second hug. Provider: partner Post-contact stressor: Women were immediately separated from their partners. The stressor involved 2 minutes of task instructions, followed by 3 components: (1) silent speech preparation (2 minutes), (2) giving a tape-recorded speech about a recent interpersonal event (one not involving their partners) that made the woman feel angry or stressed (3 minutes), and (3) post-speech recovery while listening to a replay of their own tape recorded speech (3 minutes).	Oxytocin (plasma) Blood pressure (BP) Heart rate (HR) Mean arterial pressure (MAP) Frequency of physical affection (Physical Affection Scale, PAS) Partner Support (Social Relationships Index, SRI)	Participants were grouped into 3 categories: those with low, medium and high baseline OT. The low OT group had significantly higher SBP, DBP and MAP at baseline than the high OT group. The low OT group had significantly higher baseline SBP than the moderate OT group. During the stressor periods (speech preparation, active speech and post-speech recovery), the OT groups no longer differed significantly in BP or HR although there was a tendency for the High OT group to maintain the lowest mean BP levels across events. OT group differences in baseline HR were also seen. The low OT group had significantly higher baseline HR than the high OT or the moderate OT groups. Greater frequency of Partner Hugs and Partner Massages were associated with higher baseline OT level; other PAS items (kissing, hand-holding, sitting/lying close) were not reliably correlated with any OT measure. Higher SRI score was not significantly associated with higher baseline OT. Partner Hugs was consistently unrelated to OT levels obtained during speech preparation, active speech or recovery. Thus, only baseline OT was a potential candidate as a mediator of the Partner Hugs link to lower BP. Baseline OT served as a significant partial mediator of the effect of Partner Hugs on baseline SBP and MAP, and a marginally significant mediator of the effect of Partner Hugs on baseline DBP and speech preparation DBP.
Lindgren *et al.* (2013)[99]	To report and evaluate a complex touch massage intervention according to the British Medical Research Council framework. This study aimed to evaluate the effects of touch massage on levels of anxiety and physiological stress in patients scheduled for elective aortic surgery.	Sweden, Clinical	RCT	Patients scheduled for elective aortic surgery (20)	After baseline measurements, all subjects were exposed to an experimental stressful situation (Trier Social Stress Test,). Intervention group received one Touch Massage intervention performed on the hands, arms, feet and legs 3 randomised groups, received a single massage intervention of about 60 minutes including a 20-minute rest period: Provider: massage trained clinicians (nurse) Group 1: rhythmical massage Group 2: RM with aroma oil Group 3: RM with a neutral oil Plus a control group	Cortisol (plasma)	No significant differences in concentration of serum cortisol between groups

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Citation	Study aims	Setting	Study Type	Population (N=)	Intervention	Outcomes	Key findings
Lindgren *et al.* (2010)[100]	To evaluate the short-term effects of tactile massage (TM) on stress response, as measured by heart rate (HR), heart rate variability (HRV), saliva cortisol levels, and glucose metabolism in healthy volunteers, in order to test the hypothesis that TM reduces stress response by increasing parasympathetic nervous activity.	Sweden, Clinical	RCT crossover design	Healthy volunteers (22)	Intervention Group received TM performed for 80 minutes in the following order: 20 minutes each on the left hand, the right hand, the right foot, and the left foot. A combination of jojoba, sheabutter, sunflower, and vitamin E oil was used in the massage. Participants in both groups were shown to a dark room with candles and calm music and placed in the supine position. After the intervention in intervention group or rest in control group the participants rested for additional 20 minutes. Provider: massage trained clinicians (nurse) Comparator(s) Control group (CG): Participants rested in the same setting but did not receive TM.	Cortisol (salivary)	Saliva cortisol (hypothalamic–pituitary–adrenal axis activity) decreased significantly after intervention
Listing *et al.* (2010)[101]	To investigate the efficacy of classical massage on stress perception and mood disturbances, as well as on serotonin and cortisol serum levels.	Germany, Clinical	RCT	34 women diagnosed with primary breast cancer (34)	For a period of 5 weeks, the intervention group (n=17) received biweekly 30-minute classical Swedish massages. Provider: trained masseuse Comparator(s) For the same period, the control group (n=17) received no additional treatment to their routine health care	Cortisol (plasma) Serotonin (plasma)	Cortisol serum levels ($p=0.03$) were significantly reduced after massage therapy (T2) compared with baseline in the intervention group. Serum cortisol level decreased significantly from baseline to the end of the intervention period in the massage group ($p=0.03$) but increased again at follow-up. There were no significant changes in serotonin in the massage or the control group, nor between the two groups, at the end of the intervention and at follow up.
Lovas *et al.* (2002)[131]	To identify and assess the influence of human touch, through massage therapy, on the immune response of healthy subjects	Australia, Lab	Single case ABAB time-lag control	2 females in their 20s, biological sisters, controlled for socioeconomic difference (2)	Received a relaxing massage during the experimental phases (B) and no massage during baseline phases (A). One hour Swedish massage with same masseuse in uninterrupted, quiet atmosphere. Provider: trained masseuse	Cortisol (plasma)	No significant difference in cortisol
Matthiesen *et al.* (2001)[102]	To explore hand movements and sucking behavior in healthy term newborns who were placed skin-to-skin on their mothers' chests, and to study maternal oxytocin release in relation to these behaviors	Sweden, Clinical	Correlational study	Ten mothers who had uncomplicated term pregnancies, and their infants (10)	Infants whose mothers had not been exposed to maternal analgesia were video-recorded from birth until the first breastfeeding. Video protocols were developed based on observations of the videotapes. Each infant's hand, finger, mouth, and tongue movements, positions of the hand and body, and sucking behavior were assessed every 30 seconds. Provider: newborn	Oxytocin (plasma)	Periods of increased massage-like hand movements or sucking of the mother's breast were followed by an increase in maternal oxytocin. When these movements decreased the oxytocin level usually went done except when the infants started to suck. The change in the intensity of the infant's stimulation of the mother's breast by "massage" or sucking was significantly related to the change in maternal oxytocin release.

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Citation	Study aims	Setting	Study Type	Population (N =)	Intervention	Outcomes	Key findings
Mooncey *et al.* (1997)[103]	To assess the effect of mother-infant skin-to-skin contact on plasma β-endorphin and cortisol concentrations in stable, preterm infants on a newborn intensive care unit	UK, Clinical	Non-RCT	Clinically stable, pre-term infants who were breathing spontaneously (15)	Skin-to-skin contact: On the first study day the infant lay prone in his or her cot or incubator, tilted at an angle of 30–40 degrees, with no handling for an initial 40 minute period. They were undressed by their mother and held nude for a 20-minute period of maternal skin-to-skin contact between the mother's bare breasts, covered by the mother's blouse and a light blanket. The mother was seated on a standard rocking chair tilted at an angle of approximately 60°. Provider: mother Comparator(s) Infants acted as their own controls: On the second study day, which served as a control, the infant was left unhandled throughout the entire study period of 60 min. The infant remained fully clothed in a crib or incubator, lying prone at an angle of 30–40°.	β-endorphin (plasma) Cortisol (plasma)	Both cortisol and β-endorphin concentrations fell significantly after the skin-to-skin session. There was also a significant fall in cortisol levels during the control session, in contrast to β-endorphin levels, in which there was no significant change. Analysis of variance showed that the fall in β-endorphin, but not the fall in cortisol, during the skin-to-skin session was significant when compared with the control session. There was a wide variation in basal cortisol and β-endorphin levels on both days.
Morhenn, Beavin & Zak (2012)[115]	To examine the effect of massage on oxytocin and other physiologic factors, including adrenocorticotropin hormone (ACTH), nitric oxide (NO), and beta-endorphin (BE)	USA, Lab	RCT	People from the University of California, Los Angeles (UCLA) (95)	Participants received 15 minutes of moderate pressure Swedish massage on their upper backs while lying prone on a massage table with their clothes on and shirts lifted to their shoulders. Massage took place in a semiprivate room. Provider: trained masseuse Comparator(s) Control: The team asked participants to rest by sitting in chairs for 15 minutes in the same rooms where participants in the massage group had received massages.	Oxytocin (OT) (plasma) Adrenocorticotropin hormone (ACTH) (plasma) Beta-endorphin (BE) (plasma)	Massage was associated with an increase in OT and reductions in ACTH, NO, and BE. Comparing the effects of massage for the massage group with those for the rest group, there were no significant differences between groups for changes in OT, ACTH, NO, and BE. Individuals receiving massages showed a significant increase in OT between baseline and the second blood draw. A similar comparison in the control group showed a decrease in OT that trended toward significance. OLS regressions showed that massage was associated with higher OT compared to rest and that massage accounted for 2.8% of the variation in OT levels. A t-test demonstrated that massage also accounted for the significant difference in the change in OT between the two groups. Women who received massage did not release significantly more OT than men; however, women who rested did show a change marginally higher in magnitude than men. Massage alone predicted25% of the variation in OT change, and massage and gender explained 30% of the variation in the change.

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Citation	Study aims	Setting	Study Type	Population (N=)	Intervention	Outcomes	Key findings
Mormann *et al.* (2015)[129]	To directly address the amygdala's role in processing eye gaze	Germany, Lab	Non-RCT	People with epilepsy (14)	Live encounter with the researcher randomly changing gaze from direct gaze to averted gaze to closed eyes over a period of two minutes. Provider: researcher Comparator(s) Images of faces with different gaze	Amygdala activity	No significant differences in response to gaze direction for the live encounter. Further, activity was less for the live encounter than with the photo images.
Neu, Laudenslager & Robinson (2009)[104]	To examine coregulation between mothers and preterm infants in hypothalamic-pituitary-adrenocortical (HPA) system activity, as indicated by salivary cortisol levels, while mothers held their infants.	USA, Clinical	Correlational studies	Mothers and their preterm infants postconceptional age of 33 to 36 weeks. (20 dyads)	Mothers held their infants for 60 minutes in the method that was usual. 11 used the Skin-to-skin method (Kangaroo) and 9 used traditional horizontal holding. Cortisol levels were taken at the commencement of holding and at 60 minutes. Provider: mother	Cortisol (salivary)	Salivary cortisol levels of mothers and infants were significantly closer at the end of a 60-minute holding session than they were before holding began, indicating coregulation in cortisol levels. The kangaroo method was not associated with greater maternal infant cortisol coregulation.
Noto, Kudo & Hirota (2010)[121]	To determine whether salivary biomarkers are useful objective indices for assessing the effects of back massage on mental status	Japan, Lab	Pre-test Post-test	Healthy female nursing students (25)	Standardized massage of the back for 10 minutes with non-aromatic oil Provider: not stated	Cortisol (salivary) a-Amylase activity (salivary) Chromgranin A (salivary)	a-Amylase, cortisol, and chromogranin A did not decrease
Pinar & Afsar (2015)[105]	The objective of this study was to evaluate the effect of back massage on the anxiety state, cortisol level, systolic/diastolic blood pressure, pulse rate, and sleep quality in family caregivers of patients with cancer	Turkey, Clinical	RCT	Family caregivers of cancer patients (44)	Massage for 15 minutes per day for a week. Each massage session, consisting of a combination of effleurage (rhythmic, gliding strokes), petrissage (gentle kneading), friction (rhythmic pressing), and tapotement (quick, striking movements or beating), started on the dorsal-lumbar region, followed by the back, scapulas, shoulders, neck, and scalp (from frontal area to occipital area). Before the massage, the caregivers in the intervention group rested in a chair for 10 minutes in a silence room. Provider: massage trained clinician Comparator(s) The control group rested quietly in a different silence room	State anxiety (STIA) Cortisol (serum) BP HR	Anxiety scores decreased significantly in the massage group. Plasma cortisol levels in the intervention group were significantly decreased after massage. Both BP and HR, which are a physiological indicators, significantly decreased by massage in the intervention group.
Pönkänen *et al.* (2011)[133]	To investigate whether a model's direct gaze enhances ERP responses to faces and whether this enhancement depends on the mode of stimulus presentation (live or picture).	Finland, Lab	Non RCT	University undergraduates with normal or corrected-to-normal vision (20)	Static faces of an adult female displaying a neutral emotion and gazing either straight forward (direct), gazing to the left or to the right (averted), or having the eyes closed (closed). Mode of delivery was a picture. Provider: model Comparator(s) Mode of delivery was live.	Event Related Potential (ERP), N170	As hypothesized, the N170 and EPN were greater for direct vs averted gaze and closed eyes in the live condition only.

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Citation	Study aims	Setting	Study Type	Population (N =)	Intervention	Outcomes	Key findings
Post-White *et al.* (2009)[106]	To determine whether 4 weekly sessions of massage, compared with 4 quiet-time control conditions, would reduce anxiety, cortisol, fatigue, nausea, and pain in children with cancer undergoing chemotherapy and would reduce anxiety, fatigue, and mood disturbance in a parent.	USA, Clinical	RCT	Children with cancer, 1 to 18 years of age, and 1 parent or guardian. (25)	Massage therapy (MT): 4 weekly sessions. Massage included the back, legs, arms, stomach/chest, and face. After 4 sessions participants were crossed over to receive the alternative condition. Provider: trained masseuse Comparator(s) Quiet time (QT): children and parents read, rested, talked quietly, or watched a video.	Cortisol (salivary)	Changes in salivary cortisol were not significantly different between the MT and QT conditions.
Rapaport, Schettler & Bresee (2010)[42]	To determine effects of a single session of Swedish massage on neuroendocrine and immune function. It was hypothesized that Swedish Massage Therapy would increase oxytocin (OT) levels, which would lead to a decrease in hypothalamic-pituitary-adrenal (HPA) activity and enhanced immune function	USA, Lab	RCT	Subjects were medically healthy and free of any current or past Axis I psychopathology (53)	45 minutes of Swedish massage by a trained therapist. Techniques included effleurage, petrissage, kneading, tapotement, and thumb friction. An identical protocol, except that the therapist used only a light touch with the back of the hand Provider: trained masseuse	Cortisol (salivary and plasma) Oxytocin (plasma) Arginine vasopressin (AVP) (plasma) Adrenal corticotropin hormone (ACTH) (plasma)	Swedish Massage Therapy caused a relatively large decrease in AVP (as measured by effect size) and relatively small, but consistent decreases in salivary and serum cortisol levels. Massage Therapy did not increase OT nor decrease ACTH, compared to the light touch control condition.
Rapaport, Schettler & Bresee (2012)[116]	To investigate the effects of Swedish massage versus a light touch intervention on neuroendocrine and immune parameters.	USA, Lab	RCT	Subjects were medically healthy and free of any current or past Axis I psychopathology (45)	45 minutes of Swedish massage by a trained therapist. Techniques included effleurage, petrissage, kneading, tapotement, and thumb friction. Provider: trained masseuse Group 1 had the therapy 1X per week for 5 weeks. Group 2 had therapy 2X per week for 5 weeks. Comparator(s) light touch with the back of the hand. Group 3 had the therapy 1X per week for 5 weeks. Group 4 had therapy 2X per week for 5 weeks.	Cortisol (salivary and plasma) Oxytocin (plasma) Arginine vasopressin (plasma) Adrenal corticotropin hormone (plasma)	Twice-weekly massage potentiates neuroendocrine changes so that massage therapy might be mediated through OT and AVP. The twice-a-week massage group demonstrated greater changes in OT, AVP, ACTH, and cortisol than the twice-a week touch group, changes that were sustained over a 3–4-day period between treatments.
Stringer, Swindell & Dennis (2008)[107]	Massage both with and without essential oils can be given to isolated haematology patients safely; and the physiological and psychological benefit demonstrated following massage in ambulatory cancer care is evident.	UK, Clinical	RCT	Isolated haematological oncology patients (39)	Single session (20 minutes) of Aroma therapy massage of light effleurage on body part chosen by patient. Provider: massage trained clinician Comparator(s) (1) Single session (20 minutes) of Base oil massage of light effleurage on body part chosen by patient (2) Rest for 20 minutes	Cortisol (plasma)	Reduction in stress hormone levels following single sessions of massage in isolated patients undergoing high-dose chemotherapy.

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Citation	Study aims	Setting	Study Type	Population (N=)	Intervention	Outcomes	Key findings
Taylor *et al.* (2003)[108]	To examine the effects of adjunctive postoperative massage and vibration therapy on short-term postsurgical pain, negative affect, and physiologic stress reactivity	USA, Clinical	RCT	Women who underwent an abdominal laparotomy for removal of suspected cancerous lesions (150)	Usual Care (UC) plus massage therapy: standardized 45-minute sessions of gentle Swedish massage on the 3 consecutive evenings after surgery. Provider: trained masseuse Comparator(s) (1) UC plus vibration therapy: 20-minute sessions of inaudible vibration therapy (physiotones) on the 3 consecutive evenings after surgery, as well as additional sessions as desired. (2) Usual postoperative care	Cortisol (urinary)	After adjusting for the patients' characteristics, no significant differences were found between the three treatment groups with regard to 24-hour urine free cortisol
Tsuji *et al.* (2015)[109]	The objective was to measure the impact on Oxytocin levels in autistic children when mothers provided gentle touch massage	Japan, Home	Pre-test post-test	Children with autism spectrum disorder (ASD) aged 8–12 years (7)	20 minutes prior to bedtime, every day for 3 months. Participants' mothers were trained in massage by a massage therapist.This involved gentle and warm massage with weak pressure for the child's body. Provider: mother Comparator(s) 4 month period of non-massage following cessation of intervention.	Oxytocin (salivary)	The results indicated that ASD children and their mothers exhibited higher salivary concentrations of OT during the repeated massage period for 3 months, compared to those during the non-massage (rest) period for 4months.
Ulmer-Yaniv *et al.* (2016)[134]	The current study focused on human adults during periods of parental and pair bond formation. Plasma OT, b-End, and IL-6 were measured in new parents, new lovers, and singles and behavioral synchrony during social interactions micro-coded to understand how functioning of these systems support the expression of synchrony, a social experience critical for the establishment of new bonds.	Israel, Lab	Non-RCT	Healthy young adults, with at least. 35 singles who were not involved in a romantic relationship during the past six months (17 men and 18 women), 50 individuals (25 couples) who began a romantic relationship within the past four months, and 115 new mothers and fathers (71 mothers and 44 fathers, not couples) of 4–6 month-old first-born infants. (200)	Parents were instructed to play with the infant for approximately 10 minutes "the way they play at home". Lovers were videotaped in a positive interaction for approximately 10 minutes; they were asked to plan "the best day ever" to spend together. Interactions were videotaped and coded for time for gaze, affective facial expression, vocalization and touch. It is not clear what occurred with the 'singles' group.	Oxytocin (OT) (plasma) Beta endorphin (b-End) (plasma) Interlukin-6 (IL-6) (plasma)	OT significantly increased during periods of parental and romantic bonding and was highest in new lovers. In contrast, IL-6 and b-End were highest in new parents and lowest in singles. Biomarkers became more tightly coupled during periods of bond formation and inter-correlation among hormones was highest during romantic bonding. Structural equation modeling indicated that the effects of IL-6 and b-End on behavioral synchrony were mediated by their impact on OT, highlighting the integrative role of the oxytocinergic system in supporting human social affiliation. Findings suggest that periods of bond formation are accompanied by increased activity, as well as tighter cross-talk among systems underpinning affiliation, reward, and stress management.
Wandell *et al.* (2010)[110]	To study the effect of tactile massage (TM) or relaxation exercises on metabolic control (HbA1c) in patients with type 2 diabetes. The secondary aim was to study stress parameters (cortisol and catecholamines).	Sweden, Clinical	Quasi-RCT	Patients with type 2 diabetes aged 35–75 years of age, with metformin treatment. (53)	10 weeks of TM once/week (n=26) and follow up 3 months later. Provider: trained masseuse Comparator(s) 10 weeks of relaxation using a compact disc once/week (n=27) and follow up 3 months later.	Cortisol (urinary)	No significant difference in cortisol levels at follow-up for either group

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Citation	Study aims	Setting	Study Type	Population (N=)	Intervention	Outcomes	Key findings
Wardell & Engebretson (2001)[117]	To test a framework of relaxation or stress reduction as a mechanism of touch therapy through examination of select physiological and biochemical effects and the experience of 30 minutes of Reiki (a form of touch therapy).	USA, Lab	Pre-test post-test	Healthy adults (23)	Reiki touch (3 repeats). Treatments were given in the afternoon and early evening to avoid normal circadian rhythm changes in cortisol, which are most dramatic before noon. Provider: trained masseuse	Cortisol (salivary)	There was no significant change in cortisol levels before and after treatment (15 dropped, 7 rose).
Wikström, Gunnarsson & Nordin (2003)[118]	To investigate the effects of tactile stimuli (massage) on plasma oxytocin and neuropeptide Y (NPY)	Sweden, Lab	Pre-test post-test	Volunteer subjects; staff and students of Linköping University and their family members (21)	Swedish classic massage was performed at 9am for 30 minutes (+/−2), using unscented vegetable oil. Massage was administered to the back, including the posterior neck and shoulders, with the subject in the prone position. No verbal communication occurred during the massage. Provider: trained masseuse	Oxytocin (plasma) Neuropeptide Y (NPY)	No overall difference in oxytocin concentrations before and after massage was found either for men or for women. Focusing on the difference (II-I) between concentrations immediately before and after the massage session, a sex difference was found for oxytocin as well as NPY.
Wu *et al.* (2014)[124]	The effects of aromatherapy massage on multiple neurobiological indices such as quantitative psychological assessments, electroencephalogram (EEG) power spectrum pattern, salivary cortisol and plasma brain-derived neurotrophic factor (BDNF) levels	South Korea, Lab	RCT	Females whose children were diagnosed with attention deficit hyperactivity disorder (25)	Aromatherapy massage for 40 minutes twice per week for 4 weeks (eight times in total). Included bath, then 20 ml of Jojoba oil containing mixed essential oils (lavender, geranium) with effleurage, friction, petrissage and vibration treatment. Provider: trained masseuse Comparator(s) Control group: no treatment	EEG activity Plasma brain-derived neurotrophic factor (BDNF) Cortisol (salivary and plasma)	Significant enhancement of alpha and reduction of delta after a 15-minute aromatherapy massage. No significant differences in basal EEG patterns. Salivary cortisol levels were significantly decreased when they were measured at approximately 15 minutes after the one-time aromatherapy massage treatment, compared to the time point just before treatment. Basal cortisol levels in plasma were not substantially changed after the 4-week program in both the control and therapy groups. There were no significant differences in basal cortisol after 4 weeks.

BP, blood pressure; CCU, coronary care unit; CT, cortisol; GA, gestational age; GHT, gentle human touch; KC, kangaroo care; MSFP, Modified Still Face Procedure; NE, norepinephrine; NK cells, natural killer cells; OT, oxytocin; PIPP, Premature Infant Pain Profile; QTN, Qi no touching; QTT, Qi touching; RCT, Randomized controlled trial; SSC, skin-to-skin contact; TM, tactile massage; TTM, traditional Thai massage; WC, warm contact.