Topical Review

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Evidence of distorted proprioception and postural control in studies of experimentally induced pain: a critical review of the literature

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Abstract

Objectives: Deficits in proprioception and postural control are common in patients with different musculoskeletal pain syndromes. It has been proposed that pain can negatively affect proprioception and postural control at a peripheral level, however research is limited to animal studies. Human studies have shown that it is more likely, that the link between pain and proprioceptive deficits, lies within changes in the central nervous system where noxious and non-noxious stimuli may overlap. In clinical studies, causality cannot be determined due to other factors which could confound the assessment such as pathophysiological features of the underlying musculoskeletal disorder and different psycho-social influences especially in patients with chronic pain. On the other hand, experimentally induced pain in healthy participants is able to control most of these confounding factors and perhaps offers an assessment of the effects of pain on proprioception and postural control. The aim of this paper is to critically appraise the literature related to the effect of experimentally induced pain on proprioception and postural control. Results from these studies are discussed and limitations are highlighted for future research.

Methods: A search of databases (Medline, Scopus, PubMed) was conducted as well as reference check from relevant articles published since 2000. Fifteen studies which explored the effect of experimentally induced pain on postural control and ten studies which explored the effect of experimentally induced pain on proprioception were included.

Results: We found that in the majority of the studies, postural control was negatively affected by experimentally induced pain. Results for proprioception were mixed depending on the body region and the way the painful stimuli were delivered. Kinesthesia was negatively affected in two studies, while in one study kinesthesia was enhanced. Joint position sense was not affected in four out of five studies. Finally, force sense was affected in three out of four studies.

Conclusions: From a clinical point of view, findings from the available literature suggest that experimentally induced pain impairs postural control and could potentially increases the risk for falls in patients. Interventions aiming to reduce pain in these patients could lead to preservation or improvement of their balance. On the other hand, the same conclusion cannot be drawn for the effect of experimentally induced pain on kinesthesia and joint position sense due to the limited number of studies showing such an effect.

Keywords: anticipatory postural adjustments; experimentally induced pain; force sense; joint position sense; kinesthesia; postural control; proprioception.

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Introduction

Proprioception

Proprioception is defined as the perception of body orientation and position as well as the perception of body and limb motion in three-dimensional space [1, 2]. Proprioception

involves a complex interaction between the sensory information relayed by the peripheral nervous system and the central nervous system (CNS) processing [3]. This interaction, is integrated with other somatosensory, visual and vestibular information in order to meet motor control demands [4, 5].

Kinesthesia, joint position sense and the sense of force, effort and heaviness have been suggested as submodalities of proprioception [5, 6]. Kinesthesia is the sense of movement and the direction of the movement [7–9]. Joint position sense (JPS) is the awareness of the location of a joint in space [9]. Although, both kinesthesia and JPS share inputs from muscle spindles [8], they should be viewed as separate subdivisions of proprioception [10] since there is evidence that movement and position are processed through different mechanisms in the CNS [11] and distinct sites in the motor cortex [12].

Force sense is the perception of forces that are produced by muscles [13–15] while the sense of effort is the conscious sensation of how strenuous a task is [10, 16]. The sense of heaviness is described as the perception of the weight of objects and is more accurate during movement [14, 15]. The sense of force and heaviness is generated by peripheral and CNS influences, while the sense of effort is centrally processed and independent of afferent feedback [14]. However, whether central or peripheral mechanisms play the most dominant role for these senses is debatable [17]. An important distinction between these three senses and Kinesthesia and JPS is that the former is always associated with motor commands while JPS can be present in a passive limb [15]. Tests of force sense typically assess the ability of an individual to replicate a sub-maximal force that has previously been generated under varying conditions. Force parameters include the magnitude, angle, and direction of the produced force.

Postural control requires the maintenance of an upright stance and is an essential motor behavior in daily activities which was found to be highly variable [18]. The complex task of postural control depends upon the integration of sensory inputs from the visual, vestibular and proprioceptive system and the constant monitoring of motor output [19]. If one or more of these components is compromised, then muscles are activated in order to reduce postural oscillations and maintain postural equilibrium. Postural control can be assessed during different balance tasks in quiet standing and perturbed standing. Also, anticipatory postural adjustments are important motor control strategies during reactive tasks and should be considered in the assessment of postural control.

Proprioceptors

Proprioceptors are specialized mechanosensory neurons distributed throughout the body within muscles, joints, tendons, skin and fascia [20, 21]. Mechanical deformations serve as the initiating stimuli for the proprioceptors, which is converted into neural signals and then conveyed to the CNS for integration and proprioception [3]. Although these events occur in a similar manner in all proprioceptors, different types of receptors decode specific variables of the mechanical stimuli such as the direction, the magnitude, the speed and the type of the mechanical stimulus and they do this in a task-dependent manner.

Muscle proprioceptors are the muscle spindles that are embedded in the body of skeletal muscles in parallel with the extrafusal muscle fibers [22]. Muscle spindles are considered the most important receptors in proprioception [23, 24], and are activated by the change in muscle length and by the rate of this change [21].

Joint proprioceptors, namely Ruffini endings – Pacinian endings are categorized in 3 types. Type I mechanoreceptors are present in the external layers of joint capsules and are slowly adapting receptors while type II joint mechanoreceptors are located in the deeper layers of joint capsules and adapt rapidly to strain [21]. Type III joint mechanoreceptors are embedded in joint ligaments and adapt slowly [21]. Collectively, joint proprioceptors have been labeled “limit detectors”, because first their activation peaks at the extremes of joint range of movements [25] and second, they are unable to signal direction of movement or JPS in the midrange [10].

Muscle-tendon proprioceptors are the Golgi tendon organs (GTOs) which are located at the musculotendinous junctions and are innervated by fast-conducting Ib afferent fibers [26]. GTOs are contraction receptors that respond significantly to changes in muscle tension [26]. Experimental evidence suggest that GTOs effectively monitor active sub-maximal muscle contractions [10], and even small changes in muscle length, predominantly during weak isometric contractions [27]. Skin proprioceptors are activated when the skin is deformed in different directions. The four types of skin mechanoreceptors are Meissner corpuscles, Pacinian corpuscles, Merkel endings and Ruffini endings [28]. All four types play an important role in kinesthesia since they respond rapidly to skin strain [29], but only slowly adapting Ruffini endings are thought to signal JPS [29, 30]. Types of proprioceptors and their special characteristics are shown in Table 1.

Table 1: Types of proprioceptors and special characteristics.

Proprioceptors				
	Muscle proprioceptors	**Joint proprioceptors**	**Muscle-tendon proprioceptors**	**Skin proprioceptors**
Types	Muscle spindles	Ruffini endings Pacinian corpuscles	Golgi tendon organs	Meissner corpuscles pacinian corpuscles Merkel endings Ruffini endings
Location	Body of skeletal muscles in parallel with the extrafusal muscle fibers	Type I: External layers of joint capsules Type II: deeper layers of joint capsules Type III: Joint ligaments	Musculotendinous junctions	Skin
Stimulation	Changes in muscle length and velocity of these changes	Type I: Slowly adapting receptors Type II: adapt rapidly to strain Type III: Respond slowly to strain	Changes in muscle tension and active sub-maximal muscle contractions	Respond rapidly to skin strain

Central nervous system in proprioception

While proprioceptors are regarded as the hardware, the CNS is viewed as the software where conscious and nonconscious proprioception occurs [31]. Merely the sensory input from proprioceptors is not sufficient for proprioception and the CNS processing is an integral part in a chain of complex physiological and psychological events [1]. The sensory input from different body parts is initially integrated at the spinal cord level [3]. First order afferent neurons create synapses with interneurons at the dorsal horn, which are modulated by higher levels of the CNS i.e. brain stem and cortex, through descending signals [5]. Two ascending pathways relay information to higher centers of the CNS, namely the dorsal lateral tracts and the spinocerebellar tracts [32]. Dorsal lateral tracts are responsible for conscious proprioception since their signals terminate at the somatosensory cortex, while spinocerebellar tracts are involved in nonconscious proprioception by providing input to areas of the cerebellum [4, 33].

Pain and distorted proprioception – neurophysiological mechanisms

Studies have demonstrated loss of proprioception during evoked pain, but the exact mechanisms by which pain affects peripheral or central processing remain speculative. At a peripheral level, it seems that the activation of Aδ and C nociceptors causes a reflex excitation of γ-motoneurones which alters muscle spindle sensitivity [34]. However, this hypothesis has only been confirmed in animal model studies [35, 36]. Hellstrom et al. [35] injected bradykinin in the masseter muscles of anaesthetised cats, and found an increased static fusimotor drive of the muscle spindle system. Thunberg et al. [36] injected hypertonic saline in the leg muscles of anaesthetised cats and found a statistically significant increase in muscle spindle firing rate.

In contrast, human studies have shown that experimentally induced pain (EIP) does not cause changes in muscle spindle activity in relaxed leg muscles [37, 38] or during voluntary contractions [39]. Birznieks et al. [37] used microneurography to record nerve impulses directly from muscle spindle afferents of leg muscles after intramuscular injections of hypertonic saline, and found no change in muscle spindle discharge rate. Fazalbhoy et al. [38] injected hypertonic saline in the tibialis anterior of healthy humans and was unable to alter the firing rate of the majority of the muscle spindles. Finally, Smith et al. [39] explored the effect of EIP via hypertonic saline on ankle dorsiflexors during voluntary contractions and found no change in firing rates of muscles spindles during the painful stimulus.

It is more likely, that the link between pain and proprioceptive deficits, lies within changes in the CNS. Human imaging studies have shown areas of the CNS where noxious and non-noxious stimuli may overlap. For example, the primary motor cortex is involved in proprioception [40, 41] and also receives nociceptive input [42]. Also, the primary somatosensory cortex has been shown crucial in the processing of noxious and non-noxious information [43, 44].

Experimentally induced pain

EIP has been used in healthy participants to assess the direct effect of pain on proprioception. Isolating pain in EIP studies has the advantage of standardizing parameters such as the location, duration, intensity and nature of the painful stimulus [45] and also eliminates the physiological, cognitive and behavioral consequences of pain which might confound results. From a clinical point of view, if pain alone is responsible for disturbing proprioception, then effective pain reduction can prevent proprioceptive deficits.

In EIP studies, the most extensively used algogenic substance is hypertonic saline [46–52]. The latest hypertonic saline model for EIP, uses computer-controlled infusions of the substance, injected either directly in the muscles [34, 48], joints [50], subcutaneously [53] or in other periarticular tissues [46, 47, 49]. The intensity of induced pain, depends on the concentration, the volume, and the infusion rate of the solution [54]. This model of experimental pain is preferred for its safety and because it can be compared to clinical pain due to the similarities in intensity, quality and distribution of the evoked pain, without actual mechanical tissue damage or inflammation [55]. Another substance that is used in EIP studies is nerve growth factor (NGF) [56]. It has been shown that, NGF does not cause tissue damage, but can induce pain that lasts for up to 14 days and therefore better resembles the mechanisms involved in the transition to persistent pain [57].

Other methods of delivering painful stimulus that have been used in EIP studies include electrical stimulation of the skin [58, 59], thermal stimulation of the skin [60] and pressure on body parts with rigid objects [61, 62].

EIP vs clinical pain

EIP studies are suitable to explore causality between pain and proprioception because they can potentially control for possible confounding factors that are seen in pain patients such as the pathophysiological features of the underlying musculoskeletal disorder (e.g. inflammation, joint effusion, structural changes, maladaptive movement behaviors, motor control disturbances), or in the case of chronic pain CNS alterations even in the absence of peripheral tissue damage [63]. All these factors can affect proprioception. For example, the catabolic effect of circulating inflammatory chemicals may affect proprioception through direct changes in electrophysiological properties of muscle and joint proprioceptors [64]. Also, inflammation of an injured tissue causes protective movement behavior and muscle spasm both of which can also affect proprioception [65].

On the other hand, another important difference between EIP and clinical pain is that the later should always be viewed within a bio-psycho-social framework that recognizes its multifactorial nature [66]. Hence, the question arises whether EIP studies can directly replicate the complexity and uniqueness of a person's pain experience since EIP is generated in a strictly controlled experimental environment. In addition, EIP is of short duration and not damaging (low threat value) and thus cannot be compared to chronic pain where alterations in brain structure and function (e.g. central cortical reorganization) have been related to distorted proprioception [67, 68]. Consequently, EIP research can only offer insights about pain in its acute phase.

One additional factor that should not be ignored, is that pain disrupts the attention during any test of proprioception in EIP and clinical pain studies [48, 49, 69]. Chronic pain has been shown to affect working memory [70], while EIP has also been shown to affect some aspects of attention such as orientation and alerting attention, but not executive attention [69]. A study by Moore et al. [71] compared EIP to chronic pain (fibromyalgia patients) and found differences in the type of cognitive tasks that were affected between these two pain states. EIP affected participants' performance on an attention span task and an attentional switching task, while patients with fibromyalgia showed impairments in the performance of a divided attention task. These findings suggests that EIP and chronic pain exert a different effect on attention possibly due to different psychological or neural mechanisms that interfere with attention [71].

In clinical pain studies, proprioception has been explored extensively in relation to different musculoskeletal syndromes and injuries and it is well accepted that injury can result in changes in the proprioceptive system. In the shoulder joint, proprioceptive alterations have been noted in patients with rotator cuff injury [72], sub-acromial impingement [73] and multidirectional instability [74]. Kinesthesia and JPS are reduced in athletes with a history of ankle sprain injuries [75, 76] while patients with distal radius fractures demonstrate impairments in proprioception of the wrist [77]. On the other hand, healthy controls, show no proprioceptive impairments at the shoulder [50], and ankle [34]. Also, no changes in JPS were observed in the wrist with EIP [56].

In summary, causality in the relation of clinical pain and proprioceptive deficit cannot be determined due to the difficulties of isolating other features associated with these

disorders. EIP studies offer a way to explore casual effect in proprioception and postural control and will be extensively reviewed in the following section. However, their extrapolation to chronic pain warrants attention.

Review of studies

EIP in studies of postural control

Impairments in postural control have been explored in studies that applied EIP at muscular and non-muscular sites of the knee joint. A model of infrapatellar fat pad pain induced by hypertonic saline injection was used in two studies which measured standing balance [46, 47] with mixed results. In the first study [46], pain was induced unilaterally in the fat pad of twelve healthy individuals and caused no disturbances of postural control during static or dynamic balance testing. The other study, found increased sway displacements in medial-lateral and anterior-posterior directions during quiet standing on a force platform, only when hypertonic saline was administered in both knees [47]. This probably happens due to some "sensory reweighting" mechanism, where the non-painful knee compensates in maintaining postural stability, but such adjustment is not possible when both knees are affected.

When EIP was applied in muscles of the knee, postural stability was compromised in two studies [48, 78]. Hirata et al. [78], used injection of hypertonic saline in the vastus medialis, vastus lateralis and hamstring muscles of one leg in nine subjects. Compared to baseline and control injection, EIP impaired postural control during quiet stance and after unexpected forward perturbation. The largest sway displacements were noted in the anterior-posterior direction. Suda et al. [48], also found that intramuscular injections of hypertonic saline in both vastus medialis and lateralis muscles of sixteen healthy adults, reduced postural stability and increased postural sway, when subjects were challenged with a cognitively demanding task. This suggests that pain can impair postural stability in a task-dependent manner.

Further support for the complex interaction between pain and secondary cognitive tasks during a balance test is provided by the fact that certain types of tasks acting to distract attention away from pain could in fact improve balance. Hirata et al. [79], showed that healthy individuals that were under experimental pain of the leg, showed improvements in postural sway when they had to maintain a laser at a visual target. This could be due to the sensory reweighing mechanism of the CNS where visual sensory information was prioritized over the painful stimulus. Providing additional sensory information to people in pain also improves postural stability possibly due to the required shift of attention away from pain. Hirata et al. [80] confirmed this by showing that center of pressure displacements during quiet stance were minimized in a group of sixteen healthy individuals who received EIP and were instructed to lightly touch a curtain during their pain.

One additional method to induce pain perception, is the application of noxious heat stimulation. In a study by Blouin et al. [60], a painful cutaneous heat stimulation of 45 °C was delivered by thermal grills applied bilaterally on the calves. The results showed deterioration of postural control during quiet standing compared to a group which received non-noxious heat stimulation of 40 °C. The use of thermal grills is an efficient experimental method of inducing painful stimulation of skin thermoreceptors through temperatures that range from 42 to 44 °C [81]. Thermal grills used in this study have the advantage in that the grills are in no contact with the skin, thus preventing mechanical activation of low-threshold mechanoreceptors.

The effect of EIP on balance is region specific [61]. Painful stimulation with a rigid squared object to the plantar surface of both feet caused displacement in the center of foot pressure while the same stimulation to the palms of both hands had no effect. Similar results were shown when electrical stimulation was used to induce pain [59]. Electrical stimulation of high intensities only, applied to the dorsum of the feet but not the dorsum of the hands, impaired postural control in quiet stance. Probably this is because lower limbs directly participate in postural control and have a more profound destabilizing effect when in pain compared to upper limbs. Axial skeleton might also be important for postural control as Vuillerme and Pinsault [58] demonstrated that EIP elicited by painful electrical stimulation on both trapezius muscles in sixteen young males impaired postural control and performance during quiet standing.

The same authors [62] conducted another study in which they compared painful stimulation to non-painful stimulation, applied on the sole of the feet in three different sensory conditions. One group had their eyes open, the other had their eyes closed and the third group had their head tilted backwards. Only painful stimulation degraded upright postural control especially in the absence of vision. In addition, it was also shown that disturbances in posture were more significant when sensory information from the vestibular system and the neck were disturbed. Generally, postural control was enhanced by visual stimuli which lends support to the role of the CNS in sensory re-weighting.

Distribution of pain also matters. In one study [82], intramuscular injections of hypertonic saline induced in the medial gastrocnemius and tibialis anterior simultaneously, did not cause attenuated postural control during quiet standing and after unexpected perturbations unless the pain spread in larger areas of the calf region. This finding was confirmed by Matre et al. [34], and could, at least in part, explain why other studies that induced pain in small areas of the knee [49] or shoulder [50] did not find changes in proprioception. It seems that a larger distribution of pain is needed to take priority of the individual's attention and therefore cause disturbances in proprioception and postural stability [34].

EIP has been shown to cause impairments in anticipatory postural control during reaction task movements when hypertonic saline is induced in muscles of the trunk [83], the knee [84] and the infrapatellar fat pad [85]. Hodges et al. [83] evaluated the effect of EIP on the feedforward recruitment of trunk muscles during a postural task of shoulder flexion. Results showed that the onset and amplitude of most trunk muscles was altered in a different manner during acute pain, however, the most consistent changes towards delayed activation and reduced amplitude were observed in the transversus abdominis muscle. Shiozawa et al. [84] used experimental muscle pain in tibialis anterior and vastus medialis muscles of nine healthy subjects and recorded EMG from thirteen muscles during shoulder flexion and bilateral heel lift tasks. Results demonstrated decreased peak muscle activation of the painful and synergy muscles during the performance of heel lifts and faster activity onset of non-painful muscles in both tasks. Shiozawa et al. [85], also found that EIP in the infrapatellar fat pad causes delayed onset activity in vastus medialis, vastus lateralis and tibialis anterior muscles during the bilateral heel lift task while the contralateral vastus medialis showed early onset.

These results indicate that experimental muscle pain modulates muscle activity as an adaptation strategy to avoid injury, while activates postural muscle early as a compensatory mechanism to maintain balance. This is consistent with the theory of motor adaptation to pain of Hodges et al. [86] which recognizes the complex nature of motor control adaptations that accompany pain. The theory proposes that pain is associated with a motor adaptation that may vary between different tasks and individuals depending on the perceived threat of pain or injury. Therefore, these adaptations are not uniform and may cause increased activity in some muscles, decreased activity in others or a combination of both.

Summarizing and interpreting the results from these studies, one can highlight the important role of attention in postural control. This is because (i) only higher intensities of pain, which attract attention more, distort postural control [82], (ii) proprioceptive deficits manifest more readily during cognitive demanding tasks [48] and (iii) postural alterations due to pain manifest only when pain is induced in the limbs directly involved in postural control [59, 60]. Also, the effects of experimental pain on the anticipatory postural adjustments of muscles involve a redistribution of muscle activity that is not stereotypical and can vary between muscles and the tasks performed [83–85]. Finally, the importance of the CNS as a therapeutic target in postural disorders via sensory reweighting is highlighted. Summary of the results of studies for postural control are shown in Tables 2 and 3.

EIP in studies of joint position sense and kinesthesia

In a study by Bennell et al. [49], knee JPS was tested in sixteen healthy individuals under three experimental conditions: moderate intensity EIP by unilateral injection of hypertonic saline into the infrapatellar fat pad, a distraction test and a baseline control. Measures of JPS included active matching of different angles in non-weight bearing and single leg stance. Results showed that EIP did not alter JPS and this was irrespective of pain intensity. It is possible that the size of pain distribution was not sufficient enough to affect proprioception as suggested by the previous studies in postural control. Interestingly, JPS, especially in weight-bearing, was affected by attention demanding tasks similar to other studies on proprioception [87] and postural control [88]. In contrast, another study by Matre et al. [34], found disturbances in movement detection thresholds, but not in JPS, when hypertonic saline was injected in tibialis anterior and soleus muscles despite the high intensity and distribution of pain. The largest errors occurred in the ability to detect movement changes at the limits of plantar flexion and dorsiflexion.

It is also possible that pain affects JPS differently in the axial and appendicular skeleton. A recent study by Summers et al. [56], explored the effect of EIP through intramuscular injection of nerve growth factor on JPS of the wrist. Researchers injected nerve growth factor in the extensor carpi radialis brevis muscle and measured JPS immediately after the injection and after four days. This was the first study to explore longer term effect of pain on JPS. Results showed no changes in wrist joint position error.

In contrast, Malmstrom et al. [52], injected the paraspinal muscles on one side of the cervical spine in eleven

Table 2: EIP in studies of postural control.

Studies	No. of subjects	Type of EIP	Site of EIP	Balance measurements	Affected postural control
Hirata et al. [47]	12	Hypertonic saline	Infrapatellar fat pad	Moveable force platform CoP	No (unilateral EIP) Yes (bilateral EIP)
Suda et al. [48]	16	Hypertonic saline	Vastus medialis oblique, vastus lateralis oblique	Force platform CoP Quiet standing	Yes
Hirata et al. [82]	9	Hypertonic saline	Gastrocnemius and tibialis anterior	Moveable force platform CoP Quiet and perturbed standing	Yes (when pain spread in larger areas)
Blouin et al. [60]	10	Noxious heat stimulation	Calves	Force platform CoP Quiet standing	Yes
Pradels et al. [61]	10	Painful stimulation with rigid squared object	Plantar surface of feet	Force platform CoP Quiet standing	Yes
Pradels et al. [62]	14	Painful stimulation with rigid squared object	Plantar surface of feet	Force platform CoP Quiet standing	Yes
Corbeil et al. [59]	10	Painful electrical stimulation	Dorsum of feet	Force platform CoP Quiet standing	Yes
Vuillerme and Pinsault [58]	16	Painful electrical stimulation	Trapezius muscles	Force platform CoP CoM Quiet standing	Yes
Bennell and Hinman [46]	12	Hypertonic saline	Fat pad	(i) Moveable force platform CoP (ii) Step test	No
Hirata et al. [78]	9	Hypertonic saline	Vastus medialis oblique, vastus lateralis oblique, biceps femoris	Moveable force platform CoP Quiet and perturbed standing	Yes (quiet and perturbed standing)
Hirata et al. [79]	16	Computer pressurized cuff	Upper arm and lower leg	Force platform CoP	Improved postural control when secondary task was performed
Hirata et al. [80]	16	Hypertonic saline	Vastus medialis oblique	Force platform CoP	Improved postural control when additional sensory feedback was provided

*CoM, center of mass; *CoP, center of pressure.

Table 3: EIP in studies of anticipatory postural adjustments.

Studies	No. of subjects	Type of EIP	Site of EIP	Measurements during reaction tasks	Affected anticipatory postural adjustments
Hodges et al. [83]	7	Hypertonic saline	Longissimus	Abdominal and paraspinal muscles EMG	Yes
Shiozawa et al. [84]	9	Hypertonic saline	Vastus medialis oblique, tibialis anterior	Upper limb, lower limb, and trunk muscles EMG	Yes
Shiozawa et al. [85]	12	Hypertonic saline	Infrapatellar fat pad	Vastus medialis oblique, vastus lateralis oblique, tibialis anterior muscles EMG	Yes

healthy participants with hypertonic saline and examined repositioning errors during a head on trunk repositioning test, at a 30° target angle of rotation to the injected side. Interestingly, position matching errors were recorded even after the pain had subsided, suggesting a more complex prolonged effect of pain on proprioception.

The effect of EIP on kinesthesia and JPS seems to be different. Hypertonic saline injected, in the sub-acromial space of twenty healthy individuals did not have any effect on passive JPS and interestingly, enhanced movement sense as, expressed by a significant improvement in the detection of movement direction [50]. Improvement of shoulder movement sense after pain, was probably a protective mechanism by the CNS and is possibly related to increased attention to the limb.

Moreover, another study [53], examined the effect of intramuscular and subcutaneous hypertonic saline on the ability of 12 healthy individuals to detect the direction of passive movement of the interphalangeal joint of the thumb. Pain initiated in the flexor pollicis longus muscle resulted in impaired movement detection and the same was observed with subcutaneous pain over the skin area of the thumb. When pain was induced in flexor carpi radialis, a muscle that does not act on the thumb, pain had no effect on proprioception indicating that impairments were site specific and related to tissues and areas that had a movement specific proprioceptive role.

EIP in studies of force sense

EIP was shown to negatively affect force sense at the elbow joint in one study [51]. Two methods of EIP were explored. One was through intramuscular injections of hypertonic saline in the bicep muscle and the other was through cutaneous heat stimulation in the skin area of the same muscle. The participants were then instructed to match a predetermined submaximal isometric contraction. Results showed torque matching errors with both painful stimuli when comparisons were made with the non-injected arm or with painful skin stimulation in areas away from the biceps muscle. Muscle pain stimulation has been shown to inhibit areas of the motor cortex [42]. This could be a possible mechanism for the disruption of force sense observed in this study.

Similar results were demonstrated in a study where researchers injected hypertonic saline in the bicep muscle and instructed participants to match different levels of isometric contractions in a one-dimensional task (measures of one force component) and a three-dimensional task (measures of three force components) [89]. Matching the force was affected only in the one-dimensional task suggesting that pain effects are task dependent. Improved proprioception in the three-dimensional task could be interpreted as a search for an alternative motor control strategy to overcome disrupted proprioception found in one-directional force matching. In contrasts, task stability for a three-dimensional task was not shown for the knee joint in another study [90]. In this study, participants performed isometric knee extensions before and after the injection of hypertonic saline into the infrapatellar fat pad. Painful contractions at low target forces were associated with failure to sustain the required force matching task. Differences on the force output of the three-dimensional task between these two studies could be explained by the diverse effect that experimental pain has on different tissues (muscles vs infrapatellar fat pad) and the joints under examination. Painful joints of the lower limb display a different role in proprioception than joints of the upper limb.

Mista et al. [91] compared persistent nerve growth factor induced pain to acute saline induced pain in the extensor carpi radialis brevis muscle of healthy participants. The motor task before and after pain included matching a submaximal isometric target force. No significant differences in force error were found for both pain models although acute pain increased force variation and force direction compared to the pain-free state while persistent pain only affected force direction. These alterations in force variation and force direction possibly suggest altered muscle recruitment and alternative motor strategies due to pain. Summary of the results of studies for kinesthesia, JPS and force sense are shown in Table 4.

Conclusions and clinical suggestions

Summarizing the results, EIP was found to impair postural control for the majority of the studies reviewed [47, 48, 58–62, 78, 82], one study found no changes [46], while two studies found improved postural control when a secondary task was performed [79] or when additional sensory feedback was provided [80]. Anticipatory postural adjustments were affected by EIP in three studies [83–85]. Kinesthesia was negatively affected by EIP in two studies [34, 53], while in one study kinesthesia was enhanced [50]. JPS was shown to be affected by EIP in one study [52] while it was not in four studies [34, 49, 50, 56]. Finally, force sense was affected by EIP in three studies [51, 89, 90] and unaffected in one study [91].

Table 4: EIP in studies of kinesthesia, JPS and force sense.

Studies	No. of subjects	Type of EIP	Site of EIP	Measurements	Affected JPS	Affected kinesthesia	Affected force sense
Bennell et al. [49]	16	Hypertonic saline	Infrapatellar fat pad	Videotape images	No	Not examined	Not examined
Matre et al. [34]	11	Hypertonic saline	Tibialis anterior and soleus muscles	Computer controlled platform	No	Yes	Not examined
Summers et al. [56]	28	Nerve growth factor	Extensor carpi radialis muscle	3D motion analysis system	No	Not examined	Not examined
Malmstrom et al. [52]	11	Hypertonic saline	Paraspinal muscles of cervical spine	3D motion analysis system	Yes	Not examined	Not examined
Weerakkody et al. [53]	12	Hypertonic saline	(i) Skin of thumb (ii) Flexor pollicis longus muscle	Linear servomotor device	Not examined	Yes	Not examined
Sole et al. [50]	20	Hypertonic saline	Sub-acromial space	Isokinetic dynamometer	No	No (enhanced kinesthesia)	Not examined
Weerakkody et al. [51]	8	(i) Hypertonic saline (ii) Painful heat stimulation	Biceps brachialis muscle	Padded boards with strain gauges	Not examined	Not examined	Yes
Mista et al. [89]	12	Hypertonic saline	Biceps brachialis muscle	Three -dimensional force sensor	Not examined	Not examined	No (three-dimensional task Yes (one dimensional task)
Salomoni et al. [90]	15	Hypertonic saline	Infrapatellar fat pad	Three -dimensional force sensor	Not examined	Not examined	Yes
Mista et al. [91]	26	Nerve growth factor Hypertonic saline	Extensor carpi radialis brevis	Three -dimensional force sensor	Not examined	Not examined	No

Despite the advantages of EIP to study proprioception, caution is advised in extrapolating the results of these studies as limitations also exist and need to be considered. Even in ideal experimental conditions, it is impossible to exclusively target nociceptors without activating non-nociceptive receptors [92] and this could potentially cause a "bottom up" pain inhibitory effect [45]. For example, EIP via electrical stimulation of the skin, will result in the activation of both small and large diameter nerve fibers and therefore cannot be considered as a specific method of activating nociceptors [92]. Thermal skin stimulation also activates low-threshold non-nociceptors [45]. Hypertonic saline injected in muscles, has the advantage, that although it too excites non-nociceptive nerve fibers, this happens usually in a non-detectable degree that does not have a large influence on the sensory effects of EIP [92].

The results of the current review suggest that attention is an important component of proprioception and motor control [48, 82, 87, 88]. Complexity of the task and the appreciation of danger is another variable that affects the results [93, 94]. These variables are different in acute and chronic pain and also in EIP and clinical pain [71]. Clinical pain and especially of chronic nature, alters CNS function considerably. Perhaps interventions that lower the threat value of clinical pain might be able to free CNS resources and improve proprioception and motor control especially during cognitive demanding tasks.

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