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Integration of multiple simultaneous stimuli within and between somatosensory sub-modalities

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Abstract

Psychological characterisation of the somatosensory system often focusses on minimal units of perception, such as detection, localisation, and magnitude estimation of *single* events. Research on how *multiple* simultaneous stimuli are aggregated to create integrated, synthetic experiences is rarer. Yet, increasing evidence suggests that the somatosensory integration of composite patterns is regulated by nonlinear mechanisms occurring at different stages of the perceptual processing. As a consequence, the bulk of knowledge concerning the perception of isolated events may be insufficient to grasp the complexity of uni- and cross-modal interactions.

This thesis aims to shed a light on the mechanisms underlying the integration of multiple simultaneous stimuli, within and between different sub-modalities of the somatosensory system.

First, across several psychophysical experiments, we investigated the ability of healthy individuals to perceive the total intensity of composite somatosensory patterns. We found that the overall intensity of tactile, cold, or warm patterns was systematically overestimated when the multiple simultaneous stimuli had different intensities (Chapter 2). Thus, perception of somatosensory totals is biased towards the most salient element in the pattern. Furthermore, we demonstrated that peak-biased aggregation is a genuine perceptual phenomenon which does not rely on the discrimination of the parts, but is rather based on the salience (i.e. the signal-to-noise ratio) of each stimulus (Chapter 3).

Next, we studied a classical thermal illusion to assess participants' ability to localise thermal stimuli delivered on the fingers either in isolation, or in uniform and non-uniform patterns (Chapter 4). We found that despite a surprisingly high accuracy in reporting the

location of a single stimulus, when participants were presented with non-uniform patterns, their ability to identify the thermal state of a specific finger was completely abolished.

Lastly, we investigated the perceptual and neural correlates of thermo-nociceptive interaction during the presentation of multiple thermal stimuli (Chapter 5). We replicated the classical suppressive effect of warmth on pain. Crucially, we also found that inhibition of pain was independent from both the position and the number of thermal stimuli administered, providing insights about the level of somatosensory processing at which the interaction takes place.

Overall, our results suggest that nonlinear integration of multiple stimuli, within and between somatosensory sub-modalities, may be an efficient way by which the somatosensory system synthesises the complexity of reality, providing us with an extended and coherent perception of the world, in spite of its deep bandwidth limitations.

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Chapter 1.

From the perception of single events, to the integration of multiple simultaneous somatosensory stimuli

Synopsis:

This Chapter introduces the area of interest of this thesis. Section 1.1 provides the justification for the present work. Section 1.2 presents a brief overview of organisation of the somatosensory system, focussing on the processing of single inputs across different sub-modalities. Section 1.3 introduces the results from recent studies on the integration of multiple simultaneous stimuli. Finally, section 1.4 presents the research questions behind the thesis and a brief overview of the experimental works conducted to answer such questions.

1.1 Introduction

In our everyday lives we massively rely on the information coming from the *bodily senses* to guide our interactions with the environment. We come back home at night and, without looking, we easily find the keys in our backpack. We open the door, sensing the cold, smooth surface of the handle, and, still in the dark, we grope around with our hand until we reach for the light switch. We have a slight stomach ache. While we put the kettle on, one shoulder starts itching, and we unerringly reach and scratch the exact point where the sensation originated. Few minutes later we are pouring our favourite infusion in a mug, a warm sensation is pleasantly spreading from the mug to our fingers. Abruptly, our mobile phone vibrates in our pocket, and we spill a drop of boiling water on our hand. The hand hurts, and we mechanically start rubbing it with the other, in order to alleviate the pain.

Somatosensation plays a key role in all these hypothetical scenarios, providing information about the events occurring *on* and *into* our body, and enabling us to implement the best actions that can increase the chances and the quality of our survival. Yet, most of these activities take place automatically, without even reaching our awareness, and the importance of somatosensation, compared to other sensory inputs, is often largely underrated. For example, when asked which sense they would choose to lose between sight and touch, most people pick touch, asserting that vision is more important and valuable for existence (Robles-De-La-Torre, 2006; Goldstein, 2008). Therefore, it is perhaps appropriate starting this work spending few words on the significance of somatosensation for our existence, and the necessity to improve our understanding of the mechanisms underlying somatosensory integration.

1.1.1 Somatosensation: the most essential and complex of our senses

For a long time, philosophers, physiologists, and neuroscientists have tried to answer the very same question about the importance of the somatic senses. In one of his major biological treatise, *De Partibus Animalium*, Aristotle carefully scrutinises all the constituent elements of animals, asking himself what is the essential attribute that makes them different from plants. After discarding the blood (*"It [is] plain that the purpose of the blood in sanguineous animals is to subserve the nutrition of the body"*; *De Partibus Animalium*, II. iii.), the stomach (*"Plants get their food from the earth […]. Animals […] are provided with a stomachal sac, which is as it were an internal substitute for the earth"*; ibidem, iii.), and the brain (*"The brain, then, tempers the heat and seething of the heart"*; ibidem, vii.), the philosopher reaches the following conclusion:

> "*We define an animal as something that has the power of sensation, and chiefly the primary sensation, which is Touch; and the organ through which this sensation is effected is the flesh. And flesh is either its primary organ (comparable to the pupil in the case of sight), or else it is the organ and the medium of the sensation combined in one […]. [Touch] sense-organ is the only one which is corporeal"*
>
> (*De Partibus Animalium*, II. viii.)

And, similarly, in *De Anima*:

> "*The body of the animal must have tactile sensation, if the animal is to survive. For the other senses, that is to say, smell, sight, hearing, have media of sensation, but a being which has no touch will be unable when it comes into contact with things to avoid some and seize others. And if this is so, it will be impossible for the animal to survive. […]*

> *Touch is the one sense that the animal cannot do without. The other senses which it possesses are, as we have said, the means, not to its being, but to its well-being"*
>
> (*De anima*, I. xii.-xiii.)

Aristotle's conceptualisation of animal organs and their functions may sound outdated nowadays. However, his intuition about the significance of the *bodily senses* for the survival of living creatures is fully corroborated, after more than two millennia, by the studies conducted on the smallest and simplest organism equipped with a nervous system. *C.elegans*, a transparent nematode just about the size of a comma, is composed by 959 cells only, and it is considered a genetically hardwired automaton that can swim forward or backward (Waterson, 1998). Modern physiologists have asked, similarly to Aristotle, what kind of information such a simple organism does rely on for driving its behaviour. The rudimentary nervous system of *C. elegans* does not allow the processing of any visual or auditory information. Yet, almost the totality of its interactions with the environment are successfully driven by the detection of temperature and touch (Oren-Suissa, Hall, Treinin, Shemer, and Podbilewicz, 2010; Voglis and Tavernarakis, 2005) (see Figure 1.1). In fact, the ablation of touch receptors by laser microsurgery leads to lethargy and drastic reduction of spontaneous movements, which are initiated only in case of starvation (Calfie, Sulston, White, Southgate, Thomson, and Brenner, 1985; Driscoll and Kaplan, 1996).

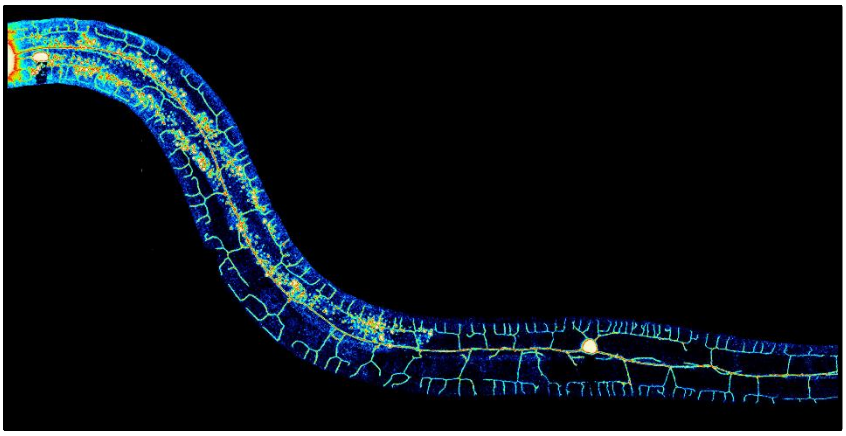


Figure 1.1. Mechanoreceptive system of *C. elegans*.

A *C. elegans* treated with a fluorescent signal that highlight the bodies and dendritic arborisations of somatosensory neurons.

Apart from philosophical and biological observations, the evidence that the somatic senses are indispensable also for human existence is shown by rare medical conditions where the ability to feel sensations though the skin is lost. In such cases, due to the absence of warning signals from the thermoceptive and nociceptive systems, people suffer from the constant risk of injures and burns (Melzack and Wall, 1988; Rollman, 1991; Wall and Melzack, 1994). Crucially, the lack of tactile and proprioceptive information compromises almost every single interaction with the environment (Cole, 1995; Cole and Paillard, 1995; Robles-De-La-Torre, 2006). For example, in his book *Pride and a daily marathon*, Jonathan Cole (1995) described the conditions of Ian Waterman, a 19-year-old butcher who, following an autoimmune reaction, lost every tactile and proprioceptive sensation. After the onset of the illness, in spite of the fact that his motor system was completely preserved, the young man was absolutely unable to walk, to control his movements, or to tell the position of his limbs. Even years after the first symptoms, the simplest act of sitting or standing up on was cause of immense exertion, which the patient himself described as "*a daily marathon of effort and will*" (Cole, 1995).

Thus, converging evidence from everyday experience, philosophy, biology, and neuroscience supports the idea that somatosensation is actually indispensable for our existence. Yet, compared to other senses, the study of the somatosensory system has received surprisingly little attention. Figure 1.1 shows an approximate estimate of the number of studies published from 1960 to 2016 on the somatic senses, compared to vision. If, on the one hand, it is undeniable that the last decades have witnessed a steady growth of interest in the study of touch, thermoception, proprioception, and, pain, on the other hand, the number of published works on vision in 2016 were, alone, almost the double of those about all the somatic senses pooled together. The reason for this can be perhaps reassumed again through Aristotle words:

> "*The organ in which touch takes place is, however, as we should expect, the least simple of all the sense-organs […] because the sense of touch deals with more kinds of sense-objects than one"*
>
> (Aristotle, *De Partibus Animalium*, II. i.)

Therefore, somatosensation is probably the most important, as well as the most complex and perhaps the least understood of our senses. As a consequence, it is reasonable to think that many of the processes underlying the functioning of the somatosensory system still need to be uncovered.

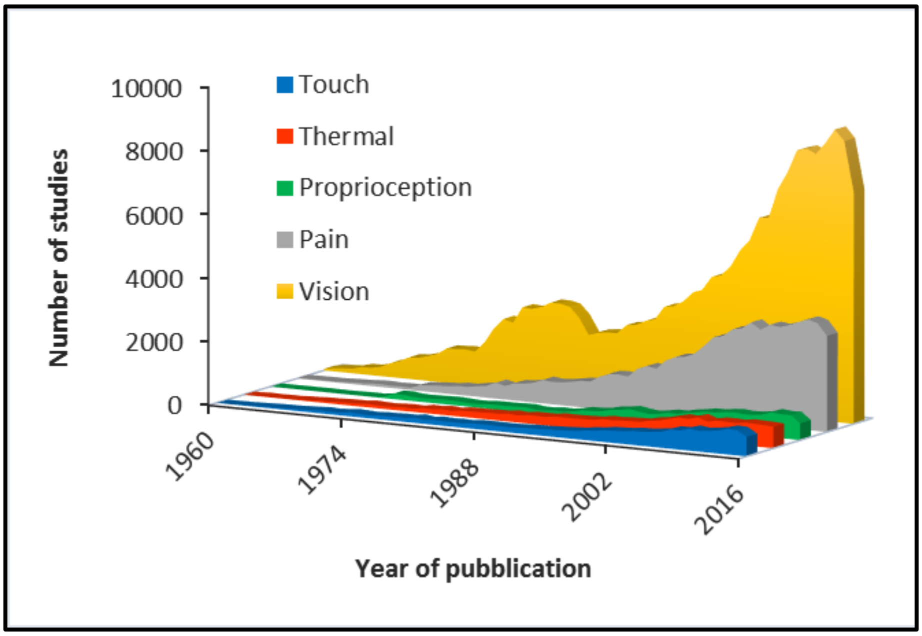


Figure 1.2. Studies published on the somatic senses, compared to vision.

Number of studies published from 1960 to 2016. Search performed on Scopus on March 2017, using “touch”, “thermal”, “proprioception”, “pain”, and “vision” as search terms in the title, and restricting the results to the field “Neuroscience”. In 2016 the number of works on vision (7272) was almost the double of those on touch (614), thermal (676), proprioception (529), and pain (3016) perception pooled together.

Clearly, the fact that the studies on somatosensation are by far less copious than those on the visual or auditory systems does not actually means that we are completely unaware of the organisation of the somatosensory system, or the processing of specific somatic inputs. Since the 1960s, the findings from physiological studies on animals have opened the way for psychologists and neurophysiologists to study the characterisation of somatosensory stimuli, from the peripheral mechanisms of transduction and sensation, to their corresponding perceptual outcomes. However, psychology of perception has traditionally focussed on the minimal units of somatosensory processing. That is, most studies have investigated how we detect (LaMotte and Whitehouse, 1986; Johansson, Vallbo, and Westling, 1980), localise (Sherrick, Cholewiak, and Collins, 1990; Harris, Thein, and Clifford, 2004; Porro, Martinig, Facchin, Maieron, Jones, and Fadiga, 2007), and discriminate (Johnson and Phillips, 1981; Stevens and Patterson, 1995) a *single somatosensory stimulus* on our body. The choice of testing a sensory system by presenting artificially isolated stimuli is easily understandable considering the necessity, in a well-designed experiment, to safeguard the internal validity of the study by decreasing the number and the complexity of the variables at play.

Nevertheless, isolated stimuli are rare in our daily lives, and successful interactions with the environment rely on the integration of several, simultaneous, often non-homogeneous events. The example of the hot mug mentioned at the beginning of this Chapter, is particularly appropriate in this regard. When we hold the mug in our hand, we undergo to at least two different phenomena which may elude an explanation based exclusively on the analysis of single somatosensory events. First, rather than five distinct sensations coming each from a different finger in contact with the object, we feel a unique, holistic percept of a single object in our hand. This indicates that distinct somatosensory inputs from each finger have converged along the somatosensory pathways to create such a holistic percept (Gallace and Spence, 2014; Martin, 1992; MacKay, 1967).

Moreover, despite the fact that tactile and thermal inputs are processed via completely separate sensory receptors and pathways, rather than experiencing two disjointed qualities, we have the compelling perception that every simultaneous somatosensory information we get from our hand is merged into a uniform, unique representation, reflecting the properties of the mug (Pritchard, 1931; Green, 1977; Weber, 1996). Both observations clearly suggest that multiple somatosensory stimuli occurring simultaneously on our body are often automatically integrated *within* and *between* somatosensory sub-modalities.

1.1.2 General purpose and structure of the thesis

The present work is motivated by the concern that our current knowledge on the somatosensory processing of single events is insufficient to understand the integrative processes underlying the intra- and inter-channel *perceptual conjunction* taking place during multiple simultaneous stimulation. Such concern is grounded on the simple idea that the processing of holistic somatosensory percepts can be understood through the study of single events only if the merging of multiple inputs follows linear rules. If our perception of the surrounding environment is simply derived by the linear summation of each single event impinging the receptors on the skin, than an approach focussed on the minimal units of somatosensation (e.g. thresholds, acuity, precision, etc.) would be sufficient to understand how the sensory parts are integrated in a perceptual whole. However, a growing body of evidence suggests that the concurrent presentation of two (or more) somatosensory stimuli gives rise to complex, nonlinear effects at many levels of stimulus characterisation (see Section 1.3). Therefore, the perceptual outcome of multiple simultaneous somatosensory stimuli cannot be predicted by the processing of single events, and understanding the mechanisms underlying perceptual conjunction of multiple inputs requires specific investigation.

Accordingly, the present work aims to address this topic by testing several aspects of somatosensory integration, such as the perception of total intensity of tactile patterns, the localisation of thermo-tactile and purely thermal events, and the interaction between pain and multiple thermal stimuli. The next sections of this Chapter will provide a brief review of the main findings about the processing of single (Section 1.2) and multiple (Section 1.3) somatosensory stimuli. Section 1.4 will then introduce the experimental studies designed to answer the research question behind this work (Chapters 2-5).

1.2 Somatosensory processing of single events

The common definition of somatosensation is remarkably broad. In fact, the somatosensory system is conventionally defined *by contrast* with the other sensory systems, and most medical encyclopaedias refer to somaesthesis as "*a sensory activity originating elsewhere than in the specialised sense organs (eyes and ears), and conveying information about the state of the body and its immediate environment*" (Mountcastle, 1982). The apparent difficulty in identifying a more specific definition for somatosensation is clearly related to the complex organisation of the somatosensory system.

As mentioned above, whereas the so called *special senses* – vision, audition, smell, and taste – have clearly localised sensory organs (eyes, ears, nose, mouth), the *somatic sense*, instead, gather information from the entire body, including skin, muscles, tendons, and internal organs. The skin alone is the largest and heaviest sensory organ of the human body, covering an area of about ~1.8 m^2 and weighing around ~4 kg. Divided in two primary layers, epidermis and dermis, it contains the large majority of somatosensory receptors (~2,500 per cm^2 on the fingertips).

Second, while both vision and audition receive inputs from just two kinds of receptors each (rod and cones for vision, inner and outer hairy cells for audition), the somatosensory system handles information coming from up to 13 different afferent receptors. Each somatosensory receptor can be defined as the peripheral ending of a sensory neuron and its accessory structures, and is characterized by three different properties: the specific kind of stimulation energy able to detect (e.g. pressure, vibration, changes in temperature, etc.), the dimensions of its receptive field, and its adaptation rate.

Thus, if sight and hearing can be considered unimodal senses to all intents and purposes, the somatosensory system, instead, must be categorised in at least four separate sub-modalities. Moreover, each sub-modality can be in turn divided into several specific somatic sensations. Table 1.1 shows an overview of the different sensations represented by the somatosensory system, with the correspondent afferent receptors and devoted somatosensory pathway.

Sub-modality	***Sensation***	***Afferent***	***Pathway***
Pain	sharp cutting dull burning deep aching	Aδ-fibers C-fibers	neospinothalamic paleospinothalamic archispinothalamic
Temperature	warm/hot cool/cold	C-warm C-cold	paleospinothalamic neospinothalamic
Touch	itch/tickle touch pressure flutter vibration	C-tactile Merkel corp. Hair follicle Meissner corp. Pacini corp.	medial lemniscal
Proprioception and Kinaesthesia	muscle length muscle tension joint angle joint pressure	Muscle spindle Golgi tendon Golgi joint Ruffini joint Pacini joint	medial lemniscal

Table 1.1 Organisation of the somatosensory system.

The somatosensory system is conventionally subdivided in four sub-modalities each providing several sensations, characterised by dedicated afferent cells and somatosensory pathways.

A different classification of the somatosensory system was proposed at the beginning of the twentieth century by Sherrington (1907). The main advantage of Sherrington’s taxonomy – which makes it still valuable nowadays – is that it categorises the somatic sensations on the bases of their functional properties, rather than their anatomical or physiological correlates. In particular, Sherrington (1907) proposed that the functions of somatosensation can be divided in *exteroception*, *interoception*, and *proprioception*. The exteroceptive field corresponds to the receptive organs located on the surface of the skin, facing outward on the general environment, and receives information about the external events through touch (active exploration, or passive detection), thermal senses (heat and cold), and pain (damage or harm to the body coming from external events). Second, the interoceptive field receives afferent inputs from the receptors located in depth in the body, gathering information about the state of internal organs, and carrying out alimentary, digestive, and homeostatic functions. Finally, linking the internal demands and the external environment, the proprioceptive field represents the perception of the movements of the organism itself, relying on information coming from receptors located in the deep tissues of the body, such as muscles and tendons.

The present work primarily focusses on the exteroceptive aspects of somatosensory perception, investigating the integration within and between tactile, thermal, and nociceptive information.

1.2.1 Perception of tactile stimuli

Mechanoreceptors

Tactile information is registered by four different mechanoreceptors: Meissner corpuscles, Merkel cells, Pacinian corpuscles, and Ruffini endings (see Table 1.1 and Figure 1.3). As mentioned above, different mechanoreceptors are classified according to three different features: the so called *adequate stimulus* (i.e. the type of stimulation energy able to trigger an action potential), the dimensions of the receptive field, and the adaptation rate to the stimulation.

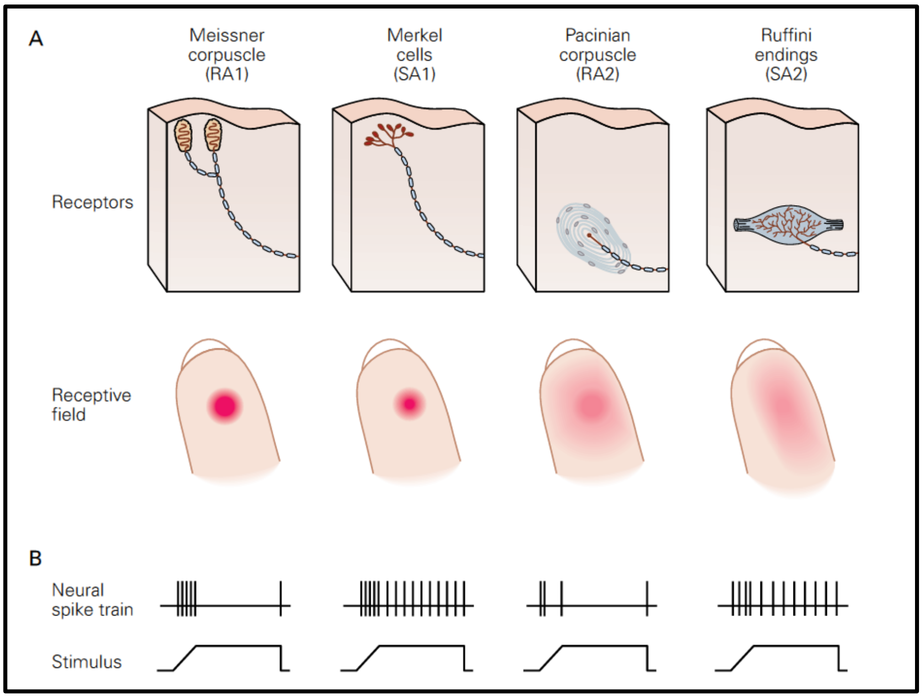


Figure 1.3. Mechanoreceptors mediating tactile sensations.

A. Small mechanoreceptors are located in the epidermis, have multiple terminals, and small receptive fields. Large mechanoreceptors are located in the dermis, have single terminals, and large receptive fields. B. Meissner and Pacinian corpuscles show rapidly adapting profiles, while Merkel cells and Ruffini endings have slow adapting rates.

Each mechanoreceptor is sensitive to a different type of mechanical pressure or distortion of the skin: touch, pressure, flutter, and vibration. Touch is conventionally conceptualised as a transient distortion of the superficial layer of the skin which involves minimal forces. Pressure, instead, involves greater forces and a displacement of both superficial and deep layers of the skin. Flutter and vibration, are more complex patterns where several touches are repeated in time at different frequencies (from 20 Hz to 50 Hz for flutter and from 100 Hz to 300 Hz for vibration). Merkel cells respond to the amount of pressure applied to the skin, have small receptive fields, and adapt slowly to the stimulation. They are sensitive to edges, points, and textures. Ruffni endings respond to skin stretch, have large receptive fields and are also slowly adapting fibers. Their proprieties make them particularly sensitive to shape and large object perception. Meissner corpuscles detect light touch, show small receptive fields, and are rapidly adapting cells. They signal the initial contact with objects and low-frequency vibration. Finally, Pacinian corpuscles are sensitive to high-frequency vibration, have large receptive fields, and adapt quickly to the stimulation, making them ideal for the detection of vibration and texture.

Somatosensory pathways for mechanical stimuli

The exact transduction mechanisms by which mechanoreceptors convey electric signals to the brain are not yet fully understood (Lampkin and Caterina, 2007; Kung, 2005). Most of tactile sensations originates when mechanically-gated ion channels in the mechanoreceptors membrane are directly activated by the stretching or deformation of the skin (Jiang, Lee, Chen, Cadene, Chait, and MacKinnon, 2002). The opening of the gates leads to an increased concentration of cations (Na^+ and Ca^{2+}) in the receptor neuron, which in turn induces the depolarisation of the cell and the generation of an action potential. In most cases, the magnitude and duration of the generator potentials are related to the applied mechanical force, with greater and longer mechanical forces inducing stronger and longer cell depolarisation. Touch, pressure, flutter, and vibration inputs are carried by large-diameter (12-20 μm), highly myelinated axons (Aβ), with a conduction velocity of about 72-120 m/s (see Table 1.2 and Figure 1.4).

	Cutaneous nerve	***Diameter (μm)***	***Velocity (m/s)***
Myelinated			
Large	Aα	12-20	72-120
Medium	Aβ	6-12	36-72
Small	Aδ	1-6	4-36
Unmyelinated	C	0.2-1.5	0.4/2.0

Table 1.2. Classification of sensory fibers according to diameter and conduction velocity.

Tactile and proprioceptive information are carried by large Aα and Aβ fibers, which are highly myelinated and conduct signals at high speed. Nociceptive inputs are carried by both Aδ and C fibers, while thermoceptive information is conveyed by C fibers only.

Given that receptors of sight, taste, and hearing are sited in the human skull, the pathways that convey these inputs to the brain are relatively short. Conversely, somatic inputs coming from the skin and muscles of the feet have to travel almost two metres to reach to the brain. The nerve fibers innervating skin mechanoreceptors have their cell bodies in the dorsal root ganglion of the spinal cord. The grey matter in the dorsal horn is divided into six functionally distinct layers (laminae). Tactile and proprioceptive information from the primary afferent fibers make synapsis in the laminae III to V of the dorsal horn.

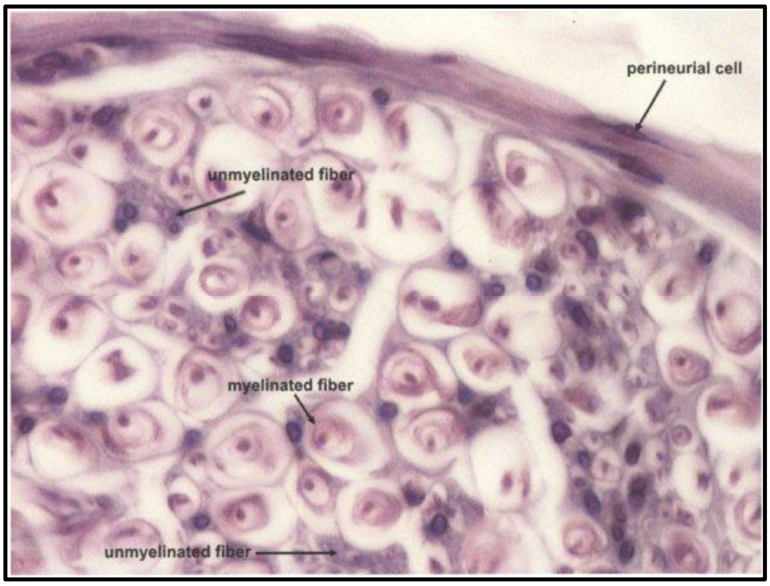


Figure 1.4. Myelinated and unmyelinated nerve fibers.

Light microscopic image of rat sciatic nerve in cross section.

Then, the inputs proceed through the dorsal column of the spinal cord until reaching the gracile and cuneate nuclei, forming the medial lemniscus, which crosses the midline in the medulla. Next, the second-order fibers terminate in the lateral and medial ventral posterior nuclei of the thalamus. Lastly, from the thalamus signals travel to the somatosensory cortex in the parietal lobe (see Figure 1.8).

Detection, localisation, and intensity of tactile stimuli

The processing of single tactile stimuli has been classically investigated with neurophysiological and perceptual tests designed to examine different aspects of stimulus characterisation, such as its detection, intensity, localisation, and discrimination.

In principle, absolute sensory thresholds are defined as the smallest stimulus energy detected by the specific afferent receptor. However, due to the intrinsic variability of sensory processes, in psychophysics detection threshold is conventionally expressed as the statistical probability to perceive 50% (or 75%) of the time a certain level of stimulation. Another classical method for assessing perceptual sensitivity is the use of discrimination threshold, or “just noticeable difference”, which is defined as the smallest amount of energy *change* in a stimulus that can be detected. Therefore, the spatial resolution of the somatosensory system (defined as acuity or sensitivity) is determined by at least three aspects: the density of mechanoreceptors on the stimulated skin area, the size of the receptive fields of such afferent cells, and the number of cortical neurons representing that body region. The innervation density of mechanoreceptors varies greatly across different areas of the body, producing regions of higher or lower sensitivity (Weber, 1834; Weinstein, 1968; Johansson and Valbo, 1979; Stevens, and Choo, 1996; Mountcastle, 2005; Mancini, Nash, Iannetti, and Haggard, 2014) (see Figure 1.5). Detection thresholds are lower on the volar aspect of the fingers and on the lips, during passive touch (Weinstein, 1968; Stevens, and Choo, 1996; Weber, 1834). Moreover, detection threshold is even lower during active exploration, producing 75% detection accuracy even for a dot of ~1μm height and 602μm diameter (Johansson and LaMotte, 1983).

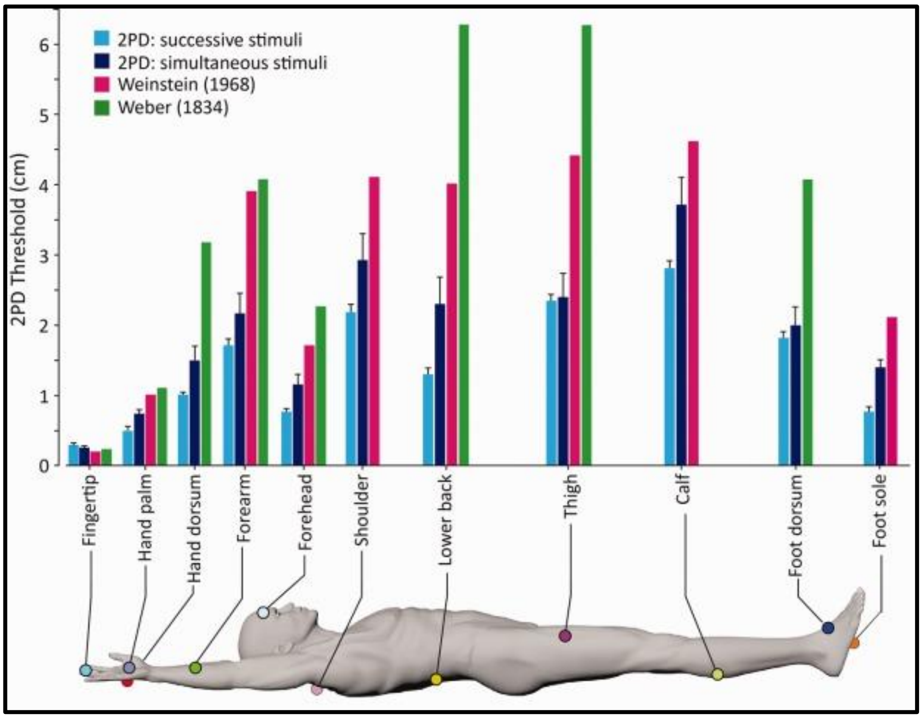


Figure 1.5. Tactile sensitivity across different body regions.

Two-point discrimination threshold for touch as measured by Weinstein (1968), Weber (1834), and Mancini et al. (2014).

Neuropsychological studies have shown a double dissociation between detection and localisation of tactile stimuli (Paillard, Michel, and Stelmach, 1983; Halligan, Hunt, Marshall, and Wade, 1995). In particular, Paillard and colleagues (1983) reported the case of a woman that, after parietal lesion, was unable to detect tactile stimuli, but could nonetheless correctly identify their location. Few years later, Halligan et al. (1995) found the opposite pattern in a neurological patient who was unable to accurately localise stimuli that they could successfully detect. Localisation errors also occur in healthy participants when they are stimulated by faint tactile stimuli such as the *von Frey hairs* (Craig and Rhodes, 1992; Schweizer, Maier, Braun, and Birbaumer, 2000; Braun, Ladda, Burkhardt, Wiech, Preissl, and Roberts, 2005). If a random finger is stimulated at intensities close to the sensory threshold, between 45% and 61% of the stimuli are mislocalised, preferentially on the neighbouring finger (Schweizer, Maier, Braun, and Birbaumer, 2000). Both detection and localisation of tactile stimuli are modulated by attention (Poranen and Hyvärinen, 1982; Hsiao, O'shaughnessy, and Johnson, 1993).

Intensity perception of brief mechanical stimuli has been mostly studied in the glabrous skin of the hand and fingers (Mountcastle, 1967; Vallbo, and Johansson, 1984; for a review see Bensmaia, 2008). Perception of stimulus intensity is regulated by a linear function of skin displacement (i.e. the force of the stimulus) (Werner and Mountcastle, 1965; Mountcastle, 1967) (see Figure 1.6). Intensity discrimination of different levels of pressure has been object of study since Weber’s foundational work, in 1834, where he postulated that the *difference limen* for the intensity discrimination of two different tactile stimuli was proportional to the strength of the stimulus itself (Weber, 1996). Then, in 1983, Fechner proposed that the subjective sensation is proportional to the logarithm of the stimulus intensity, such that if a stimulus varies as a geometric progression, the resulting perception varies, instead, in an arithmetic fashion (Fechner, 1983).

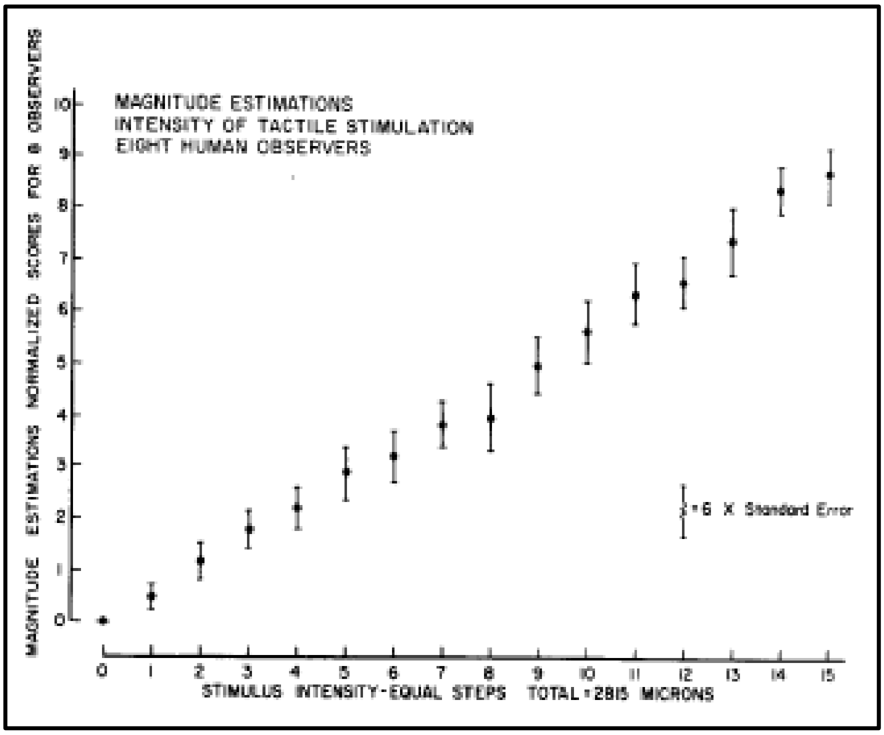


Figure 1.6. Magnitude estimate of single mechanical stimulation.

Perception of tactile intensity during single stimulation is described by a nearly perfect linear function (Mountcastle, 1967).

1.2.2 Perception of thermal stimuli

Thermoreceptors

The thermal sense can detect temperature changes taking place on localized areas of the skin or in the ambient. That is, thermoception fulfils both exteroceptive and an interoceptive functions. Moreover, temperature perception is always defined by the relative transfer of heat from/to the body. Thermoreceptors are non-specialized free nerve endings sensible to either increases (warm receptors) or decreases (cold receptors) in skin temperature (Darian-Smith, 1984). Heat receptors are situated closer to the skin’s surface, while cold receptors are found deeper in the dermis.

Both types of receptors respond in a similar way to radiant and conducted thermal stimulations and are activated only by temperatures situated within the innocuous range. In particular, both receptors respond to decreases or increases in skin temperature over a range of 10-43 °C, with cold thermoreceptors discharging most vigorously at skin temperatures around 25°C, and warm receptors being most responsive at approximately 43°C (Darian-Smith and Johnson, 1977). When the temperature of the skin is between 30-36 °C (the normal range for skin temperature) both types of receptor are spontaneously active, but generally there is no awareness of temperature. Unlike body temperature that varies by less than 1°C across healthy individuals, skin temperature can vary by as much as 12°C in normal individuals, particularly on the hands and the feet.

Somatosensory pathways for thermal stimuli

The mechanisms of thermoceptive transduction have been recently identified following the description of specific temperature-activated ion channels. Transient Receptor Potential (TPR) family of proteins regulates the transmission of mixed inward cationic current (predominantly Na+ ions) of a magnitude that is directly (warm) or inversely (cold) proportional to temperature, over a temperature range spanning from about 5-40°C (Jordt McKemy, and Julius, 2003; Lumpkin and Caterina, 2007; Ramsey, Delling, and Clapham, 2006). Warm and cold information are detected by different somatosensory first afferent peripheral axons. While warmth is conveyed by unmyelinated C fibers, the smallest (0.2-1.5 μm) and slowest (0.4-2 m/s) fibers of the somatosensory system, cold sensations are transmitted via finely myelinated Aδ fibers, which also carry nociceptive information (see Table 1.2).

Both peripheral afferents have their bodies in the posterior root ganglia of the spinal cord. Aδ fibers enter the dorsal horn of the spinal cord and make the first synapsis in laminae I, II, and V, while C fibers make synapsis in the second layer. Both fibers then decussate the body midline and form the spinothalamic tract. The spinothalamic tract terminates in the ventral posterolateral (VPL) nucleus and in the intralaminar nuclei of the thalamus. From VPL, the input is conveyed to the postcentral gyrus of the parietal cortex, while the intralaminar nuclei project to the insula and the rostral cingulate gyrus (see Figure 1.8).

Detection, localisation, and intensity of thermal stimuli

Thermoreceptors in the skin have been originally identified by as warm and cold spots. Warm and cold spots are only a few millimetres in diameter, and are distributed independently. Overall, there is a larger number of cold spots than warm spots, which means that all regions of the body are more sensitive to cold than to warmth. Thermal perception thresholds are defined as the minimum temperature change that a person can perceive. Similarly to the tactile sense, the number and density of thermoreceptors on the skin, and therefore sensitivity, varies greatly from a region to another, with the cheeks and the lips being the most sensitive area, and the feet being the least sensitive region. Interestingly, cold and warm thresholds on the hand are lower on the thenar eminence (0.02-0.07°C), rather than the fingertips (Stevens and Choo, 1998; Hardy and Oppel, 1937; Wakolbinger, Roche, Stockinger, Gustorff, and Aszmann, 2014), suggesting that the thermal sensitivity maps of the body are different from tactile acuity maps. Apart from innervation density, the ability to perceive changes in skin temperature is also affected by the rate of temperature change and the baseline temperature of the skin. For example, when the temperature change rate is slow (0.5°C/minute), even 4-5°C changes are not perceived, while rapid temperature changes (0.1°C/s) are easily detected. However, warm and cold thresholds do not decrease any further if the rate at which temperature changes is faster than 0.1 °C/s. Moreover, adapting the skin to different temperatures can increase or decrease thermal detection thresholds (Jones and Ho, 2008).

The results about humans' ability to localise thermal stimuli on the body are controversial. First, the vast majority of thermal stimuli perceived in everyday lives are in fact thermo-tactile, so that the localisation of thermal sensation can be attributed to the tactile input (Simmel and Shapiro, 1969). For example, Pritchard (1931) commented that "*it is only when the … stimulus … involves deformation of the skin that accurate [thermal] localisation is possible*". Classical studies on purely thermal stimuli supported this view. For example, Cain (1973) reported that when people have to report the location of radiant stimuli, they make 20% of errors reporting thermal sensations on the stomach when the stimulation was in fact applied to the lower back. However, other studies have demonstrated that radiant heat localisation is possible with a spatial resolution between 4.5 cm and 15 cm on the forearm and around 14 cm on the back (Nathan and Rice, 1966; Simmel and Shapiro, 1969).

Intensity perception of single warmth or cold stimuli is depends on the intensity (temperature change) and the extent of the stimulation. In particular, the relation between temperature perception and physical warmth is described by a power function where the size of the exponent depends on the areal extent of the stimulus (Marks and Stevens, 1973).

Moreover, for thermal radiant stimuli, the apparent warmth is related to absorbed irradiance by a power function whose exponent is approximately 0.7 (Stevens and Marks, 1967) (see Figure 1.7).

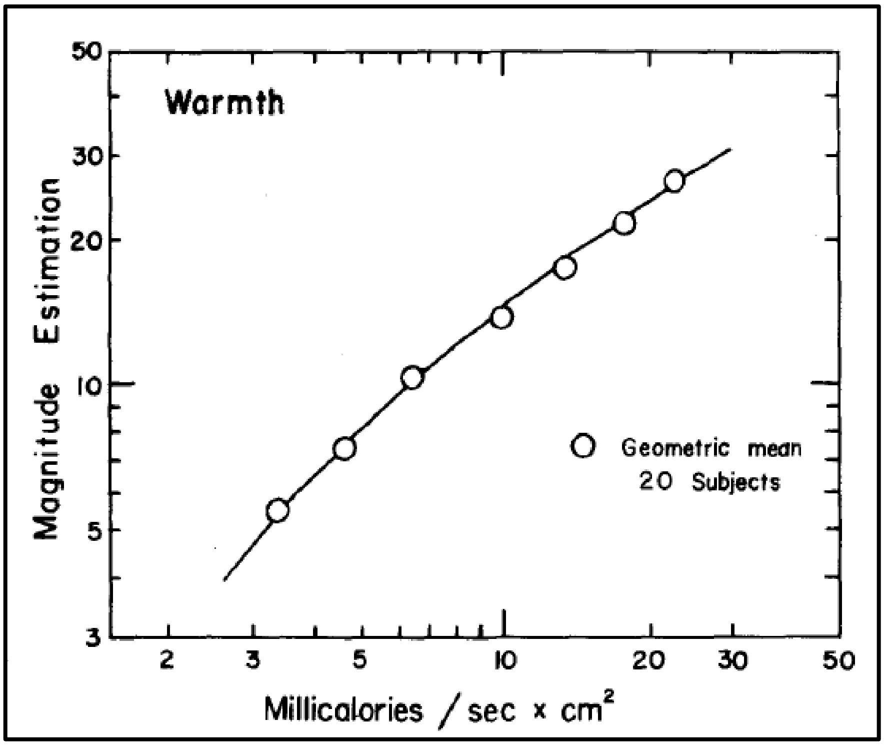


Figure 1.7. Magnitude estimate of single radiant heat stimulation.

Perception of thermal intensity during single stimulation is described by a power function of the physical irradiant flux absorbed by the skin (Stevens and Marks, 1967).

1.2.3 Perception of noxious stimuli

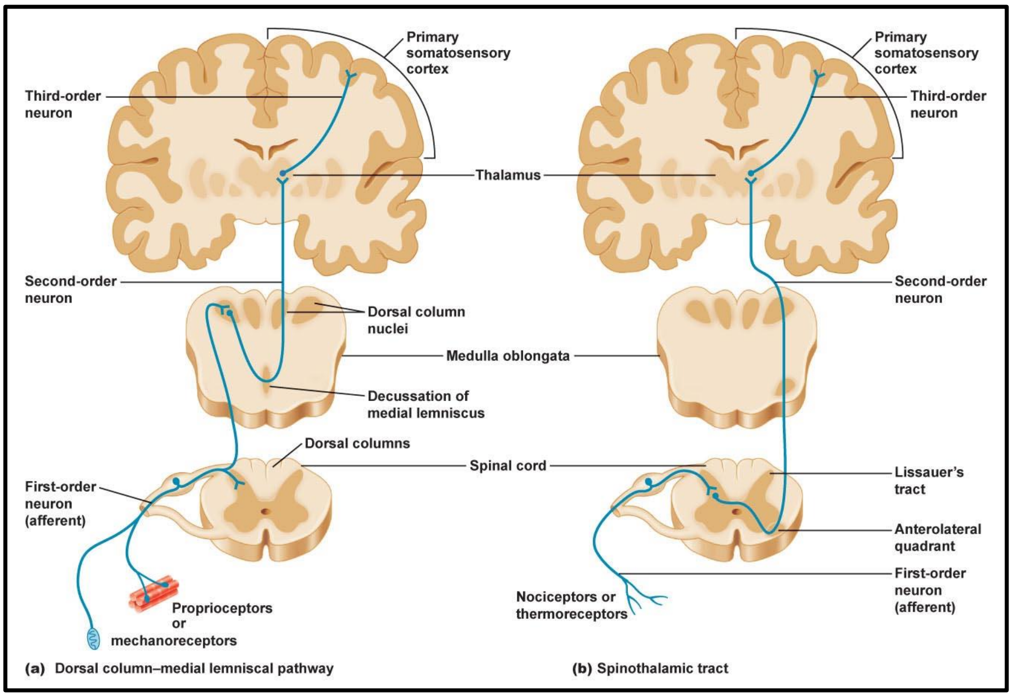
Nociceptors

The definition of pain given by the International Association for the Study of Pain (IASP) refers to "*an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described* *in terms of such damage*". Pain signal is transduced by nociceptors, sensory nerve cells that respond to damaging or potentially damaging stimuli. Since nociceptors are innervated by both Aδ fibres and C fibres, which have different conduction velocities (see Table 1.2), most painful experiences are accompanied by two different sensations: first pain, described as a quick, brief, lancinating pricking, and second pain, described as long-lasting and pervasive burning or aching (Price and Dubner, 1977).

Different types of nociceptors have been described for noxious mechanical, thermal, and chemical noxious stimuli. Mechanical nociceptors are responsible for the perception of noxious mechanical stimuli and are associated with Aδ fibres. Thermal nociceptors respond to noxious or harmful temperatures, firing when the temperature of the skin falls below 15-18 °C or rises above 45 °C. Finally, chemical nociceptors respond to the inflammatory mediators released by damaged tissues.

Somatosensory pathways for noxious stimuli

As mentioned above, different types of painful sensations are mediated by different nociceptors: mechanical Aδ and C fibers, polymodal C fibers, and high-threshold cold nociceptors (Raja, Meyer, and Campbell, 1988). Similarly to thermoceptive transduction, noxious stimuli are converted into electrical signals in free (unencapsulated) nerve endings of finely myelinated Aδ fibers, and unmyelinated C fibers (Dubin and Patapoutian, 2010; Zylka, Rice, and Anderson, 2005). Activation of nociceptors requires that noxious heat or cold, intense pressure or squeezing, or irritating chemicals stimuli depolarise the peripheral terminals with sufficient amplitude and duration. This produces receptor potentials which encode stimulus properties in a train of impulses. The somatosensory pathway for nociception is mostly overlapped with that for thermoception. The principal nociceptive pathways ascend in the anterolateral quadrant of the spinal cord. Aδ fibers make synapses in laminae I, II, and V of the dorsal horn, decussate, forming the spinothalamic tract, and project to the ventro-posterolateral thalamic nucleus.



(a) Dorsal column–medial lemniscal pathway **(b)** Spinothalamic tract

Figure 1.8. The ascending somatosensory pathways.

The dorsal column-medial lemniscus pathway (on the left) carries and processes discriminative touch and proprioceptive information from the body. The spinothalamic tract (on the right) carries and processes sharp, pricking pain and dropping temperature (cool/cold) information from the body.

Some parts of the spinothalamic tract also project to the periaqueductal grey matter. Spinoreticular tract, instead, originates by cells that are concentrated in laminae VII and VIII, decussate in the spinal cord, and reach the brainstem reticular formation, before projecting to the thalamus (intralaminar nuclei) and hypothalamus. It has been proposed that while the spinothalamic tract contributes to sensory-discriminative processing of pain, the spinoreticular tract plays a role in the motivational-affective components of pain (Willis, 1985). From the thalamus, the signal is transmitted to the somatosensory cortices, the insula, and the anterior cingulate cortex.

Detection, localisation, and intensity of noxious stimuli

Detection and tolerance pain thresholds are the most commonly used test for the investigation of nociceptive processing (Berkley, 1997; Robin, Vinard, Vernet-Maury, and Saumet 1986; Bendtsen, Jensen, Olesen, 1996; Hay, Okkerse, van Amerongen, and Groeneveld, 2016). Pain detection threshold can be defined either as the minimum intensity of a stimulus that is perceived as painful, or as the level of intensity at which 50% of stimuli would be recognized as painful (IASP). Conversely, pain tolerance threshold is the maximum intensity of a pain-producing stimulus that a subject is willing to accept in a given situation. In the specific case of heat nociceptors, skin temperatures above ~45°C ± 1°C induce the denaturation of tissue proteins and subsequent damage of the skin (Julius and Basbaum, 2001). Therefore, nociceptive threshold is similar across individual. However, the perceptual correlates of pain may instead vary a lot across people. Cold nociceptors are activated at temperatures below

~15°C, when specific transient receptor potential channels for cold induce a depolarisation of the cell (Reid and Flonta, 2001). In the case of mechanical pain, instead, the molecular basis of nociceptive transduction are less clear (Basbaum, Bautista, Scherrer, and Julius 2009).

After being matter of debated for a long time (Head, Rivers, and Sherren, 1905; Koltzenburg, Handwerker, and Torebjörk, 1993), human accuracy in localising painful stimuli across the body has been only recently assessed in a systematic way (Moore and Schady, 1995; Mancini, Bauleo, Cole, Lui, Porro, Haggard, and Iannetti, 2014). For example, Moore and Schady (1995) found that sharp pricking pain can be localised with almost equal precision to tactile stimuli, with only few millimetres of difference between the two modalities. Furthermore, in a whole-body mapping study of spatial acuity for pain, Mancini and colleagues (2014) found that, similarly to touch, the fingertips are the area of highest spatial acuity for pain in the body. Moreover, on the hairy skin of the upper limb, spatial acuity for pain and touch follows opposite proximal–distal gradients, consistent with the innervation density of mechanoreceptors and nociceptors in this body area (Mancini, Bauleo, Cole, Lui, Porro, Haggard, and Iannetti, 2014). Finally, by testing spatial acuity for pain in a participant completely lacking Aβ fibers, Mancini and colleagues (2014) also demonstrated that spatial acuity for pain does not rely on a tactile perception.

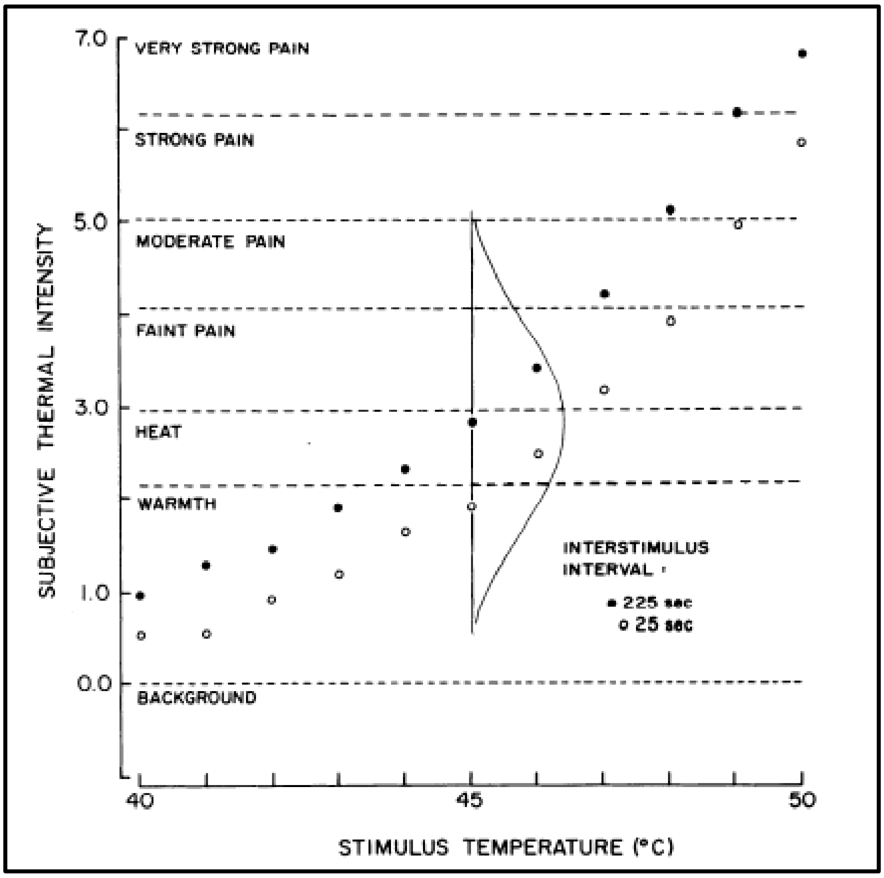


Figure 1.9. Magnitude estimate of single thermal and painful stimulation.

Perception of thermal and noxious intensity during single stimulation (LaMotte and Campbell, 1978).

Apart from coding occurrence and localisation of noxious stimuli, nociceptor also show a discharge frequency which increases with stimulus intensity. In fact, the ability to evaluate the intensity of painful stimuli is a major property of the nociceptive system (Zhang, Wang, Wang, Chang, Woodward, and Luo, 2011) (see Figure 1.9). Several studies have shown that the lateral spinothalamic pathway is involved in the discrimination of nociceptive stimulus intensity (Kenshalo, Iwata, Sholas, and Thomas, 2000; Moulton, Keaser, Gullapalli, and Greenspan, 2005), with neurons in the primary somatosensory cortex (Kenshalo, Iwata, Sholas, and Thomas, 2000), but also in the lateral thalamus (Akparin and Shi, 1994) encoding the intensity of noxious thermal stimulation.

1.3 Evidence for nonlinear effects of multiple simultaneous stimulation

The studies revised above show that somatosensory *sensations* (i.e. the transduction of physical energy applied to the body into action potentials generated by afferent cells) is most of the time a linear, isomorphic representation of the external world. However, our daily exteroceptive experience is commonly formed by an intricate mixture of many different somatic sensations merged together. In other words, our conscious perception is fundamentally dissimilar from the sensation by which it is elicited in the first place. In other words, *perception* is the final outcome of several successive transformation of this signal. Such transformations occur pervasively along the somatosensory pathway from peripheral to central processing. Moreover, the ascending input is also affected by descending signals related to our previous experiences, acquired and stored through learning and memory, and to our predictions about the world. As a consequence, at every single stage of the processing, the activity of different neural populations becomes more and more unrelated to the properties of the physical energy which originally impinged the sensory receptors. After every transformation, some aspects of the original signal are lost, other are amplified or modified. Only the features that are relevant for guiding successful interactions with the environment are extracted and submitted to further elaboration.

Accordingly, a growing body of evidence supports the hypothesis that multiple simultaneous somatosensory stimulations, both within and between sub-modalities, produce remarkable nonlinear effects that are not predicted by the linear summation of single inputs. In particular, phenomena reflecting nonlinear integration have been described, to date, for detection (Sherrick, 1964; Tamè, Farnè, and Pavani, 2011; Collins, Imhoff, and Grigg, 1996), enumeration (Gallace, Tan, and Spence, 2008; Gallace, Tan, and Spence, 2006a; Plaisier, Bergmann Tiest, and Kappers, 2009), and localisation (Green, 1982; Craig, 1989; Gadner and Spence, 1972; Gallace and Spence, 2014) of multiple simultaneous somatosensory stimuli.

1.3.1 Detection of multiple somatosensory stimuli and lateral inhibition

In 1967, the Hungarian Nobel Prize Georg von Békésy published an elegant paper showing that phenomena similar to the Mach bands, an optical illusion where the contrast between the edges of alternated dark- and light-grey bands is exaggerated (Hartline, 1949; Ratliff and Hartline, 1959), also occur in different sensory modalities. In particular, when two unimodal stimuli characterised by different intensities were applied next to each other, the apparent perception was inhibited at edge of the weak stimulus, and enhanced on the side of the strong stimulus (von Békésy, 1967). Interestingly, this was true across a variety of different somatosensory stimuli, such as pressure, shearing, vibration, or thermal (but also auditive and gustative). von Békésy therefore postulated that *“surrounding every area transmitting sensation there is an area* *simultaneously transmitting inhibition"* (von Békésy, 1967), giving start to the study of *Lateral Inhibition* in the somatosensory system. Lateral inhibition is an important form of interaction between stimuli at several levels in the somatosensory system, including primary somatosensory cortex (DiCarlo, Johnson, & Hsiao, 1998; DiCarlo & Johnson, 1999, 2000). This mechanism tends to suppress the response to a stimulus when another, nearby region of the receptor surface is strongly stimulated.

Several studies, following von Békésy's hypothesis, have shown that lateral inhibition is responsible for the nonlinear integration of multiple adjacent simultaneous tactile stimuli. Studies on the *vibrotactile masking*, for example, show that the detection of a tactile target drastically decreases when the stimulus is presented in spatial and temporal proximity with a tactile distractor (Craig, 1976). For example, Gilson (1969) showed that the maximum masking occurs when the onset of the masking stimulus is adjusted to compensate its spatial distance with the target stimulus, suggesting that the interference effect is due to a central simultaneous interaction between the two signals. Interestingly, studies employing the *double simultaneous stimulation paradigm* (Sherrick, 1964) demonstrate that interference between simultaneous touches also occurs between non-homologous fingers of different hands (Tamè, Farnè, and Pavani, 2011) (see Figure 1.10), and can produce extinction of about 6% of double stimulation in healthy individuals (Farnè, Brozzoli, Làdavas, and Ro, 2007). This results resemble those reported by Tinazzi, Ferrari, Zampini, and Aglioti (2000), which described a patient with left tactile extinction. When simultaneously given a salient stroking stimulus on the left hand and a subtler touch stimulus on the right hand, the patient perceived a stroking stimulus on the right hand. Information from both left and right stimuli was clearly processed at some level, but a pathologically-limited bandwidth (Driver and Vuilleumier, 2001) led to the quality of the left-hand stimulus being incorrectly linked to the location of the right-hand stimulus.

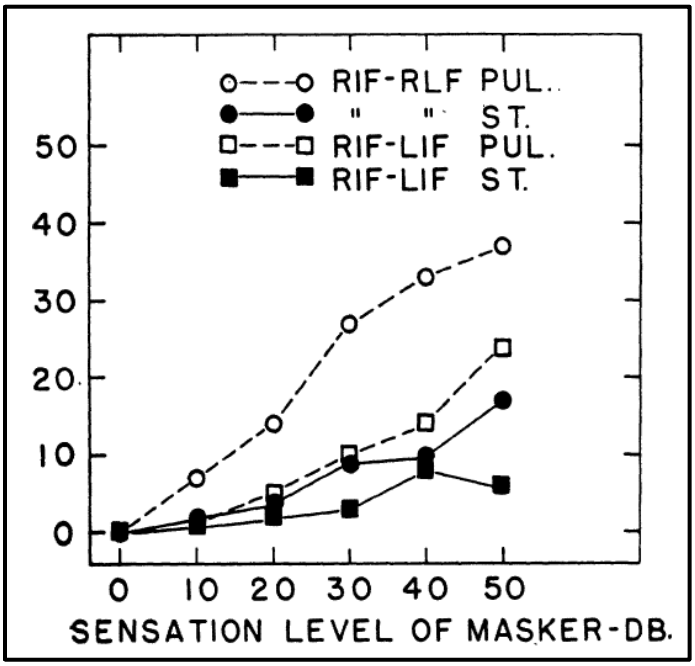


Figure 1.10. Vibrotactile masking.

The detection threshold (y-axis) for a vibratory target stimulus on the right index finger increases as the intensity of a second, masking stimulus (x-axis) delivered on the right little finger (circles) or left index finger (squares) increases. Open shapes represent pulsing masking stimulation, while filled shapes represent steady masking stimulation (Sherrick, 1964)

Numerosity judgements of somatosensory stimuli also show nonlinear effects. For example, studies on *tactile subitizing* have explored how many somatosensory stimuli can be perceived at once through a fast, accurate, pre-attentive “apprehension” process (as opposed to a slow, error prone and attentional demanding “counting” process) (Gallace, Tan, and Spence, 2006a; Plaisier, Bergmann Tiest, and Kappers, 2009; Riggs, Ferrand, Lancelin, Fryziel, Dumur, and Simpson, 2006; for a review see Gallace, Tan, and Spence, 2008). In particular, Gallace and colleagues (2006a) showed that both errors and RT in an enumeration task dramatically increase (i.e. performance decreases) when two or more vibratory stimuli are delivered simultaneously across the body, suggesting that the human somatosensory system cannot provide full awareness of more than one tactile input per time.

Such a drop in accuracy in detection and numerosity tasks induced by the simultaneous administration of multiple stimuli has often been attributed to the attention (Tamè, Farnè, and Pavani, 2011; Di Pellegrino, Basso, and Frassinetti, 1997), or to bandwidth limitation of the somatosensory system (Hill, 1974; Loomis, 1981; Driver and Vuilleumier, 2001). However, increasing evidence suggests that this phenomenon does in fact represent the outcome of nonlinear integration taking place between each single signal (Gandevia, Burke, and McKeon, 1983; Tamè, Pavani, Papadelis, Farnè, and Braun, 2015; Tamè, Moles, and Holmes, 2014).

Interestingly, the presentation of background stimulation is not always detrimental for performance. Studies on *stochastic resonance* show that concomitant presentation of specific levels of tactile noise can also have positive effects on performance, enhancing the detection of subthreshold tactile stimuli (Collins, Imhoff, and Grigg, 1996; Moss, Ward, and Sannita, 2004; McDonnel and Abbott, 2009).

1.3.2 Mislocalisation of multiple somatosensory stimuli

Apart from detection, multiple simultaneous stimulation can also dramatically affect the *localisation* of somatosensory patterns. As mentioned above, detection and localisation of a stimulus are two dissociable processes. Although all the exteroceptive modalities of the somatosensory system provide remarkably precise information about the localisation of single stimuli on the body, in the last decades, several studies have described a variety of phenomena where somatosensory integration interferes with correct localisation. In particular, early psychophysical works show that the ability to localise a tactile stimulus on the body dramatically drops when a task-irrelevant stimulus is simultaneously presented (Green, 1982; Craig, 1989). For instance, Hill and Bliss (1968) tested participants' ability to report the location of multiple simultaneous tactile stimuli delivered on eight fingers by means of an air-jet blast. Participants' perception was accurate only when less than three stimuli were presented (see Figure 1.11). Similarly, Craig (1989) asked participants to localize a tactile stimulus (target) presented at one of several locations, in a 6×24 array on their left index fingertip. A masker stimulus was also presented in half of the trials, and the accuracy between single and multiple stimulation was compared. Similarly to the results presented above about detection of multiple stimuli, Craig found that the localizability of the target stimulus was dramatically affected by the masker, strongly deteriorating participants' performance. Moreover, Green (1982) showed that errors in perceived distance correspond to errors in perceived location, suggesting an interaction between the perceptual processing of tactile location and distance.

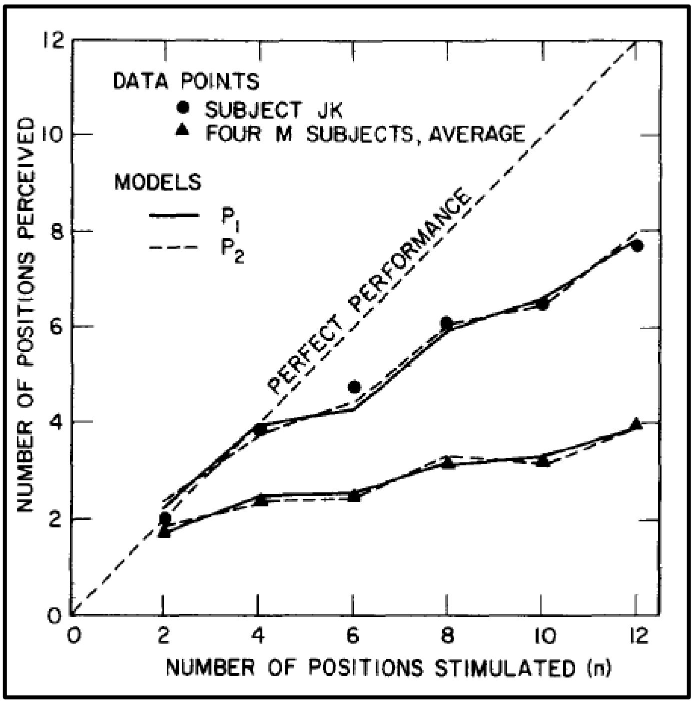


Figure 1.11. Accuracy in a localisation task in function of the number of fingers simultaneously stimulated.

Healthy participants (triangles) are not able to report the correct location of more than two simultaneous stimuli out of 12. Interestingly, blind people (circles) show higher accuracy.

Another well-known phenomenon of mislocalisation of tactile stimuli is the *funnelling illusion*, where the presentation of multiple concurrent mechanical stimuli on different points of the skin produces a single focal sensation at the centre of the stimulation pattern, in absence of any physical stimulation at that site (Gadner and Spence, 1972; von Békésy, 1960, 1967) (see Figure 1.12). Crucially, animal studies show that the primary somatosensory cortex reflects the illusory percept, rather than the true locations of the individual stimuli, indicating that the merger of the signals occurs at very early stages of the elaboration process (Chen, Friedman, and Roe, 2003; Friedman, Chen, and Roe, 2008).

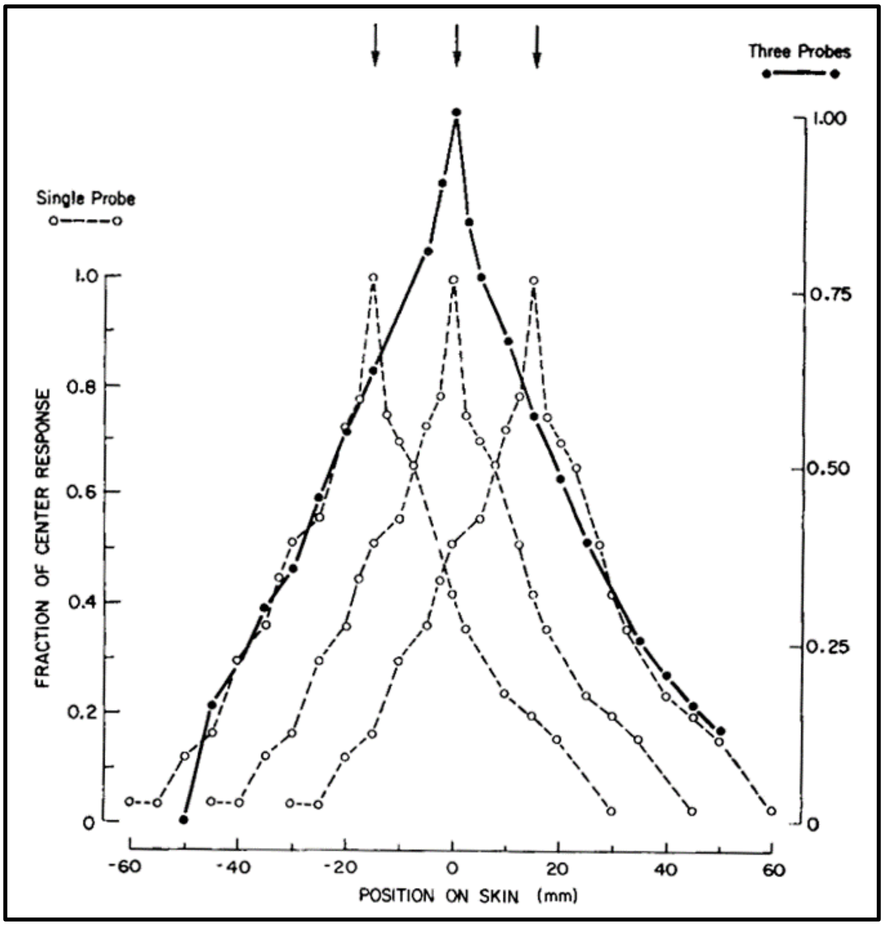


Figure 1.12. Funnelling illusion.

When single shearing stimuli (open circles) are applied 30 mm apart on the body, both localisation and intensity are correctly perceived. However, when the stimuli are presented all together, participants report a single, stronger sensation, localised at the centre of the pattern (Gardner & Spencer, 1972).

Lastly, change numbsense (Gallace and Spence, 2014, Gallace, Tan, and Spence, 2006b) is another example of scarce ability to localise a tactile stimulus when it is included in a pattern. In particular, Gallace et al.

(2006b) delivered two different patterns of multiple vibrotactile stimuli separated by a very short temporal interval and found that participants were surprisingly poor in detecting the presence of any positional change between the two patterns.

1.3.3 Spatial summation of thermal stimuli

If perception of multiple tactile stimuli gives rise to lateral inhibition, the thermoceptive system, instead, is strongly affected by *spatial summation* (Hardy and Oppel, 1937; Stevens and Marks, 1971; Marks and Stevens, 1973; Marks, 1974; Kenshalo, Decker, and Hamilton, 1967). According to the well-known Stevens' power law, the relation between temperature perception and physical warmth is described by a power function where the size of the exponent depends on the areal extent of the stimulus (Marks and Stevens, 1973). That is, extending the area of stimulation (Hardy and Oppel, 1937; Defrin and Urca, 1996; Kojo and Pertovaara, 1987; Machet-Pietropaoli and Chery-Croze, 1979), or increasing the number of thermal stimuli (Hardy and Oppel, 1937; Kenshalo, Decker, and Hamilton, 1967; Price, McHaffie, and Larson, 1989) produces an enhancement in the apparent magnitude of the target thermal stimulation.

Originally, spatial summation was thought to occur by means of a single peripheral mechanism, where increasing the surface area led to an increase in the number of activated warm receptors, and consequently, the amount of sensory input to the spinal cord (Marks and Stevens, 1973). However, the evidence that summation of warmth also occurs across dermatome boundaries (Hardy and Oppel, 1973) suggests that spatial summation is primarily an effect of central neural factors. Later investigations have also arrived at similar conclusions, supporting the idea that spatial summation is a largely centrally driven phenomenon (Defrin, Petrini, & Arendt-Nielsen, 2009). Specifically, it has been proposed that the summative mechanisms may involve the recruitment of second-order neurons in the dorsal horn and their subsequent integration onto third-order neurons at supra-spinal levels, including regions within the brainstem and cortex (Douglass, Carstens, and Watkins, 1992)

Interestingly, spatial summation can also give rise to the mislocalisation of the thermal percept, in a phenomenon called *thermal referral* (Green, 1977, 1978; Ho, Watanabe, Ando, and Kashino 2011). In particular, Green (1977) showed that, applying warm or cold stimulation on the index and ring finger of one hand produces the illusory perception of warmth/cold on the (thermally neutral) middle finger (see Figure 1.12). That is, the thermal sensation applied to the outer fingers is referred to the middle finger (Green, 1977). Crucially, the illusory thermal sensations disappears when the middle digit is lifted off the thermal stimulator (Green, 1977). Although the actual state of the middle finger is thermally neutral with and without tactile contact, the illusory thermal event on the middle finger is perceived only when all three fingers are in contact with the thermal stimulators, suggesting that tactile information is essential for thermal referral.

Importantly, Ho and colleagues (2011) have recently showed that the perceived overall intensity of the thermal pattern is correctly perceived as weaker than a condition where all three fingers are actually stimulated

(Ho, Watanabe, Ando, and Kashino, 2011). On the basis of their results, they proposed an account based on serial processing of temperature and touch signals. At a first stage, spatial summation homogenizes thermal percepts across multiple stimulated areas, producing an overall intensity percept proportional to the stimulated area. At a second stage, the overall intensity is then referred or attributed, on the basis of touch, to individual body parts.

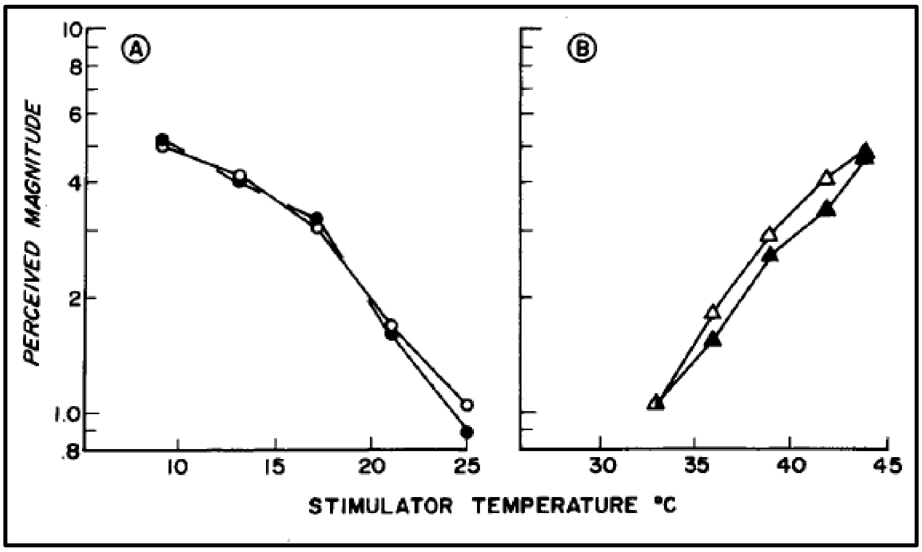


Figure 1.13. Thermal referral.

The perceived magnitude of cold (left) and warm (right) sensation at the (neutral) middle finger as a function of the stimulator temperature underneath index and ring fingers. The neutral stimulator is perceived as cold/warm as the active outer stimulators (Green, 1977).

1.4 Research questions

In contrast with the evidence about humans' remarkable accuracy in detection, localisation, and intensity estimate of single somatosensory stimuli, the co-occurrence of multiple inputs induces convergence and interference at different levels of the sensory processing. As a consequence, only partial – and often incorrect – information about multiple simultaneous stimulation is subject to full processing. The general hypothesis underlying the experimental studies of this work is that nonlinear integration of multiple inputs may be an efficient way to synthesise reality in order to deal with the bandwidth limitations of the somatosensory system.

Accordingly, we designed several experimental paradigms to investigate different aspects of somatosensory integration occurring within and between somatosensory sub-modalities, such as the perception of total intensity of tactile patterns, the localisation of thermo-tactile and purely thermal events, and the interaction between pain and multiple thermal stimuli.

1.4.1 Study 1 and 2: perception of the overall intensity of somatosensory patterns

As suggested by the studies revised in Section 1.3, the somatosensory system is deeply affected by bandwidth limitations. As a result, we generally perceive a small subset of the stimuli that impinge on the receptor surface. Over the last decades, microneurographic studies have shown that the sensation originating from a single stimulation is an isomorphic representation of stimulus energy. Conversely, the mechanisms underlying the complex interactions occurring between multiple simultaneous stimulations have not been fully uncovered yet. If someone bumps into us while we are standing at the bus stop, we are instantaneously able to identify the sensation, to localise it, and to clearly perceive its intensity. In such conditions, we have full awareness about the features of even the slightest touch. However, if once on the bus we find it terribly overcrowded, and we are squeezed between a stroller and a backpack, we no longer can form a clear representation of the identity, the number, the localisation, or the intensity of each event occurring on our body. We only have a blurred perception of the overall sensory experience. After all, it is not coincidence that crowded buses constitute the best setting for pickpockets. In such conditions, only salient events, well above the average sensation, can access our awareness.

In the studies reported in Chapter 2 and Chapter 3, we hypothesised that the administration of multiple simultaneous somatosensory stimuli would affect the perception of overall intensity such that the salience of the strongest stimulus in the pattern would bias the perception of the total intensity. To test this hypothesis, we asked participants to report the total perceived intensity of two simultaneous stimuli. Importantly, we manipulated the discrepancy (i.e. the relative difference in intensity) between the stimuli, to create different levels of salience.

In the study presented in Chapter 2, we predicted that the total of two stimuli with discrepant intensities would be perceived differently than the same total intensity distributed uniformly across the two fingers, indicating imperfect aggregation mechanisms in the somatosensory system. We found that the stronger stimulus had indeed disproportionate influence over judgements of total intensity. Moreover, we ruled out explanations based on the extinction of the weaker stimulus, and we found that peak-biased aggregation occurs within hands but not between hands. Finally, we also replicated the same results about peak-biased aggregation in other somatosensory modalities, namely, innocuous warm and cold processing.

The study presented in Chapter 3 replicated and extended this results. First, we asked whether the aggregation of two discrepant stimuli depends on the discriminability of their individual intensities. We assessed participants' accuracy in judging overall intensity versus overall discrepancy of two simultaneous stimuli. We found that accurate overall intensity judgements were possible despite a surprisingly poor ability to detect discrepancy across the stimulation. Therefore, aggregative and discriminative processes must be independent from each other. Moreover, we found that the peak bias affected both participants' sensitivity and response criterion. Finally, we found that the perception of overall intensity of a discrepant pair did not differ from that of a single strong stimulus, confirming that the peak in a multiple stimulation is taken as the most representative of the total intensity.

1.4.2 Study 3: mislocalisation of warmth during multiple thermal stimulation

Anecdotally, thermal referral was first discovered outside the laboratory, in an informal experiment where two pennies were cooled down in a freezer and a third penny was hold in one hand until it was thermally neutral. Putting the three pennies on a table in a cold-neutral-cold pattern, and touching them simultaneously with index, middle, and ring fingers of one hand produced the clear illusion that the coin under the middle finger had the same (cold) temperature than the outer coins (Green, 1978).

Such phenomenon is a striking evidence that the inputs from multiple simultaneous thermal stimuli converge at a certain level of the somatosensory processing, producing a bias in the localisation of the sensation. However, after its discovery, thermal referral has been classically interpreted as a demonstration of thermo-tactile interaction (Green, 1977; Ho, Watanabe, Ando, and Kashino, 2011; Green, 1978), rather than a purely thermoceptive mechanism. Tactile information seems indispensable for the illusion to occur, since the illusory thermal sensations disappears if the middle digit is lifted off the thermal stimulator (Green, 1977). In particular, the classical account of thermal referral postulates that the illusion is triggered by a top-down modulation linked to object representation. First, the mechanical contact between fingers and stimulators would signal the presence of a single object. Then, based to the prior that most objects have uniform temperature, the lacking information underneath the middle finger would be automatically filled-in with the temperature from the outer fingers (Ho, Watanabe, Ando, and Kashino, 2011). However, this interpretation has not been experimentally investigated, therefore, it cannot be ruled out the illusion is the result of spatial interactions of multiple thermal stimuli within the thermoceptive system alone.

The study presented in Chapter 4 aimed to test this possibility by using radiant heat to deliver multiple simultaneous purely thermal stimuli, in order to assess whether the illusory uniformity generated by thermal referral is attributable to thermoceptive integration of multiple stimuli, rather than to high-level processes of object recognition. We found that, despite thermal localisation of a single radiant stimulus was highly accurate, the simultaneous presentation of two thermal stimuli induced the same mislocalisation bias described for classical thermo-tactile thermal referral. Therefore, our purely thermoceptive results suggest that thermal referral could reflect low-level organization of the thermoceptive pathway, rather than a cognitive intermodal modulation based on tactile object perception.

1.4.3 Study 4: somatosensory interaction between pain and multiple thermal stimuli

Our findings about thermal referral indicate that the nature of most cross-modal somatosensory interactions is complex, and that careful investigation is required to determine and quantify the role played by each specific signal in creating an integrated, holistic percept. Nonetheless, understanding how different somatosensory modalities interact is an exceptional opportunity to get insights on the organisation of the somatosensory system, and apart from thermo-tactile phenomena such as thermal referral, a variety of different cross-modal interactions has been described in the last decades.

For example, the observation that touch has an analgesic effect on pain has raised the highest interest among scientist and clinicians for its great theoretical and therapeutic potential implication. In particular, touch-pain interaction has played a decisive role in the formulation of the Gate Control Theory, proposed by Melzack and Wall in 1967, which postulates that different somatosensory modalities converge and interact in the dorsal horn of the spinal cord, through a gating mechanism regulated by the size of each afferent fibre. Thus, tactile information, carried by the activity of large ($A\beta$) fibers, would get prioritised over the signal conveyed by small ($A\delta$ and C) fibers, resulting in the inhibition of pain (Wall and Sweet, 1967; Higgins, Tursky, and Schwartz, 1971; Kakigi and Shibasaki, 1992; Watanabe, Svensson, and Arendt-Nielsen, 1999). Another interesting example of somatosensory interaction across different channels is the Thermal Grill Illusion (TGI) (Thunberg, 1896; Craig and Bushnell, 1994, Craig, 2002), where presenting an alternating pattern of innocuous warm and cold stimuli induces a burning pain sensation. The findings about this illusion have led to the hypothesis of a double inhibitory interaction between warm, cold, and pain signals. In particular, noxious information is normally inhibited by a steady activity in the channel for cold thermoception, but the convergence and summation of multiple warm inputs in thermal grill conditions can in turn inhibit the cold signal and unmask pain.

The study presented in Chapter 5 focusses on the interaction between warmth and pain. Although previous experiments have shown that innocuous thermal stimuli can reduce both perception and cortical correlates of pain (e.g., Truini, Galeotti, Cruccu, and Garcia-Larrea, 2007), the nature of the relation between these two modalities is still poorly understood. In particular, we aimed to investigate whether pain perception is linearly modulated by the simultaneous administration of multiple warm stimuli. Crucially, such result would provide a clear insight on the processing level at which thermo-nociceptive interaction takes place. If inhibition of pain is stronger when the number of thermal stimuli increases, this would suggest that the inter-channel warmth-pain interaction occurs after intra-channel convergence and summation of warmth, as it happens in the thermal grill illusion. Conversely, we found that summation of warmth did not influence the degree of pain suppression, suggesting that the modulation of nociception by warmth occurs *before*, or independently of intra-channel summation of multiple thermal inputs.

Chapter 2.

Salience-driven overestimation of total somatosensory stimulation

Synopsis:

This Chapter presents a study on the perception of total intensity of somatosensory patterns, as it appears on *Cognition* (Walsh et al., 2016). We investigated the mechanisms of somatosensory integration by asking volunteers to judge the total intensity of stimuli delivered to two fingers simultaneously. Across four experiments, covering physiological pathways for tactile, cold and warm stimuli, we found that judgements of total intensity were particularly poor when the two simultaneous stimuli had different intensities. In particular, the total intensity of discrepant stimuli was systematically overestimated. This bias was absent when the two stimulated digits were on different hands. Taken together, our results showed that perception of somatosensory totals is biased towards the most salient element of the pattern.

2.1 Introduction

Our perception of the environment around us is fundamentally incomplete, yet it permits us to interact successfully with the world. Perception may be limited for two very different reasons. First, a stimulus may not generate an afferent signal to the brain, because sensory receptors are lacking, or too weakly activated. Second, a stimulus may be incorrectly perceived because the central capacity for conscious perception is not available to represent it. That is, perceptions can be affected by failures of transduction and afference, but also by limitations of central perceptual bandwidth. The latter are often discussed under the heading of ‘selective attention’. The bandwidth of most perceptual channels is profoundly limited. For example, studies of touch suggest that it is effectively impossible to perceive three or more tactile stimuli simultaneously (Gallace, Tan, & Spence, 2006; Plaisier, Bergmann Tiest, & Kappers, 2009).

As a result, we generally perceive a small subset of the stimuli that impinge on the receptor surface. Many studies of perception focus on best-case processing performance for this selected subset (Paffen, Tadin, te Pas, Blake, & Verstraten, 2006; Sathian & Zangaladze, 1996; Tadin, Lappin, Gilroy, & Blake, 2003; Van Boven & Johnson, 1994). In this paper, we consider how a perceptual system with limited bandwidth can provide broad perception of entire stimulus sets. Specifically, we asked participants to report the *total* perceived intensity of a number of simultaneous stimuli. This situation represents a challenge for perceptual systems wired for selectivity.

Salient information from an unselected channel can sometimes enter consciousness, as in the cocktail party effect (Cherry, 1953). In the case of touch, Tinazzi, Ferrari, Zampini, and Aglioti (2000) described a patient with left tactile extinction. When simultaneously given a salient stroking stimulus on the left hand and a subtler touch stimulus on the right hand, the patient perceived a stroking stimulus on the right hand. Information from both left and right stimuli was clearly processed at some level, but a pathologically-limited bandwidth (Driver & Vuilleumier, 2001) led to the quality of the left-hand stimulus being incorrectly linked to the location of the right-hand stimulus. In healthy participants, a tactile distractor stimulus interferes with perception of a target stimulus in the same modality, both within and between hands (Tamè, Farnè, & Pavani, 2011). Thus, even when bandwidth limitations or selective attention prevent full processing, some features of an unselected stimulus may be perceived. Salience—whether defined by stimulus intensity, quality or affect—may play a key role in determining which elements of stimulation enter into conscious awareness. Moreover, the most salient stimuli may have a disproportionately large influence on the perceptual scene as a whole, similar to the ‘peak’ bias (Fredrickson & Kahneman, 1993) found in the literature on human affective judgements. In general, judgements of the overall affective intensity of a temporally extended event are biased towards the moments of strongest affect within the event period, rather than the average. Low-level perceptual judgements of intensity may be similarly biased towards ‘peaks’ of intense stimulation, but evidence in support of this claim is lacking.

Here we investigate these processes in the context of somatosensory stimuli delivered to multiple digits in parallel. Everyday interactions with objects, such as grasping a piece of fruit, involve simultaneous contact between the object and several digits. The rich innervation of all the fingertips ensures that salient inputs, such as object slip, are rapidly and appropriately processed (Johansson & Westling, 1984; Lemon, Johansson, & Westling, 1995). At the same time, perceptual bandwidth is too low to support parallel percepts at each finger individually (Gallace, Tan, & Spence, 2006; Plaisier, Bergmann Tiest, & Kappers, 2009).

Indeed, the normal phenomenological content gives a single tactile experience of the object we are holding, rather than individual contact sensations at each digit (Martin, 1992). Neurons capable of responding to inputs on any finger are present at later levels of the somatosensory hierarchy, such as the secondary somatosensory cortex (Fitzgerald, Lane, Thakur, & Hsiao, 2006; Robinson & Burton, 1980; Sinclair & Burton, 1993).

Previous studies have used perceptual illusions to investigate the mechanisms that integrate multiple, simultaneous tactile or thermal stimuli. In the *funneling illusion* two closely-spaced tactile stimuli are perceived as a single, more intense stimulus at the centroid of the actual stimulation points (Gardner & Spencer, 1972). Activation in primary somatosensory cortex also reflects the illusory location of stimulation, rather than the true locations of the individual stimuli (Chen et al., 2003). In the *tactile continuity illusion*, Kitagawa and colleagues (2009) showed that brief vibrotactile stimuli interspersed with low amplitude noise are perceived as continuous stimulation. Gaps in tactile perception are filled in with illusory sensations sharing the same attributes (e.g., intensity level) as the surrounding physical stimuli. In *thermal referral illusions*, warm or cold thermal stimulators are applied to the ring and index fingers of one hand, and a neutral-temperature stimulator to the middle finger. In this configuration, all three fingers feel warm or cold (Green, 1977, 1978; Ho et al., 2010, 2011). Participants accurately perceive total thermal intensity, but distribute the perceived temperature evenly across the fingers rather than experiencing an exact copy of the intensity on the individual outer fingers referred to the neutral middle finger (Ho et al., 2011). Taken together, these illusions demonstrate an integrative quality in somatosensory processing, which acts to produce a coherent overall percept from multiple stimulations distributed in space and time. This integration might take place at multiple levels in the somatosensory pathway, from peripheral mechanisms (e.g., energy summation in skin receptors) to central mechanisms (e.g., Gestalt perceptual grouping principles).

Thus, the somatosensory system integrates sensations across digits to produce an overall percept, but this process remains poorly understood. Here, we investigated the impact of selectivity on these integration processes, by asking participants to judge the *total* intensity of discrepant somatosensory stimuli delivered to two fingers. Correctly computing the total stimulation involves summing the two individual stimuli, according equal weight to each. However, strong selectivity implies a higher weighting for the stronger stimulus in a pair – leading to an incorrect estimate of the total. Thus, errors in computing totals may provide important information about how selectivity mechanisms influence perceptual processing.

In Experiment 1, we tested participants' ability to judge the total intensity of two electro-tactile stimuli delivered to two fingers on the same hand. We predicted that the total of two stimuli with discrepant intensities would be perceived differently than the same total intensity distributed uniformly across the two fingers, indicating imperfect aggregation mechanisms in the somatosensory system. We found that the stronger stimulus had disproportionate influence over judgements of total intensity. In Experiment 2, we investigated whether the inaccurate totalling of stimulus intensity found in Experiment 1 could reflect extinction of the weaker stimulus in the pair, or rather a peak-biased integration mechanism. Our findings support the latter hypothesis by showing that the weaker stimulus is not extinguished, but does make some contribution to perception of the total. Experiment 3 found peak-biased aggregation within hands but not between hands, showing that the effect occurs within a single hemisphere. Finally, Experiment 4 showed peak-biased aggregation in other somatosensory modalities, namely, innocuous warm and cold processing, suggesting a general feature of somatosensory processing.

2.2 Methods

Participants

Twenty-one healthy right-handed human volunteers (mean age: 26, range: 19-39, 12 female) participated in Experiment 1. Two were excluded because they did not perceive any electrical stimuli on one of their fingers. A further six were excluded because suitable detection and pain thresholds to electrical stimulation of the digital nerves could not be established (see Methods, Experiment 1). The final sample size was 13. A group of twenty new participants (mean age: 22, range: 18-30, 7 female) took part in Experiment 2. Four were excluded because suitable detection and pain thresholds to electrical stimulation could not be established (see Methods, Experiment 2), leaving a final sample size of 16. Ten new volunteers (mean age: 21, range: 18-24, 7 female) participated in Experiment 3. Lastly, sixteen new participants (mean age: 24, range: 18-33 years, 11 female) took part in Experiment 4. One was excluded because of chance performance overall (mean 50% correct), leaving 15 participants in the final sample. Experimental procedures were fully explained to the participants before they provided informed written consent, but participants were kept naïve to the scientific hypotheses tested. The University College London Research Ethics Committee approved this study and experimental procedures conformed to the Declaration of Helsinki.

2.2.1 Experiment 1

Experimental setup

A pair of stainless steel ring electrodes (Technomed Europe, Netherlands) was placed on the right index finger of the participant. Electrode gel was used between the electrode and the skin. A second pair of ring electrodes was placed on either the middle finger (Figure 2.1A) or the little finger (Figure 2.1B). Transcutaneous electrical stimuli were delivered using a pair of Digitimer DS5 constant current stimulators (Digitimer Ltd., United Kingdom), controlled by a computer. Visual stimuli were generated using Psychophysics Toolbox v3 (http:// http://psychtoolbox.org/) for MATLAB (The Mathworks, Natick, MA).

The participant rested their hand palm down on a table, with the thenar and hypothenar eminences, the distal finger pads of digits 2-5 and the lateral side of the thumb pad touching the table surface. Vision of the right hand and wrist was blocked with a screen. Detection and pain thresholds for electrical stimulation of the digital nerves were measured prior to the experiment. Both fingers were stimulated simultaneously with the same current intensity, starting at 0.5 mA and then increasing in steps of 0.5 mA until the participant perceived a stimulus.

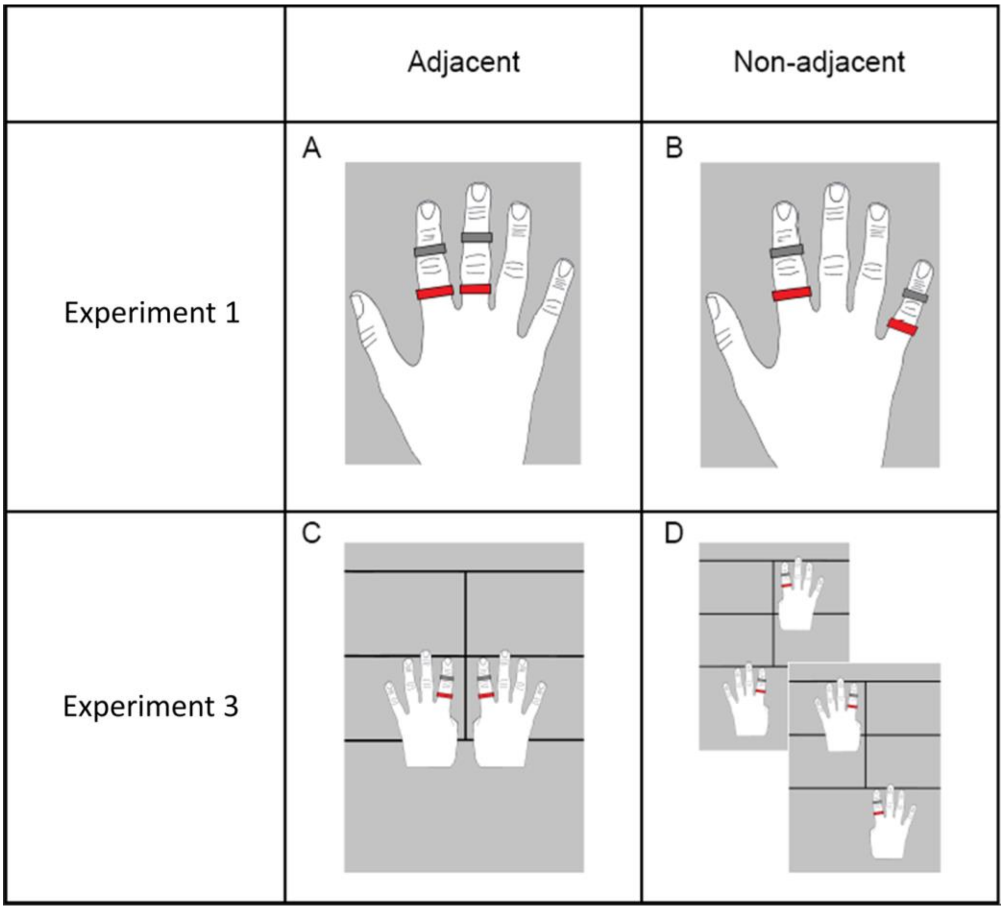


Figure 2.1. Electrode placement in Experiments 1 and 3.

In Experiment 1 (top row), electrodes were placed on adjacent digits (A) or non-adjacent digits (B). In Experiment 3 (bottom row), electrodes were placed on the index fingers of both hands. In the 'adjacent' condition (C) the hands were placed 4 cm apart and symmetrically in front of the body midline. In the 'non-adjacent' condition (D), one hand was displaced proximally 12.5 cm and the other distally 12.5 cm.

The current was then reduced in 0.5 mA steps until the stimulus was no longer detected, and then increased again until the stimulus was again perceived. This second value was used as an estimate of the detection threshold. Next, the current was increased rapidly to near pain threshold, and then the same 'up, down, up' procedure was used to measure the pain threshold. The stimulation floor for the experiment was set to double the participant’s detection threshold, and the ceiling was set to 90% of the pain threshold. Six participants were excluded at this stage because double their detection threshold was greater than 90% of their pain threshold.

Next we selected the stimulus values. In each trial of this pre-test, two pairs of stimuli were delivered, each consisting of one stimulus on the index finger and another on the middle finger. There was an interval of 1 s between the first pair and the second pair. The same stimulus intensity was delivered to the middle and index fingers within each pair, and the total of the two pairs presented in each trial could differ by 0%, 25%, 50%, 75% or 100% of the stimulation range (ceiling minus floor). Each pair was accompanied by an audible beep. After the second pair, the participant saw the question “Which beep contained the larger total shock (the first or the second)?” on a computer display, and made a button press response with the left hand. The purpose was to identify the difference in total intensity between the two stimulation pairs needed for the participant to answer correctly approximately 75% of the time. Piloting on 11 participants consistently found this difference to be 25% of the stimulus range. Therefore, for subsequent participants the stimulus selection procedure began with an intensity difference of 25% of the stimulus range. However, the pre-test was still used in each participant as screening tool, confirming the 75% correct level for total intensity discrimination. Two participants could not feel any stimulus on one finger, due to suspected peripheral neuropathy. One was detected at the setup/screening stage. The other participant reported being unable to detect stimuli on the little finger, and was excluded at this point in the experiment.

Data collection

In the main experiment, the participant performed a two interval forced choice task. Two pairs of stimuli were delivered to the participant's fingers, separated by an interval of 1 s. In the *non-discrepant reference pair* the currents on the two fingers were equal. In the other pair the currents on the two fingers could be unequal, making this the *discrepant test pair*. Three levels of discrepancy were used for the test pair: the maximum possible discrepancy within the stimulation range, 70% of the maximum and zero (i.e., non-discrepant stimuli). In all discrepant test pairs, one finger was stimulated with a current larger than the current used for each finger of the non-discrepant reference pair, even when the discrepant pair had the smaller total intensity (see Figure 2.2A and B). In a similar fashion, the smaller current in the discrepant pair was always smaller than the current used for each finger in the non-discrepant pair, even when the discrepant pair had the larger total intensity. Importantly, these constraints meant that a participant who attempted to judge total intensity by relying only on the most strongly stimulated single finger would give incorrect responses when the discrepant pair had the smaller total, but correct responses when the discrepant pair had the larger total.

Each stimulus pair was accompanied by an audible beep. After both pairs were delivered, the question “Which beep had the larger total shock (the first or the second)?” appeared on a computer monitor in front of the participant. The participant then responded by button press with the left hand.

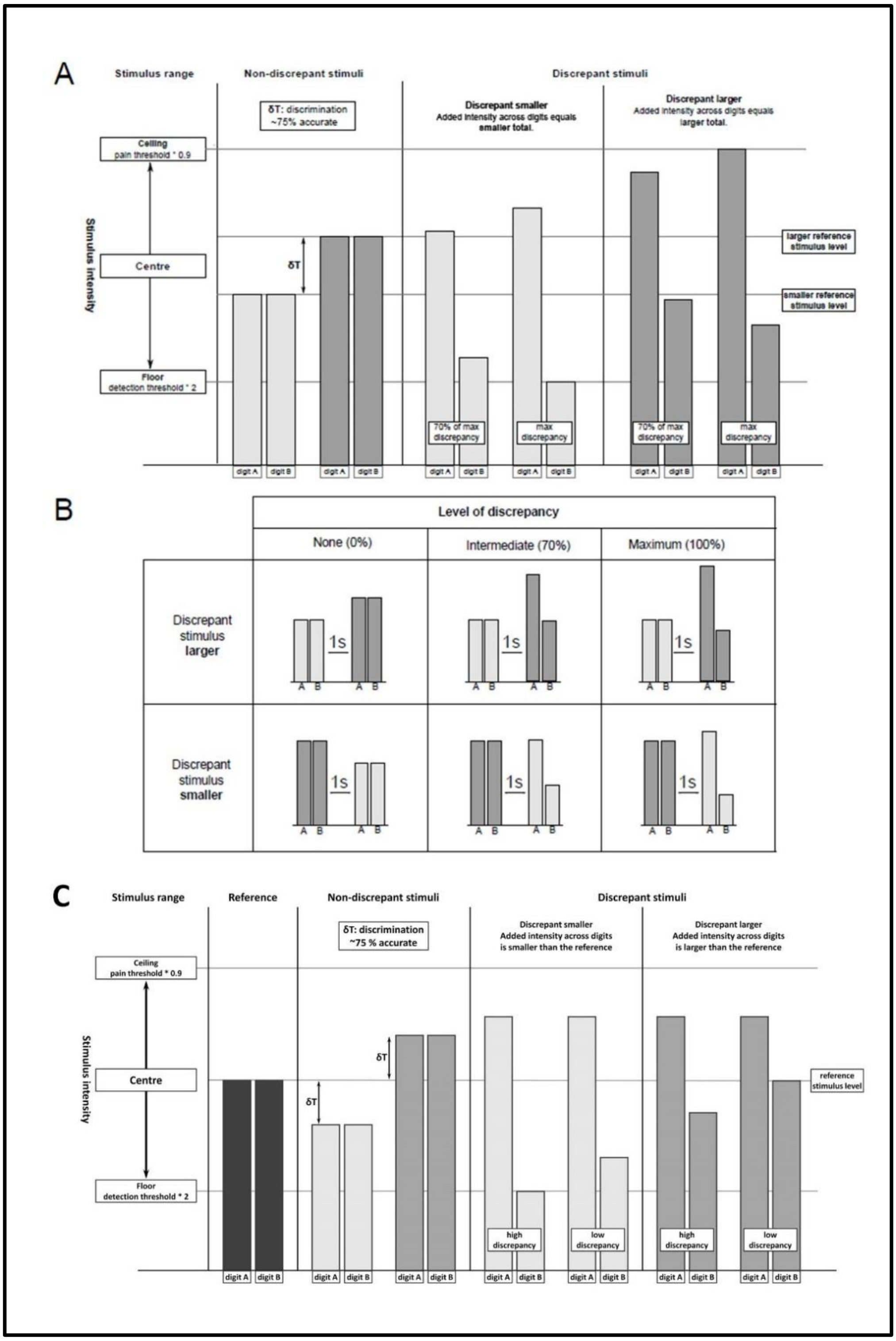


Figure 2.2. Stimuli in Experiments 1 and 3.

All stimuli in Experiment 1 and 3 A) consisted of simultaneous electrical stimulation to two digits. Overall stimulus intensity either equalled the smaller total (light grey shading) or the larger total (dark grey shading). The difference between the higher and lower totals, δT, was set to a level at which subjects scored approximately 75% correct when all stimulus pairs were non-discrepant. B) The 3x2 design of Experiment 1. Trials consisted of two paired electrical stimulations of the digits, separated by an interstimulus interval of 1 s. Critically, all three levels of discrepancy involved the same total intensity. See main text for further details. C) In Experiment 2, the intensity of the strongest stimulus in the discrepant pairs was kept constant, and the intensity of the weaker stimulus was varied to produce different amounts of discrepancy. Any difference in accuracy between conditions would then be due to the contribution of the weaker stimulus to the perceived total intensity.

We used a factorial within-participants design with three independent factors. The first factor was which stimulus pair had the larger *total* (test or reference). The second factor was the level of *discrepancy* in the test pair (0, 70% max. or 100% max.) and the third factor (*adjacency)* was whether the stimulated fingers were adjacent (index and middle) or non-adjacent (index and little). The first and second factors were randomised, while the third was blocked. The order of blocks was counterbalanced across participants. Within each block, half of the trials delivered the discrepant test pair first, and the other half delivered the non-discrepant reference pair first. Furthermore, in half of the trials the index finger received the larger stimulus for the discrepant pair, and this was reversed for the other half. Each trial was repeated 10 times, and the order of trials within a block was randomised. This made a total of 240 stimulus pairs for each experimental block. The participant was given a 1-minute break every 60 trials and a 5-minute break halfway through.

2.2.2 Experiment 2

Experiment 1 manipulated the discrepancy between two transcutaneous electrical stimuli, while keeping the total intensity of the pair constant (Figure 2.2A and B). Discrepancy was thus confounded with the intensity of each individual stimulus in the discrepant pair; a highly discrepant pair necessarily involved one stimulus with very high intensity and another with very low intensity. Consequently, effects of discrepancy could alternatively be explained by a strategy in which participants processed only the strongest stimulus in the discrepant pair, comparing it to the intensity of either stimulus in the non-discrepant pair. That strategy would rely on processing a single stimulus rather than aggregation of the two stimuli to produce a percept of total intensity.

Experiment 2 tested this possibility by holding the intensity of the strongest stimulus in the discrepant pair constant, and varying the intensity of the weaker stimulus. If participants disregarded the weaker stimulus, and considered only the stronger stimulus in their judgements of total intensity, then no effect of discrepancy should be found in this experiment.

Experimental procedures were broadly similar to Experiment 1. In each trial, participants received both a non-discrepant pair of electrical stimuli (the reference pair) and a discrepant pair of electrical stimuli (the test pair), separated by an interval of 1 s. However, the method used to set stimulus intensities differed from Experiment 1. In particular, the intensity of the non-discrepant pair was always set at the midpoint of each participant’s stimulation range (i.e., the range between double the detection threshold and 90% of the pain threshold). For the discrepant pair, the intensity of the stronger stimulus was invariably set at 70% of the stimulation range, while the intensity of the weaker stimulus varied between four possible intensities (0%, 15%, 45% and 60% of the stimulation range). These proportions were chosen as the most suitable for each discrepant pair to meet the following constraints: 1) to have either a smaller or larger total intensity than the non-discrepant reference pair, 2) to have the total intensities of the discrepant pairs equally spaced around the total intensity of the non-discrepant reference pair, 3) to set the intensity of the stronger stimulus in the discrepant pair higher than the intensity of each individual stimulus in the non-discrepant reference pair, 4) to hold the intensity of the stronger stimulus constant across all discrepant pairs, and 5) to vary discrepancy level (Figure 2.2C).

Moreover, to prevent floor/ceiling effects, we used a pre-test to check that accuracy in discriminating the non-discrepant reference pair from non-discrepant versions of the test pairs with the smallest and largest totals lay between 65% and 85%, over 40 trials. If accuracy was higher than 85%, the test pair total was adjusted to be more similar to the reference pair total (i.e., increased if it was the smaller total, or decreased if it was the larger total). If accuracy was lower than 65%, then the pre-test was simply repeated, because it was not possible to make the test pair total less similar to the reference pair total under the constraints described above. Participants were excluded from participating in the experiment if their performance was still not within the specified range after three successive adjustments (4 exclusions out of 20 participants recruited).

The main experiment consisted of a 2 (discrepant pair total: larger vs. smaller) x 2 (discrepancy: low vs. high) within-participants design. Both the presentation order of non-discrepant and discrepant pairs and the location of the strongest stimulus in the discrepant pair (right index or middle finger) were fully counterbalanced across trials. Each comparison between the non-discrepant reference pair and each type of discrepant pair was repeated 10 times, giving a total of 160 trials. Vision of the right hand was blocked by a screen for the duration of the experiment.

2.2.3 Experiment 3

The experimental setup was the same as in Experiment 1 with two key exceptions. First, the stimulation electrodes were placed on the left and right index fingers. Thus, participants determined the total of two stimuli delivered simultaneously to different hands. Second, the spatial distance between the fingers was controlled by moving the hands on the table between three spatial configurations. In the first condition, the hands were adjacent on the table, and the inter-index distance approximated the index-middle distance from the first experiment (Figure 2.1C). The other two conditions separated the tips of the index fingers by 25 cm in the sagittal plane (Figure 2.1D). The experiment was performed in four blocks of 120 trials each: two identical ‘hands adjacent’ blocks, one ‘hands apart’ block with left hand forward, and one ‘hands apart’ block with right hand forward. The two hands-apart blocks were combined, because our predictions concerned only the distance between the hands, not the position of either hand. For efficiency, stimulus setup used a single block of 120 trials in the ‘hands adjacent’ condition to confirm that total intensity could be discriminated with approximately 75% accuracy (see Experiment

1). Finally, the same trial structure and randomisation was used as in Experiment 1 with the exception that the order of blocks was randomised.

2.2.4 Experiment 4

The fourth experiment investigated perception of total thermal stimulation rather than electrical stimulation. Pairs of thermal stimuli were delivered via two computer-controlled Peltier-type thermodes with 13-mm diameter pen-shaped probes (Physitemp NTE-2A, Clifton, NJ). The two probes were fixed to a bar, approximately 2.5 cm apart. Stimulus delivery was controlled by a high-power servo motor (Hitec HS-805BB, Poway, CA) which moved the bar carrying the probes into contact with the index and middle fingers.

The purpose of this experiment was to test spatial integration of innocuous warm and cold stimuli to produce percepts of total thermal energy. Warm and cold temperatures were always tested in separate blocks. The temperature ranges for warm and cold stimuli were chosen to activate specific physiological pathways associated with warm and cold sensation (Hensel & Iggo, 1971; Morin & Bushnell, 1998; Schepers & Ringkamp, 2010). Extreme hot and cold temperatures were avoided, as we did not want to stimulate nociceptors, nor produce pain. These multiple constraints meant that we could not set stimulation levels individually as in Experiment 1. Instead, we set fixed levels of thermal stimulation based on the physiological ranges of target receptors reported in the literature (see above), and a pilot study of 9 volunteers who did not participate in the main study. From the pilot data, we determined warm and cold stimulation levels that were not painful and that yielded, on average, 65-75% accuracy in discriminating total intensity of non-discrepant stimulus pairs (Table 1). Discrimination of total temperature was better in the warm than in the cold range, so we used smaller temperature differences in the warm condition than in the cold condition, but the *relative* temperature discrepancy levels of the discrepant stimulus pairs were the same in both temperature ranges (medium discrepancy level 75% of high discrepancy level). Participants judged which stimulus pair had the greater total warmth/coldness (as appropriate), the first or the second.

		Warm range		**Cold range**	
		Test pair warmer	**Test pair less warm**	**Test pair colder**	**Test pair less cold**
Reference pair: Non-discrepant	**Stimulus 1**	37.00°C	38.00°C	21.00°C	19.00°C
	Stimulus 2	37.00°C	38.00°C	21.00°C	19.00°C
Test pair: Non-discrepant	**Stimulus 1**	38.00°C	37.00°C	19.00°C	21.00°C
	Stimulus 2	38.00°C	37.00°C	19.00°C	21.00°C
Test pair: Discrepant (75% max.)	**Stimulus 1**	35.75°C	34.75°C	22.00°C	24.00°C
	Stimulus 2	40.25°C	39.25°C	16.00°C	18.00°C
Test pair: Discrepant (100% max.)	**Stimulus 1**	35.00°C	34.00°C	23.00°C	25.00°C
	Stimulus 2	41.00°C	40.00°C	15.00°C	17.00°C

Table 2.1. Warm and cold stimulation levels used in Experiment 4.

Each participant completed three blocks of 24 trials each in the warm temperature range and another three blocks in the cold temperature range. Blocks of the same temperature range were done consecutively, and the order of warm/cold conditions was counterbalanced across participants (e.g. WWWCCC or CCCWWW). Additionally, a short practice block (10 trials) was given before the first warm block and before the first cold block to familiarise participants with the task and the temperature range. A rest period of at least three minutes was given before switching temperature ranges, and the skin surface temperature was checked with an infrared thermometer at the end of the rest period to ensure that it had returned to baseline.

Participants sat at a table with their left hand placed palm-up. On each trial, the thermode probes would descend and touch the participant's index and middle fingers for 1 s, and then retract. After a 3 s delay, the probes would descend and touch the participant's fingers again, retracting after 1 s. The participant would then press a button with the right hand to indicate whether the first or second pair was warmer (in the warm condition) or colder (in the cold condition) *in total*. Each trial contained one stimulus pair with the same temperature on both probes (the non-discrepant reference pair) and a test pair that could be discrepant. As in Experiment 1, the test pair could either have the same temperature on both probes (i.e., non-discrepant), an intermediate difference in temperature between the two probes (medium-discrepant), or a larger difference in temperature between the two probes (highly-discrepant). Levels of discrepancy were set so that the temperatures in the highly-discrepant stimulus pairs fell within the range of innocuous warm/cold sensation. The medium discrepancy level was set to 75% of the high discrepancy level. The interval containing the discrepant pair (first or second) was counterbalanced within blocks, as was the site of the more extreme temperature in discrepant pairs (index or middle finger). To avoid peripheral effects such as receptor adaptation, vascular responses and persistent changes in skin temperature, the first and second stimulus pairs were delivered to different parts of the fingers (one pair to the distal finger pads and the other to the middle finger pads). Half the participants received the first stimulus pair on the distal pads and the second on the middle pads, and the other half received the reverse order of finger pad stimulation. The inter-trial interval was 5 s.

2.3 Results

2.3.1 Experiment 1

Total intensity judgements

A 2 (finger adjacency: adjacent or non-adjacent) x 2 (test pair total: larger or smaller) x 3 (discrepancy level: none, 70%, or maximum) within-participants ANOVA was performed on percentages of correct responses. The data violated the assumption of sphericity, so a Greenhouse-Geisser correction was applied where necessary. There was a significant main effect of discrepancy ($F_{1.35,17.53} = 6.44$, $p = 0.014$). Accuracy at judging total intensity decreased monotonically as discrepancy increased. The ANOVA showed neither a main effect of finger adjacency ($F_{1,13} = 0.003$, $p = 0.961$), nor an interaction between adjacency and discrepancy ($F_{2,26} = 0.84$, $p = 0.445$).

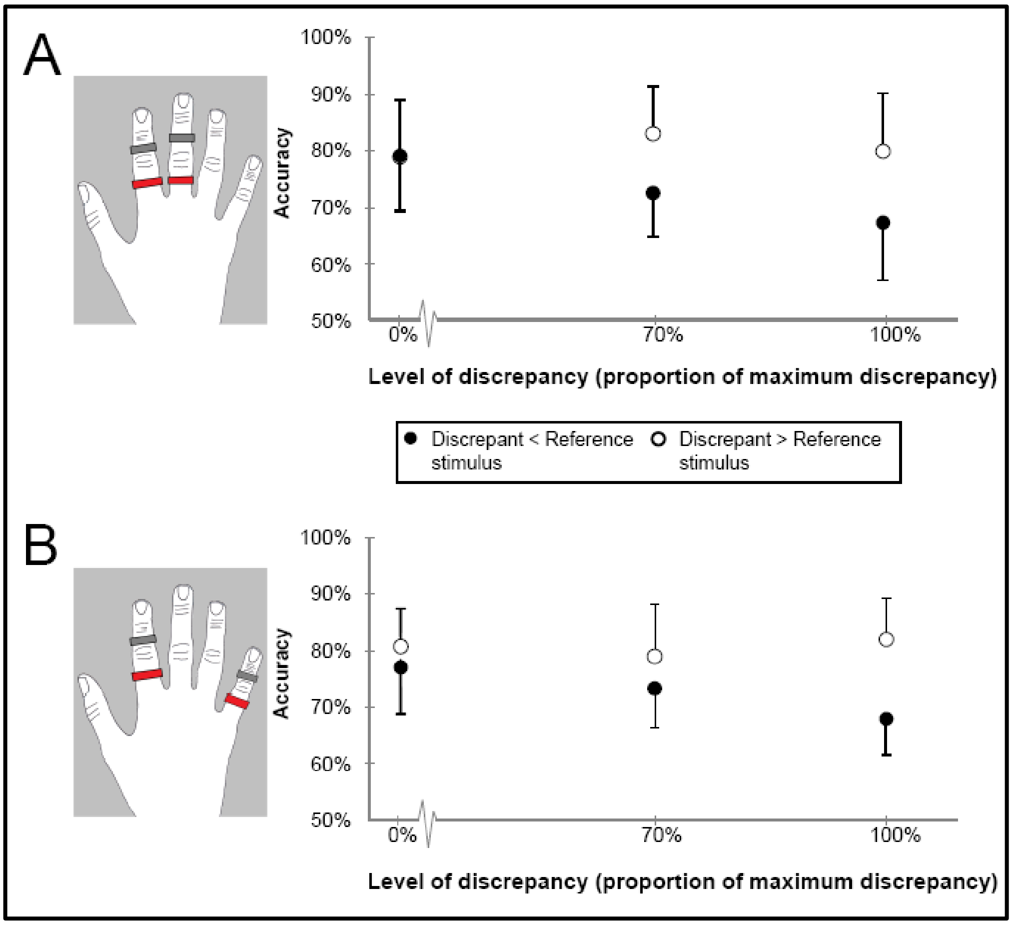


Figure 2.3. Accuracy of intensity judgements in Experiment 1.

Participants' accuracy decreased with discrepancy when the discrepant stimulus had a smaller total intensity, but not when the discrepant stimulus had a greater total intensity. Note similar effects when stimulated fingers are adjacent (A) or non-adjacent (B). Error bars show standard error of the mean.

Figure 2.3 separately plots data from the blocks with stimulation on adjacent and non-adjacent fingers. Because our test pair was sometimes non-discrepant, we arbitrarily and equally divided such trials into the 'test pair smaller' and 'test pair larger' categories. Discrepancy only affected participants' performance when the discrepant test pair had a smaller total than the non-discrepant reference pair. The ANOVA showed a main effect of test pair total, ($F_{1,13} = 14.48$, $p = 0.002$) and a significant interaction with discrepancy level ($F_{1.43,18.56} = 8.03$, $p = 0.006$). Simple effects contrasts were used to clarify this interaction. Discrepancy affected accuracy at judging total intensity when the test pair was the smaller total ($F_{1.15,14.90} = 10.62$, $p = .004$), but not when the test pair was the larger total ($F_{2,26} = 0.32$, $p = .726$).

2.3.2 Experiment 2

Contribution of the weak stimulus to total intensity judgements

First, to determine whether Experiment 2 replicated the effect of discrepancy found in Experiment 1, we compared participants' performance in the pre-test, where they compared non-discrepant versions of the smallest and largest test pair totals to the non-discrepant reference pair total, with their accuracy in judging the discrepant versions of the same totals in the main experiment. The 2 (test pair total: smaller or larger) x 2 (discrepancy level: non-discrepant or discrepant) repeated measures ANOVA showed no main effect of test pair total ($\mathrm{F}_{1,15} = 0.35$, $p = 0.564$), but a significant main effect of discrepancy ($\mathrm{F}_{1,15} = 9.49$, $p = 0.008$). Accuracy was higher overall when test pairs were non-discrepant (73.3% correct; CI: 70.3%, 76.2%) rather than discrepant (66.5% correct; CI: 62.1%, 70.9%; Figure 2.4). Crucially, the interaction between test pair total and discrepancy level was significant ($\mathrm{F}_{1,15} = 8.24$, $p = 0.012$). Simple effects contrasts showed that discrepancy did not affect judgements of the larger totals ($\mathrm{F}_{1,15} = 0.47$, $p = 0.505$). The smaller test pair was incorrectly judged to have the larger total intensity more often when it was discrepant

(63.1% correct; CI: 57.1%, 69.2%) than when it was non-discrepant (75% correct; CI: 71%, 79%) ($F_{1,15}$ = 14.60, p = 0.002). Consistent with Experiment 1, participants overestimated the total intensity of discrepant stimulus pairs.

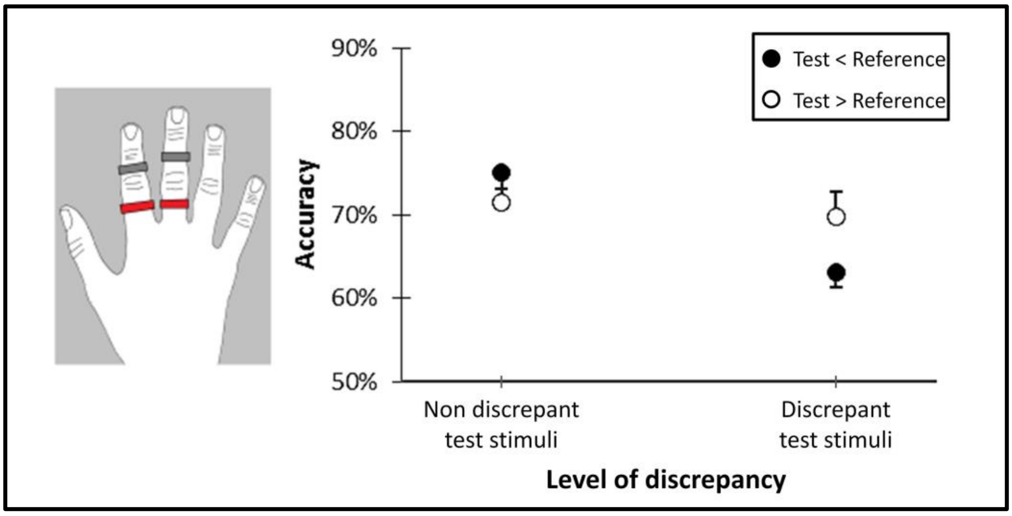


Figure 2.4. Accuracy of intensity judgements in Experiment 2.

Accuracy in judging total intensity decreased with discrepancy when the discrepant stimulus had a smaller total intensity, but not when the discrepant stimulus had a larger total intensity. Note the similarity to Experiment 1. Error bars show standard error of the mean.

Next, we tested whether this overestimation occurred because participants based their judgements entirely on the intensity of the strongest stimulus in each pair. If this were the case, then there should be no main effect of discrepancy level, nor interaction between discrepancy level and discrepant pair total, because these effects depended only on the level of the weaker stimulus. Instead, there should only be a main effect of discrepant pair total. That is, a participant considering only the stronger stimulus in the discrepant pair would tend to be more accurate when the discrepant pair is, in fact, the larger total, and less accurate when the discrepant pair is actually the smaller total, *irrespective of discrepancy level*.

A 2 (discrepant pair total: smaller or larger) x 2 (discrepancy level: low or high) within-participants ANOVA on percentages of correct responses showed a significant main effect of discrepant pair total ($F_{1,\ 15} = 5.34$, $p = 0.036$), but no main effect of discrepancy level ($F_{1,\ 15} = 71.19$, $p = 0.341$). Overall, accuracy was lower when the discrepant pair was smaller in total (58.8% correct; CI: 53.1%, 64.5%) than when it was larger in total (67.7% correct; CI: 62.9%, 72.4%). Importantly, there was a significant interaction between discrepant pair total and discrepancy level ($F_{1,\ 15} = 11.65$, $p = 0.004$). Simple effects contrasts showed that accuracy was not affected by discrepancy when the discrepant pair was larger in total than the non-discrepant reference pair ($F_{1,\ 15} = 2.19$, $p = 0.159$). However, when the discrepant pair was smaller in total, accuracy at judging total intensity *increased* with discrepancy. That is, participants made more accurate total intensity judgements when the actual difference between the discrepant and non-discrepant pair totals was larger (63.1% correct; CI: 63.6%, 69.2%), compared to when this actual difference was smaller (54.5% correct; CI: 47.7%, 61.3%; $F_{1,\ 15} = 9.58$, $p = 0.007$; Figure 2.5). This result confirms that participants indeed processed the weaker stimuli of discrepant pairs, and considered both the stronger stimulus and the weaker stimulus when judging the total intensity of the pair.

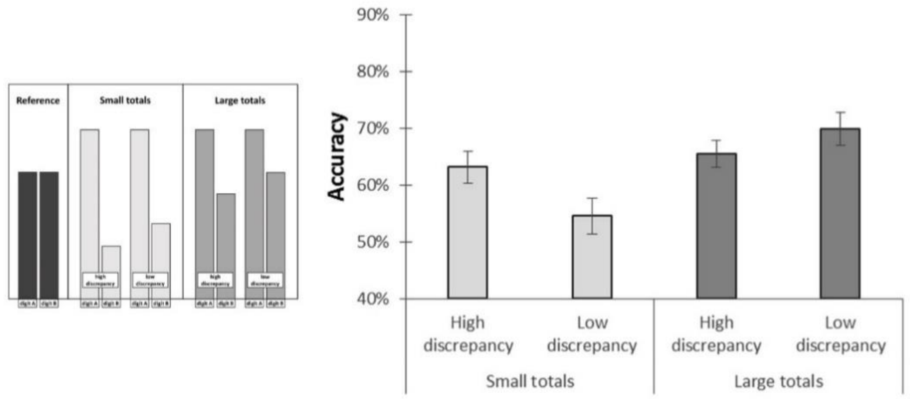


Figure 2.5. Accuracy in the different condition of Experiment 2.

When the intensity of the strong stimulus in the discrepant pair was held constant and only the weak stimulus varied, accuracy increased with the actual difference in total intensity between the two stimulus pairs, confirming that the weak stimulus contributed to the perception of the discrepant pair total. Error bars show standard error of the mean.

2.3.3 Experiment 3

Total intensity judgements between hands

A 2 (spatial proximity: hands together or hands apart) x 2 (test pair total: larger or smaller) x 3 (discrepancy level: none, 70%, or maximum) within-participants ANOVA was performed on percentages of correct responses when participants judged the total intensity of two stimuli delivered to different hands. No Greenhouse-Geisser corrections were necessary. We did not observe any significant effects of discrepancy on total intensity judgements (Figure 2.6). With hands together, participants' mean performance was 82.1% (CI: 75.2%, 89.1%) correct with zero discrepancy and 78.8% (CI: 73.0%, 84.5%) with maximum discrepancy. The main effects of discrepancy ($F_{2,18} = 2.72$, $p = 0.093$) and discrepant pair total ($F_{1,9}$ = 0.60, p = 0.459) were both non-significant. The spacing between the index fingers did not have an effect ($F_{1,9}$ = 0.05, p = 0.835). Furthermore, none of the interactions between these factors were significant ($p \geq 0.10$ in all cases).

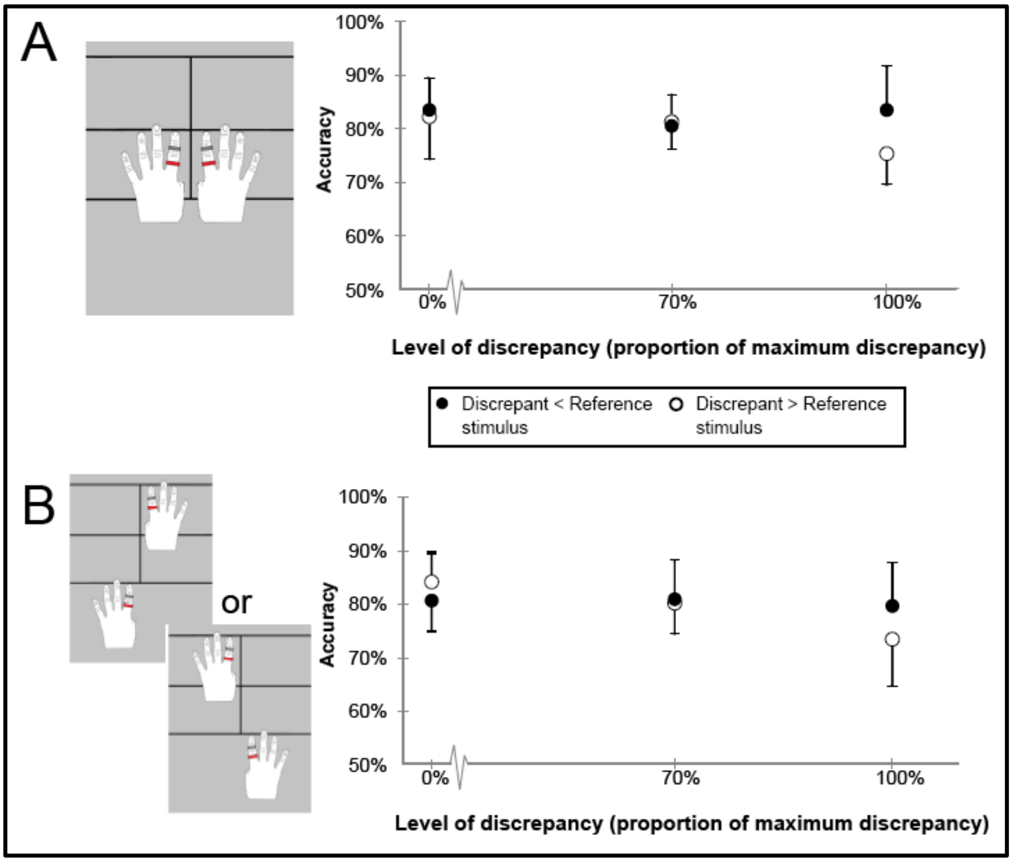


Figure 2.6. Results of Experiment 3.

Discrepancy does not affect perception of total intensity for stimuli distributed across two hands. Note similar results when hands are together (A) versus apart (B). Error bars show standard error of the mean.

We additionally used Bayesian analysis to determine whether our data actually supported the null hypothesis, or were merely insufficiently powered for detecting an effect of discrepancy on perception of total stimulation intensity. In the previous experiments, discrepancy only had an effect when the discrepant pair was smaller in total than the reference pair. Therefore, the key finding would be an interaction between discrepancy level and test pair total. We conducted a Bayesian ANOVA (JASP 0.7.5.5) comparing the null model to an alternative model with the factors test pair total (larger or smaller), discrepancy level (none, 70%, or maximum), and the interaction between test pair total and discrepancy. The Bayes factor (null/alternative) showed that the data were 4 times more likely to occur under the null model than under the alternative model, $BF_{01} = 4.00$, error = 2.98%. This indicates that the data are not under-powered, and they provide substantial evidence for the null hypothesis.

2.3.4 Experiment 4

Total thermal intensity judgements

Responses to thermal stimulation were analysed with a 2 (temperature range: warm or cold) x 2 (test pair total: more or less extreme temperature) x 3 (discrepancy level: zero, 75% or maximum) within-participants ANOVA. The assumption of sphericity was violated, so a Greenhouse-Geisser correction was applied where necessary. There was a main effect of temperature range ($F_{1,14} = 11.01$, $p = 0.005$), with a mean of 73.5% correct (CI: 68.3%, 78.8%) in the cold condition and 64.2% correct (CI 61.5%, 66.8%) in the warm condition. This indicates that the task was easier in the cold condition than in the warm condition, despite our attempts to balance difficulty across temperature ranges. Note that smaller temperature differences were used in the warm temperature range than in the cold temperature range based on the pilot study. This adjustment was necessary to avoid near-ceiling performance in the warm condition. Importantly, performance was well above chance and well below ceiling in both cases.

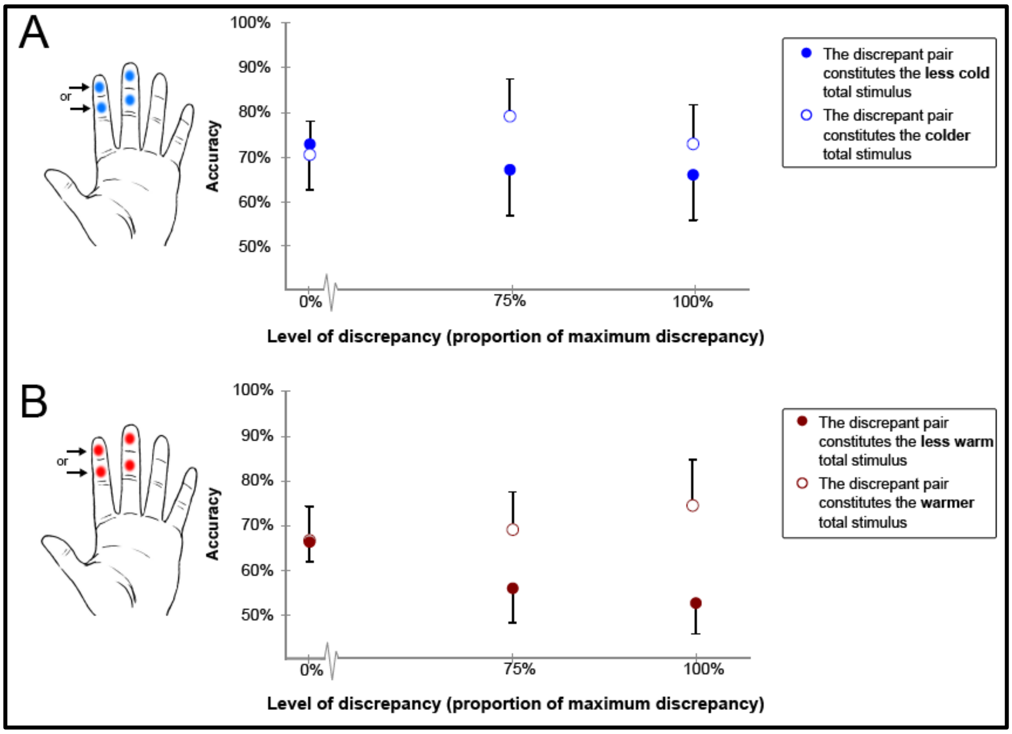


Figure 2.7. Results of Experiment 4.

Accuracy decreased with discrepancy when the discrepant stimulus had the smaller total intensity. Note similarity between cold range (A) and warm range (B), and with Experiment 1. Error bars show standard errors of the mean.

There was also a main effect of test pair total ($F_{1,14} = 37.05$, $p = 0.00003$). Accuracy was higher when the total of the test pair was a more extreme temperature (warmer in the warm condition or colder in the cold condition) than the non-discrepant reference pair (73.2% correct; CI:

70.3%, 76.1%) compared to when the test pair was less extreme (64.4% correct; CI: 60.9%, 68.0%). Moreover, the interaction between test pair total and discrepancy level was significant ($F_{2,28} = 8.99$, $p = 0.001$). Simple effects contrasts were used to clarify this interaction. There was an effect of discrepancy when the test pair total was the less extreme temperature ($F_{2,28} = 6.38$, $p = 0.005$). Accuracy at judging total intensity decreased as discrepancy increased (Figure 2.7). In contrast, discrepancy did not significantly affect accuracy at judging total intensity when the test pair total was the more extreme temperature ($F_{2,28} = 2.53$, $p = 0.097$).

2.4 Discussion

Our somatosensory experience of the surrounding world emerges from continual integration of multiple, individual points of stimulation. Here we investigated this integration process by asking healthy volunteers to judge the total intensity of two somatosensory stimuli delivered simultaneously to two different digits. We found a strong and reliable overestimation bias in judging the total of discrepant stimulus pairs, indicating a biased somatosensory aggregation mechanism.

Across our four experiments, we investigated effects of discrepancy on total intensity judgements of transcutaneous electrical stimuli (Experiments 1-3), contact-heat stimuli and contact-cold stimuli (Experiment 4). Despite the fact that these three kinds of stimulation activate distinct peripheral receptor types and afferent fibres (Desmedt & Cheron, 1980; Hensel & Iggo, 1971; Schepers & Ringkamp, 2010; Yarnitsky & Ochoa, 1991), we observed the same overestimation bias in all three cases. Our results therefore suggest that such a bias may be a general principle underlying spatial integration in the somatosensory domain.

Experiment 2 clearly shows that the overestimation bias cannot be explained by participants simply relying on the strongest stimulus, without attempting to perceive the total of both stimuli. Judgements of total intensity were influenced by varying the intensity of the weaker stimulus in the discrepant pair, even when the intensity of the stronger stimulus was held constant. Indeed, participants were more likely to correctly perceive the discrepant pair as smaller in total when the weaker stimulus itself was smaller (and, thus, there was a larger difference between the totals of the discrepant and non-discrepant pairs). This means that participants must have registered both individual intensities, and attempted to sum them, rather than simply attending to the stronger stimulus only. Our pattern of results therefore reflects a mechanism that attempts to total multiple stimuli, but does so in a manner biased by the stronger stimulus.

This is the first investigation of a key form of neural integration in the somatosensory system, namely, the capacity to perceive the total of a number of simultaneous stimuli. Perceptual psychology has traditionally studied *minimal* units of somatosensation, focussing on thresholds, acuity, selectivity and precision (e.g., Graziano, Alisharan, Hu, & Gross, 2002). However, there is growing evidence that somatosensory bandwidth is deeply limited, and, as a consequence of this limitation, perception of whole somatosensory scenes is imperfect. Gallace and colleagues (2006) showed that only 2 or 3 simultaneous tactile stimuli can be individually perceived. Extinction of double simultaneous stimulation (Driver &

Vuilleumier, 2001) suggests that brain damage can reduce this bandwidth to just 1. Our findings are perfectly in line with this growing literature, extending the effects of bandwidth limitations in the somatosensory system to judgements of total intensity.

Studies of visual search (Treisman & Gelade, 1980) have indicated two distinct ways that perceptual systems can function despite capacity limitations. First, serial sampling strategies can shift selective attention from one stimulus to another. Such strategies can build up a representation of the total over time, through a series of glimpses. However, the stimuli in our experiment were brief and simultaneous. Moreover, somatosensory ‘iconic’ storage – i.e., very short term memory in a sensory form (Sperling, 1960) – is around 700 ms (Harris, Miniussi, Harris, & Diamond, 2002). Serial sampling is therefore not a viable strategy for brief stimuli. Second, the perceptual system can attempt to process multiple stimuli in parallel, despite limited bandwidth. Below we discuss in turn some of the most likely somatosensory mechanisms relevant to parallel processing, which may be relevant to our findings. These include lateral inhibition, filling-in, and peak biases based on stimulus salience.

Lateral inhibition is an important form of interaction between stimuli at several levels in the somatosensory system, including primary somatosensory cortex (DiCarlo, Johnson, & Hsiao, 1998; DiCarlo & Johnson, 1999, 2000). This mechanism tends to suppress the response to a stimulus when another, nearby region of the receptor surface is strongly stimulated. A strong hypothesis of reciprocal inhibition between stimulated fingers in our task, weighted by individual stimulus intensities, would predict that the weaker stimulus in a discrepant pair should be partly or wholly extinguished, prior to perceiving the total. However, lateral inhibition alone appears unable to account for our results for three reasons. First, lateral inhibition would tend to produce underestimation of the totals of discrepant stimuli, while we found overestimation. Second, lateral inhibition classically operates between adjacent digits, in a strict spatial gradient (Buonomano & Merzenich, 1998). It is a principle of operation of early somatosensory areas (Gandevia et al., 1983). In our design, lateral inhibition would lead to stronger effects of discrepancy when stimulating adjacent, as opposed to non-adjacent digits. While caution is clearly required in interpreting null results, we saw no evidence for such a difference (Experiment 1). Third, judgements of total intensity were affected when the intensity of the weaker stimulus in the discrepant pair was varied, but the intensity of the stronger stimulus was held constant (Experiment 2). This result clearly demonstrates that the concurrent weak stimulus was not extinguished, nor disregarded in judgements of total intensity. Rather, both the stronger stimulus and the weaker stimulus contributed to the perceived total intensity of a discrepant pair.

Alternatively, participants may have “filled in” information about the intensity of the weaker stimulus in the discrepant pair, based on the intensity of the stronger stimulus. This could produce the observed overestimate. Such filling-in effects have previously been demonstrated for tactile (Kitagawa et al., 2009) and thermal stimulation (Green 1977, 1978; Ho et al., 2010, 2011). The results of Experiment 2, however, do not support a filling-in mechanism. When the discrepant test pair was smaller in total than the non-discrepant reference pair, and the intensity of the stronger stimulus in the discrepant pair was held constant, the intensity of the weaker stimulus influenced estimations of the total. Because the stronger stimuli were constant, reducing the intensity of the weaker stimulus resulted in a lower total intensity for the discrepant test pair, and thus better discrimination from the non-discrepant reference pair. Experiment 2 therefore shows that information about the intensity of the weaker stimulus was not lost. In fact, the intensity of the weaker stimulus informed participants' judgements of total intensity, in a manner consistent with a genuine attempt at integration.

A third possible explanation for our findings could be a form of peak bias, based on stimulus salience. Salience is a term widely used in psychology. It may involve a number of factors, including intensity, quality or affect (Fecteau & Munoz, 2006; Vuilleumier, 2005; Wolfe, 1992). In a perceptual system with parallel rather than strictly serial organisation, percepts of the total may depend strongly on the most salient part, as salient stimuli may be selected for more detailed perceptual analysis, leaving fewer resources for processing less salient stimuli. In the case of our discrepant stimulus pairs, which were uniform in quality and lacking in affective valence, intensity would determine stimulus salience. Therefore, a mechanism sensitive to stimulus salience might account for the overestimation bias we found in judging the total of discrepant stimuli.

This overestimation followed the pattern of a peak bias, with judgements of total intensity being driven towards the most intense and salient element of stimulation. Peak biases are well established within the literature on memory for affective experiences (for a review, see Fredrickson, 2000). Overall judgements of affect are disproportionately influenced by moments of peak affect. Similarly, comparisons of moment-to-moment pain ratings with retrospective judgements of overall pain show that memories for both acute and chronic pain are driven by moments of peak pain intensity (Redelmeier & Kahneman, 1996; Stone, Schwartz, Broderick & Schiffman, 2005). All our stimuli were set below pain thresholds, and had no affective valence or special meaning for the participants. Nevertheless, our data were consistent with the notion that the salient peak serves as a proxy for an overall experience. We thus provide novel evidence that peak biases occur in low-level perceptual experiences, and not merely in higher-level affective judgements.

Our data provide additional information about the spatial organisation of the somatosensory peak bias. First, Experiment 3 showed that the mechanism operates within a single brain hemisphere. We found strong overestimation for discrepant pairs of stimuli on the same hand, but not when the two stimuli in the pair were delivered to homologous digits on different hands. Second, it appears to be independent of selective *spatial* attention. In Experiment 1, we found no difference between judging the total of adjacent and non-adjacent fingers. Additionally, in Experiment 3, we found no effect of the distance between the hands on the ability to judge the total intensity of stimuli delivered to both hands. Although caution is required in drawing conclusions from these null results, our findings are unlikely simply to reflect lack of power, since spatial attention effects are common in somatosensory perception (e.g., Eimer & Forster, 2003; Forster & Eimer, 2005). Attentional studies report a perceptual cost to dividing attention between two spatial locations (Forster & Eimer, 2005; Posner, 1978), yet our task of judging total intensity appeared not to reflect this cost. Furthermore, a Bayesian analysis of the data from Experiment 3 indicated that the study was not under-powered, and that the results do, in fact, support the null hypothesis that the overestimation bias does not occur when two stimuli are delivered to different hands. Thus, spatial proximity does not seem to play a major role in combining stimulus intensities to form a total, either in somatotopic space within a single hemisphere (no effect of fingers stimulated in Experiment 1) or in external space (no effect of hand positions in Experiment 3). Taken together, these results suggest the bandwidth limitation occurs at early, lateralised levels of somatosensory representation, rather than in a single, central channel of awareness (Broadbent, 1982). Judgements of total stimulation depend on a process of aggregation located prior to the remapping of tactile signals into external space (Azañón, Longo, Soto-Faraco, & Haggard, 2010; Azañón & Soto-Faraco, 2008); which is thought to occur in the parietal cortex.

Together, our four experiments demonstrate a mechanism of biased aggregation within the somatosensory system. Specifically, the most salient element (i.e., the most intense point of stimulation) makes a larger contribution to judgements of the total than less salient elements. This overestimation bias does not bear the hallmarks of lateral inhibition, namely, a strict spatial gradient and extinction of weak stimuli. Moreover, the bias does not seem to arise from a filling-in process, as information about the individual intensity of the weaker stimulus in the pair is not lost. Rather, our findings appear to reflect a peak bias in somatosensory perception, by which the contribution of each individual stimulus to perception of the total is weighted by its salience, or intensity. This process occurred independently within each hemisphere, but was otherwise unaffected by the spatial locations of the stimuli. We thus provide the first evidence for a peak bias in a purely perceptual judgement.

Chapter 3.

When all is more than the sum of its parts: integration of multiple discrepant tactile stimuli

Synopsis:

The data presented in Chapter 2 suggest that the integration of multiple simultaneous somatosensory is not explained by the linear sum of each event. Here, we investigated the nonlinear properties of somatosensory integration during total intensity judgements of double transcutaneous electrical stimuli. In particular, we tested whether somatosensory totalling relies on the ability to perceive the discrepancy between single events (experiment 1), whether discrepancy in overall intensity judgements affects participants' sensitivity or response criterion (experiment 2), and how the salience of each stimulus affects the perception of total intensity (experiment 3). We found that aggregation of two simultaneous events did not require the ability to discriminate between single intensities. Moreover, both participants' sensitivity and response bias were modulated by discrepancy. Lastly, the overestimation of the total was explained by the salience of the stronger stimulus in the pair.

3.1 Introduction

Perceiving touches on the skin surface usually refers to the processing of a single somatosensory event. That is, most studies have focussed on how we detect (LaMotte and Whitehouse, 1986; Johansson, Vallbo, and Westling, 1980), localise (Sherrick, Cholewiak, and Collins, 1990; Harris, Thein, and Clifford, 2004; Porro, Martinig, Facchin, Maieron, Jones, and Fadiga, 2007), and discriminate (Johnson and Phillips, 1981; Stevens and Patterson, 1995) a *single tactile stimulus* on our body. A scenario in which multiple simultaneous somatosensory stimuli reach different portions of the skin has been partially neglected. Yet, isolated stimuli are rare in our daily experience, and successful interactions with the environment rely on the integration of several, simultaneous, often non-homogeneous events. Holding a glass of water with the fingertips leads to a unique, holistic percept, rather than to five distinct sensations. Thus, distinct somatosensory inputs from each finger are merged along the somatosensory pathways to create a coherent percept (Gallace and Spence, 2014; Martin, 1992; MacKay, 1967).

However, somatosensory processing of holistic percepts can be understood through the study of single events only if the merging of multiple inputs follows linear rules. In other words, if the "somatosensory whole" is simply the linear sum of its parts, than an approach focussed on the minimal units of somatosensation (e.g. thresholds, acuity, selectivity, precision, etc.) would be sufficient to understand somatosensory integration. Conversely, a growing body of evidence suggests that the concurrent presentation of two (or more) somatosensory stimuli gives rise to complex, nonlinear effects at many levels of stimulus characterisation. In fact, nonlinear integration has been showed, to date, for detection (Sherrick, 1964; Tamè, Farnè, and Pavani, 2011; Collins, Imhoff, and Grigg, 1996), enumeration (Gallace, Tan, and Spence, 2008; Gallace, Tan, and Spence, 2006a; Plaisier, Bergmann Tiest, and Kappers, 2009), and localisation (Green, 1982; Craig, 1989; Gadner and Spence, 1972; Gallace and Spence, 2014) of multiple simultaneous somatosensory stimuli.

Studies on *vibrotactile masking*, for example, show that the detection of a tactile target drastically decreases when the stimulus is presented in spatial and temporal proximity with a tactile distractor (Craig, 1976; von Békésy, 1967). Similarly, studies employing the *double simultaneous stimulation* paradigm (Sherrick, 1964) demonstrate that interference between simultaneous touches also occurs between non-homologous fingers of different hands (Tamè, Farnè, and Pavani, 2011), and can produce *extinction* of about 6% of double stimulation in healthy individuals (Farnè, Brozzoli, Làdavas, and Ro, 2007). Interestingly, studies on *stochastic resonance* (Collins, Imhoff, and Grigg, 1996) show that concomitant presentation of specific levels of tactile noise can also have positive effects on performance, enhancing the detection of subthreshold tactile stimuli.

Numerosity judgements of somatosensory stimuli also show nonlinear effects. For example, studies on *tactile subitizing* have explored how many somatosensory stimuli can be perceived at once through a fast, accurate, pre-attentive “apprehension” process (as opposed to a slow, error prone and attentional demanding “counting” process) (Gallace, Tan, and Spence, 2006a; Plaisier, Bergmann Tiest, and Kappers, 2009; Riggs, Ferrand, Lancelin, Fryziel, Dumur, and Simpson, 2006; for a review see Gallace, Tan, and Spence, 2008). In particular, Gallace and colleagues (2006a) showed that both errors and RT in an enumeration task dramatically increase when two or more vibratory stimuli are delivered simultaneously across the body, suggesting that the human somatosensory system cannot provide full awareness of more than one tactile input per time.

A different subset of studies has investigated the (mis-)localisation of multiple simultaneous somatosensory stimuli. Early works form Green (1982) and Craig (1989) show that the ability to localise a tactile stimulus on the body dramatically drops when a task-irrelevant stimulus is simultaneously presented. Similarly, in the *funnelling illusion*, the presentation of multiple concurrent mechanical stimuli on different points of the skin produces a single focal sensation at the centre of the stimulation pattern, in absence of any physical stimulation at that site (Gadner and Spence, 1972; von Békésy, 1960, 1967). Crucially, animal studies show that the primary somatosensory cortex reflects the illusory percept, rather than the true locations of the individual stimuli, indicating that the merger of the signals occurs at very early stages of the elaboration process (Chen, Friedman, and Roe, 2003; Chen, Turner, Friedman, Zhang, Gore, Roe, and Avison, 2007; Friedman, Chen, and Roe, 2008). *Change numbsense* (Gallace and Spence, 2014, Gallace, Tan, and Spence, 2006b) is another example of scarce ability to localise a tactile stimulus when it is included in a pattern. In particular, Gallace et al. (2006b) delivered two different patterns of multiple vibrotactile stimuli separated by a very short temporal interval and found that participants were surprisingly poor in detecting the presence of any positional change between the two patterns. Interestingly, mislocalisation of multiple simultaneous stimuli also occurs in other somatosensory sub-modalities. For example, applying a warm-neutral-warm pattern across index, middle, and ring fingers of one hand produces an illusory phenomenon called *thermal referral* (Green, 1977; Ho, Watanabe, Ando, and Kashino 2011; Cataldo, Ferrè, di Pellegrino, and Haggard, 2016), where all three fingers feel warm. In particular, Cataldo and colleagues (2016) showed that despite accurate localisation of single purely thermal events, people are unable to spot non-uniform patterns when multiple thermal stimuli are simultaneously applied to the fingers, suggesting nonlinear integration of spatial information within the thermoceptive system.

Altogether, these studies suggest that our somatosensory perceptual system is deeply affected by bandwidth limitations, and that concurrent inputs interfere with each other at different levels of processing. As a consequence, only partial - and often incorrect - information about multiple simultaneous stimulation is subject to full processing. Thus, nonlinear integration of multiple inputs may be an efficient way to synthesise reality in order to deal with the bandwidth limitations of the somatosensory system.

Besides occurrence, numerosity, and localisation, stimulus intensity is another fundamental dimension which every perceptual system must deal with (Bensmaia, 2009). One may ask whether intensity judgements in a context of multiple simultaneous stimulation are also affected by similar nonlinear effects. The first attempt to address this question comes from a recent study by Walsh and colleagues (Walsh, Critchlow, Beck, Cataldo, de Boer, and Haggard, 2016), where participants were asked to judge the *overall intensity* of electro-tactile stimulation delivered simultaneously to two fingers of the same hand. Crucially, the intensity of each stimulus in the pair was manipulated in order to obtain different levels of discrepancy in the pattern, while keeping the overall physical intensity the same. If somatosensory totalling relies on linear additive processes, the distribution of physical intensity across the fingers should not produce any difference in participants' perception. Conversely, when participants were asked to judge the overall intensity of discrepant double stimulations, their accuracy decreased in function of the difference in intensity between the two stimuli. The perceived overall intensity cannot therefore be explained by a linear summation of the intensity of each stimulus. Interesting, the overall intensity was systematically overestimated according to a *peak-biased aggregation* mechanism, in which the most salient input (i.e. the strongest stimulus in the pair) biased the perception of the total (Walsh, Critchlow, Beck, Cataldo, de Boer, and Haggard, 2016). Although this evidence supports the notion of nonlinear integration of somatosensory cues, the mechanisms underlying this process remain unclear. Totalling the intensity of two inputs may reflect both perceptual and cognitive processes.

Here, across three different experiments, we use discrepant and non-discrepant electro-tactile stimuli to investigate the mechanisms underlying the perception of overall intensity. First, we asked whether the summation of two discrepant stimuli depends on the discriminability of their individual intensities. This would depict somatosensory integration as a serial process where, after single intensities detection, a comparator would calculate the relative difference between the stimuli to feed a successive accumulator with the weights assigned to each input. Conversely, perception of overall intensity may rather rely on an automatic module, independent from single intensities discrimination. Experiment 1 tested these two models by assessing participants' accuracy in judging *overall* *intensity* versus *overall discrepancy* of two simultaneous stimuli. We found that accurate overall intensity judgements were possible despite a surprisingly poor ability to detect discrepancy across the stimulation, suggesting independence between aggregative and discriminative processes. This result is even more remarkable considering that the information about the physical intensity of each single stimulus could be correctly retrieved.

Second, we investigated whether the salience-driven overestimation bias described by Walsh and colleagues (2016) derives from a genuinely perceptual change in participants' sensitivity or from a bias. Accordingly, in Experiment 2 we tested aggregation of double simultaneous stimuli using a paradigm based on a signal detection approach. We found that as the discrepancy between two stimuli increased, the perceptibility of total intensity decreased. The drop in sensitivity was also mimicked by a change in response criterion, suggesting that when totalling was affected by discrepancy, participants' response criterion become more liberal, leading to an overestimation of the total intensity.

Finally, Walsh and colleagues (2016) hypothesised that the salience of the strong stimulus in a pattern drives the overestimation of the total. Our Experiment 2 supported this hypothesis, and Experiment 1 suggested that salience detection does not rely on the discrimination of the parts, but, rather, on the physical intensity of the stimuli. Yet, the extent to which the salience of a single input leads to the overestimation of the total remains unclear. Experiment 3 aimed to directly quantify this, by investigating the perceived intensity of double discrepant and non-discrepant stimulations as compared to the perceived intensity of single weak and strong stimuli.

We found that the overall intensity of a discrepant pair did not differ from that of a single strong stimulus, suggesting that the peak in a multiple stimulation is taken as the most representative of the total intensity.

3.2 Methods

3.2.1 Experiment 1

Participants

Twenty healthy right-handed volunteers (10 female, mean age ± SD: 25.5 ± 4.1 years) participated in Experiment 1. Two participants were excluded because the tactile stimulation range (i.e. the range between the detection threshold and the pain threshold to electrical stimulation of the digital nerves) was too small to generate the whole set of experimental stimuli (stimulation range < 2 mA; see below). Data from two further participants could not be analysed due to a technical malfunctioning. The final sample size of Experiment 1 was n = 16. The experimental protocol was approved by the research ethics committee of University College London. The study adhered to the ethical standards of the Declaration of Helsinki. All participants were fully informed about the experimental procedures and provided their written informed consent before the beginning of each experiment.

Experimental design and procedure

Experiment 1 aimed 1) to compare participants’ accuracy in totalling the intensity of two tactile stimuli with their ability to discriminate between the individual intensity of each event in the pair; and 2) to investigate whether information about each event in the pair is still accessible after global (aggregative/discriminative) judgements of the total percept.

To this purpose, we implemented a 2 (task: aggregation/discrimination) x 2 (rating: weak/strong stimulus) within-subjects design, where participants performed, in two separate blocks, either an aggregation task ("judge the total intensity of the pair"), or a discrimination task ("judge the discrepancy of the pair"). For each block, in 83% of the trials participants were administered with both a discrepant and a non-discrepant pair, separated by 1s delay. One of the pairs had the large total intensity and the other the small total intensity. Each stimulus was associated with an audible beep, and participants performed a two interval forced choice task, judging which beep had either the larger total intensity (aggregation block) or the larger discrepancy between the two fingers' intensity (discrimination block). In the 17% of the trials (catch trials), participants were presented with a single discrepant pair, and where asked to rate from 1 to 10 the intensity of either the strong stimulus or the weak stimulus of the pair. Catch trials were associated with a different beep and were randomly distributed along each block. To provide an anchoring for the magnitude estimation, at the beginning of each block and after every 20 trials, participants were presented with the whole stimulation range (floor and ceiling).

The order of the blocks (aggregation/discrimination) was counterbalanced between participants. In each block, the presentation order of small/large and discrepant/non-discrepant pairs, the localisation of the strong stimulus in discrepant pairs (index/middle), and the target of the catch trials (strong/weak stimulus) were counterbalanced within participants. Each main trial was repeated 20 times (160 per block), and each catch trial was repeated 16 times (32 per block), for a total of 192 trials per block.

Experimental setup

Transcutaneous electrical tactile stimuli were delivered through a constant current stimulator (DS5, Digitimer, Ltd., United Kingdom), controlled by a computer. A pair of stainless digital ring electrodes (Technomed Europe, Netherlands) was applied to the proximal and intermediate phalanges of index and middle fingers of the right hand. Electrical impedance between each electrode and the skin was kept below 5kΩ throughout all the experiment by means of self-adhesive conductive gel patches. Participants were asked to rest their right hand down on a support, with thenar and hypothenar eminences, distal finger pads and lateral side of thumb pad touching the surface. Vision of the hand was blocked by a screen. Visual stimuli for the task were generated using the Psychophysics Toolbox v3 (http://psychtoolbox.org) for MATLAB (The Mathworks, Natick, MA).

Detection and pain thresholds for electrical stimulation of the digital nerves were measured prior to the experiment. In a staircase procedure, the same stimulation intensity was delivered simultaneously to both fingers, starting from 0.5 mA and then increasing in steps of 0.5 mA until the participant perceived the stimulus. After the first detection, the current was reduced in steps of 0.5 mA until the stimulus was no longer perceived, and then increased again with the same steps. The current intensity able to evocate the second detection was taken as participant’s detection threshold. Pain threshold was established with the same procedure, but in this case participants were asked to report whether the stimulation was painful or not (cfr. Walsh, Critchlow, Beck, Cataldo, de Boer, and Haggard, 2016). In order to set stimulus values within the participants' tactile range only, we selected current intensities that were clearly above detection threshold (floor: 1.5 x detection threshold), but below pain threshold (ceiling: 90% of pain threshold). Small and large total intensities were set respectively at the 37.5% and 62.5% of the stimulation range (ceiling minus floor) for each participant (cfr. Walsh, Critchlow, Beck, Cataldo, de Boer, and Haggard, 2016).

We then verified that participants' accuracy in judging the total intensity of non-discrepant pairs was approximately around 75%. This was done to avoid ceiling and floor effects in participant performance during the main phase of the experiment. Non-discrepant pairs (small or large) were simultaneously delivered on participants index and middle fingers, and participants were asked to judge the overall intensity of each pair by pressing one of two keys corresponding to "small"/"large" total. At the beginning of the block participants were presented with a small and a large total example. After 20 trials, performance was checked. If accuracy was lower than 60% (or higher than 80%), the difference between the two totals' intensity was increased (reduced), and the block was repeated until performance was as intended (group mean accuracy ± SD: 75.6% ± 6.8% correct). Finally, from each total we derived a discrepant pair characterized by the 70% of the maximum possible discrepancy within the stimulation range (see Figure 3.1).

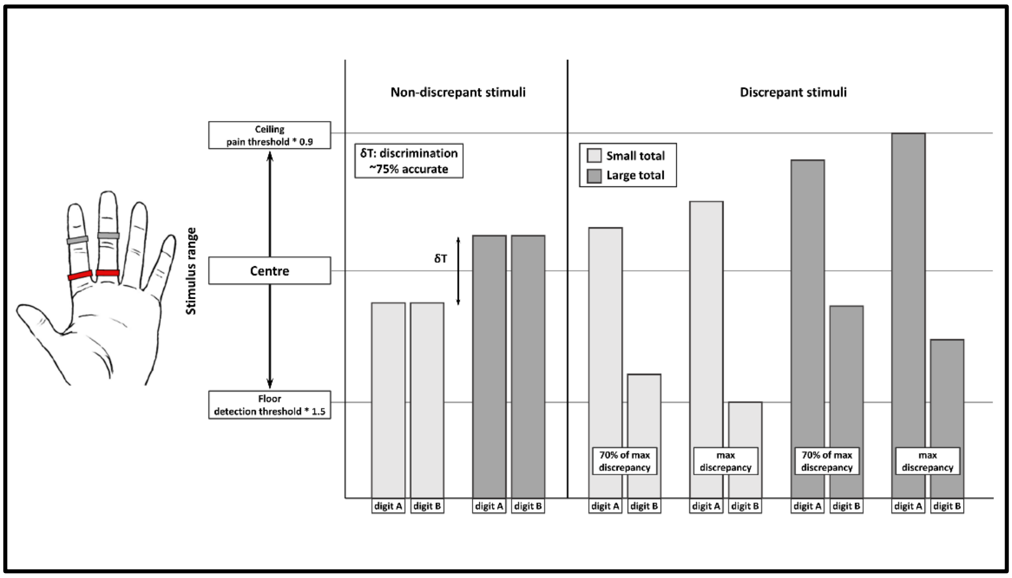


Figure 3.1. Electrode placement and stimuli's intensity in Experiments 1.

In Experiment 1, electrodes were placed on participants' right index and middle fingers. The intensity of the electro-tactile stimulation in each condition was established on the basis of individual detection and pain thresholds. Non-discrepant stimuli were used to set participants' performance around ~75% of correct discrimination between small and large pairs. Discrepant stimuli had the 70% or 100% of maximal discrepancy for both small and large totals.

3.2.2 Experiment 2

Participants

Twenty healthy right-handed volunteers (10 female, mean age ± SD: 25.7 ± 2.4 years) took part in Experiment 2. The study adhered to the ethical standards of the Declaration of Helsinki and was approved by the Department of Psychology of the University of Bologna. All participants were fully informed about the experimental procedures and provided their written informed consent before the beginning of each experiment.

Experimental design and procedure

Experiment 2 aimed to 1) replicate the overestimation bias found in previous studies (Walsh, Critchlow, Beck, Cataldo, de Boer, and Haggard, 2016), and 2) to investigate the mechanisms underlying this bias adopting a signal detection approach. In particular, we tested whether the overestimation bias in the aggregation of two discrepant tactile stimuli was due to a change in participants' sensitivity and/or response criterion.

Accordingly, we designed a 2 (totals: small/large intensity) x 3 (discrepancy: 0%, 70%, and 100% discrepancy) within-subjects paradigm. Small/large totals were sequentially administered in a random order. Each stimulus was associated to an audible beep. Participants were asked to judge the overall intensity of each pair by pressing one of two keys corresponding to "small"/"large" total. The intensities of each pair were set at one out of the three different levels of discrepancy (0%, 70%, and 100%). The presentation order of the stimuli was fully randomized within participants. The localisation of the strongest stimulus in the discrepant trials was counterbalanced between index and middle fingers. Each stimulus was repeated 20 times, giving a total of 240 trials. Participants were given a short break every 60 trials.

Experimental setup

Transcutaneous electrical nerve stimulation was delivered by means of a constant current stimulator (DS7, Digitimer, Ltd., United Kingdom). Two pairs of self-adhesive surface electrodes (SU15N1 electrodes, SEI

EMG, Padova) connected to the stimulator were applied to the hairy skin of proximal and intermediate phalanges of participants' index and middle fingers. Instructions and visual stimuli were presented using the E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). Participants rested their right hand palm down on a table. Vision of the stimulated hand was blocked with a screen.

The procedure for establishing detection and pain thresholds was the same as Experiment 1. The floor and ceiling levels were set at 2 x detection threshold and 90% of the pain threshold, respectively. The 37.5% and 62.5% of the stimulation range (ceiling minus floor) was selected as stimulus intensities for the small and the large totals, and then we subdivide the two totals among the fingers according to three different levels of discrepancy: 0% (no discrepancy), 70% (low discrepancy) and 100% (high discrepancy) of the maximum possible discrepancy within the stimulation range (see Figure 3.1).

Participants performed a familiarization task (30 trials) where non-discrepant small and large pairs were sequentially presented in a random order. Participants were asked to judge the overall intensity of each pair by pressing one of two keys corresponding to "small"/"large" total. This phase served both to let participants familiarize with the totals, and to make sure that their accuracy in judging non-discrepant pairs was not at ceiling (group mean accuracy ± SD: 81.6% ± 7.6% correct).

3.2.3 Experiment 3

Participants

Fourteen healthy right-handed volunteers (10 female, mean age ± SD: 23.9 ± 4.1 years) participated in Experiment 3. Three of these were excluded because the stimulation range was too small to produce suitable stimuli's intensity (stimulation range < 3 mA). A further participant was excluded because electrical stimulation of the middle finger did not produce any clear and reliable perception. Hence, the final sample size for Experiment 3 was n = 10. The experimental protocol was approved by the research ethics committee of University College London. The study adhered to the ethical standards of the Declaration of Helsinki. All participants were fully informed about the experimental procedures and provided their written informed consent before the beginning of each experiment.

Experimental design and procedure

Experiment 3 aimed to 1) assess whether the same amount of physical stimulation gave rise to different perceived intensity when it was distributed across fingers in a discrepant versus a non-discrepant fashion, and 2) to test whether perception of total intensity of a double stimulation relies on the salience of the strongest stimulus in the pair. Accordingly, we used a staircase paradigm to compare the perceived intensity of either single (small/large) or double (non-discrepant/discrepant) tactile stimulations.

The main phase of the experiment was divided in four blocks. In each block, participants were presented with one ascending and one descending staircase for each of the following conditions: small single stimulation, large single stimulation, double non-discrepant stimulation, and double discrepant stimulation (see Figure 3.2). The double discrepant condition was composed by two sub-blocks, in order to counterbalance the localisation of the strong stimulus among index and middle finger. Data from the two sub-blocks were pooled in the analysis. The single small stimulus corresponded to the intensity of one stimulus of the non-discrepant pair, while the single large stimulus corresponded to the strongest stimulus of the discrepant pair. The staircase procedure was similar to that described above. In each trial, a reference stimulus was presented on the index finger alone (single stimulation) or on index and middle fingers simultaneously (double stimulation). The comparison stimulus, instead, was always delivered on the ring finger. Blocks were presented in a counterbalanced order across participants. In each block, the two staircases (comparison starting from the floor or the ceiling level of the ring finger) were interleaved. Each staircase ended after seven reversal, and the average of the last three reversal was taken as a measure of the perceived intensity in each condition (Levitt, 1970). Participants were given a short break after each block.

Experimental setup

We used the same experimental setup as in Experiment 1, and a thresholding procedure similar to that of Experiment 2. However, in this case three fingers (index, middle and ring fingers) were stimulated during the experiment, and each finger’s detection and pain threshold was assessed separately. Rather than using the same physical intensity for each finger, in the present paradigm we opted for defining all the relevant stimulation intensities for the index finger first, and then finding the corresponding perceived isointensities for the other fingers. We reasoned that the same physical electrical stimulation might produce different percepts on each finger, due to their inherent dissimilarities (circumference, length, innervation territory, number of receptors, threshold, etc.) (Warren, Bobich, Santello, Sweeney, and Tillery, 2008; Bobich, Warren, Sweeney, Helms Tillery, and Santello, 2007). Hence, to control for this possibility, we decided to level out any eventual physical difference by using perceived isointensities.

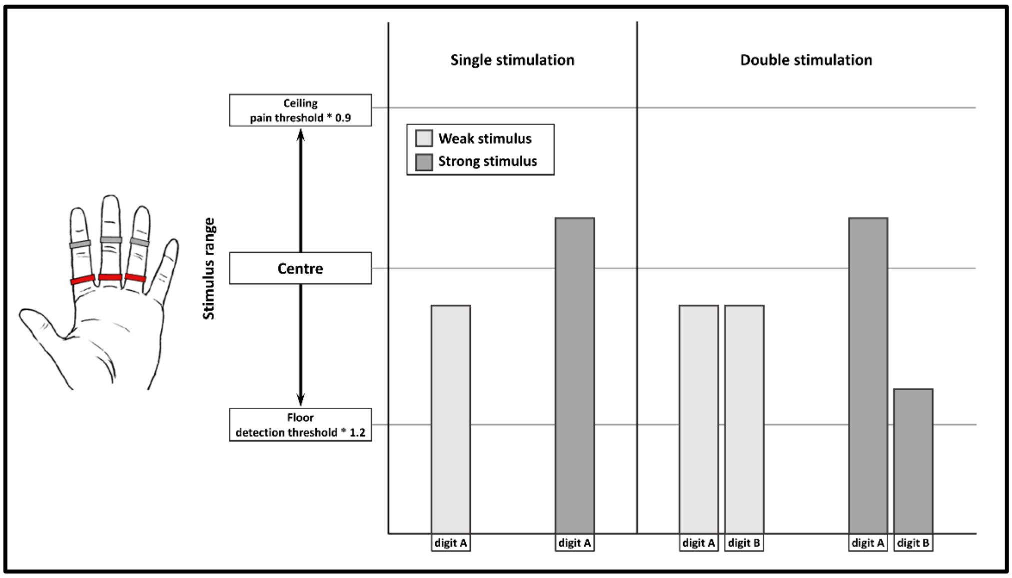


Figure 3.2. Electrode placement and stimuli's intensity in Experiments 3.

In Experiment 3, electrodes were placed on participants' right index, middle, and ring fingers. Single weak and strong stimuli, and double non-discrepant and discrepant pairs were delivered on index and/or middle fingers, and participants adjusted the intensity of a comparison stimulus on the ring finger until the PSE was identified for each condition.

After establishing floor (1.2 x detection threshold) and ceiling (90% x pain threshold) stimulation levels for the index finger, we set the 37.5% of the stimulation range (ceiling minus floor) as the intensity for each event in a non-discrepant pair. A floor level of 1.2 x, rather than 2 x detection threshold was required in this experiment in order to have a wider stimulation range. Then we calculated the two values that gave the 70% of the maximum possible discrepancy for the same total intensity. Thus, we obtained three stimulation intensities for the index finger: 1) the intensity of each event of the non-discrepant pair, 2) the strong, and 3) the weak stimulus intensity for the discrepant pair. For each of these values we used a staircase procedure (see below) to find the corresponding isointensities on middle and ring fingers. Each condition was blocked (i.e. one staircase for each intensity). In each block, a reference intensity was always delivered to the index finger first. After 500 msec, a comparison stimulus was presented either on the middle or the ring finger. Participants were asked to press one of two buttons (up or down arrow key) in order to adjust the physical intensity of the second stimulus until it matched the intensity of the reference stimulus. Each staircase always started at the floor level of the selected finger and the comparison intensity changed adaptively depending on participants' response. The staircase procedure for each finger ended after the seventh reversal, and the average of the last three reversals was taken as an estimate of the point of subjective equality between fingers.

3.3 Results

3.3.1 Experiment 1

Aggregation and discrimination of the parts for the perception of the whole

We first focussed on the main trials of each block. To assess whether an accurate discrimination of the parts is required in order to judge the total intensity of a double stimulation, we performed a 2 (Block: aggregation/discrimination) x 2 (Total Intensity: small/large) repeated measures ANOVA on the accuracy level showed in each condition (see Figure 3.3). We found a significant main effect of Block ($F_{1, 15} = 14.357$, $p = 0.002$; $\eta 2 = 0.489$). Participants' accuracy in the aggregation task was significantly higher (mean ± SD: 81.5% ± 13.28%) than that in the discrimination task (mean ± SD: 61.88% ± 22.38%). The main effect of Total Intensity ($F_{1, 15} = 0.122$, $p = 0.732$) and the interaction between the factors ($F_{1, 15} = 1.115$, $p = 0.308$) were both non-significant. Accurate judgements of total intensity (i.e. aggregation) were possible even if discrimination of the overall discrepancy was just above chance level.

Next, we tested participants' perception of the intensity of each single event in a discrepant pair. A 2 (Block: aggregation/discrimination) x 2 (Total Intensity: small/large) x 2 (Single Event's Intensity: weak/strong) repeated measures ANOVA on participants' ratings in the catch trials showed no main effect of Block ($F_{1, 15} = 0.086$, $p = 0.774$), but a significant main effect of both Total Intensity ($F_{1, 15} = 13.476$, $p = 0.002$; $\eta 2 = 0.473$) and Single Event's Intensity ($F_{1, 15} = 65.352$, $p < 0.001$; $\eta 2 = 0.813$). None of the interactions between factors was significant ($p > 0.077$ in every case). Overall, participants rated the intensity of each event as stronger

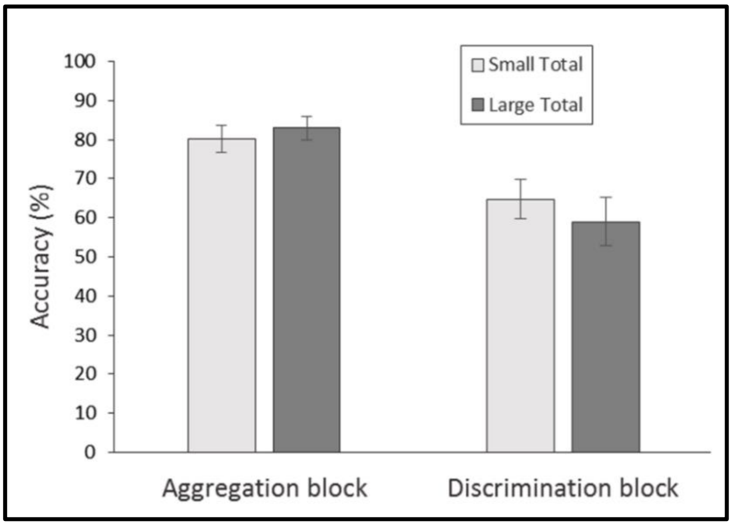


Figure 3.3. Accuracy in the Aggregation/Discrimination block in Experiment 1.

Participants' performance was significantly higher in the Aggregation block compared to the Discrimination block. This suggests that accurate judgement of total intensity was possible even if discrimination of the overall discrepancy was just slightly above chance level. Error bars show standard error of the mean

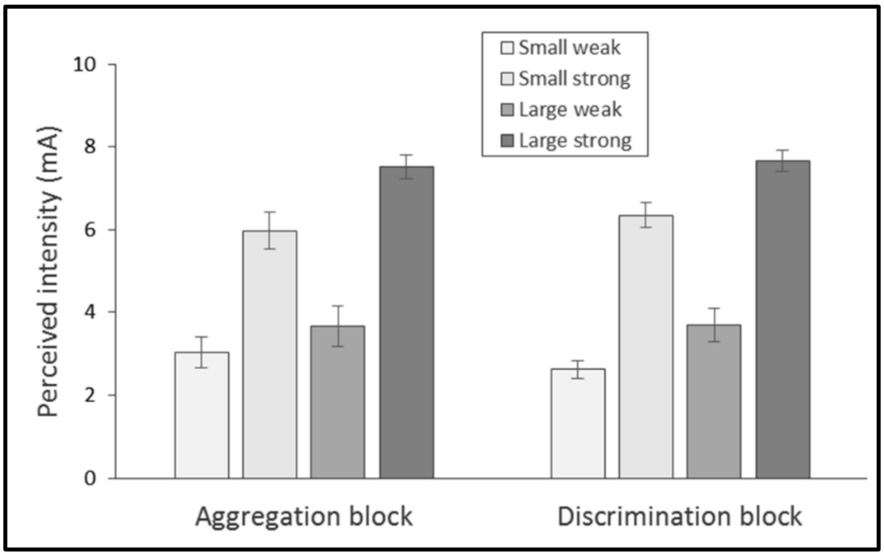


Figure 3.4. Magnitude estimate of single events in Experiment 1.

Participants were able to correctly rate the intensity of each stimulus (weak/strong event, small/large total) in both the Aggregation and the Discrimination block. Error bars show standard error of the mean when the stimulus was from a large total (mean ± SD: 5.639 ± 0.273) than from a small total (mean ± SD: 4.498 ± 0.209). Moreover, regardless of block and total intensity, the strong event in the pair was rated as greater (mean ± SD: 6.879 ± 0.254) than the weak stimulus (mean ± SD: 3.256 ± 0.325) (see Figure 3.4).

3.3.2 Experiment 2

Sensitivity and response bias in judgements of total tactile intensity

To test whether our results replicated the nonlinear overestimation bias described by Walsh and colleagues (2016), we run a 2 (Total Intensity: small/large) x 3 (Discrepancy: 0%, 70%, or 100%) repeated measures ANOVA on participants' performance in each condition (see Figure 3.5A). When the data violated the assumption of sphericity, a Greenhouse-Geisser correction was applied. The analysis revealed no significant effect of Total Intensity ($F_{1, 19} = 0.196$, $p = 0.663$), but a significant main effect of Discrepancy ($F_{1.51, 28.77} = 6.509$, $p = 0.008$; $\eta 2 = 0.255$). Pairwise comparisons between each level of discrepancy showed that accuracy was significantly lower in the 100% discrepant condition compared both with the 70% discrepant condition (mean difference: -6.650, $p = 0.021$; CI -12.182, -1.118; Cohen's dz = -2.516) and the 0% discrepant condition (mean difference: -11.411, $p = 0.010$; CI -19.73, -3.091; Cohen's $d_z = -2.871$). The interaction between the main effects of total and discrepancy was also significant ($F_{1.309, 24.878} = 20.189$, $p < 0.001$, $\eta 2 = 0.515$). Separate paired sample t-test analyses showed that the main effect of discrepancy arose because all conditions significantly differed from each other when the total intensity was small (*p* < 0.001 in all cases), but not when it was large (*p* > 0.232 in all the cases). Moreover, a significant difference between the totals emerged both in the 0% and the 100% discrepant condition (*p* < 0.014 in both cases) (see Figure 3.5A). At increasing levels of discrepancy, participants were worse at judging the total intensity of double discrepant tactile stimulations. In particular, similarly to Walsh et al.'s (2016) results, a systematic overestimation error was observed when the total intensity of discrepant stimuli was small.

We used a signal-detection approach to investigate whether the overestimation of discrepant stimuli was due to a perceptual process and/or to a response bias. We arbitrarily defined a hit as a "large" response when the large total was presented, and a false alarm as a "large" response when the small total was delivered. Sensory discriminability (d'), calculated as z(pHIT) - z(pFA) and response bias (C), calculated as 0.5 * [z(pHIT) + z(pFA)], were then estimated from the hit rate and false alarm rate. First, a one-way (Discrepancy: 0%, 70%, and 100%) repeated measures ANOVA was performed on the d' values to compare the perceptual discriminability of double tactile stimulations at increasing levels of discrepancy. Data violated the assumption of sphericity, therefore Greenhouse-Geisser correction was applied. Discrepancy had a significant effect on d' ($F_{1.526,\ 28.997}$ = 5.446, *p* = 0.015; η2 = 0.223). We then performed two paired sample t-tests to compare each level of the factor. We found that participants' sensitivity was significantly higher in the 0% discrepancy condition (mean ± SD: 2.026 ± 0.86) compared to both the 70% (mean ± SD: 1.614 ± 0.76, *p* = 0.029) and

100% (mean ± SD: 1.472 ± 0.66, *p* = 0.017) discrepancy condition (see Figure 3.5B).

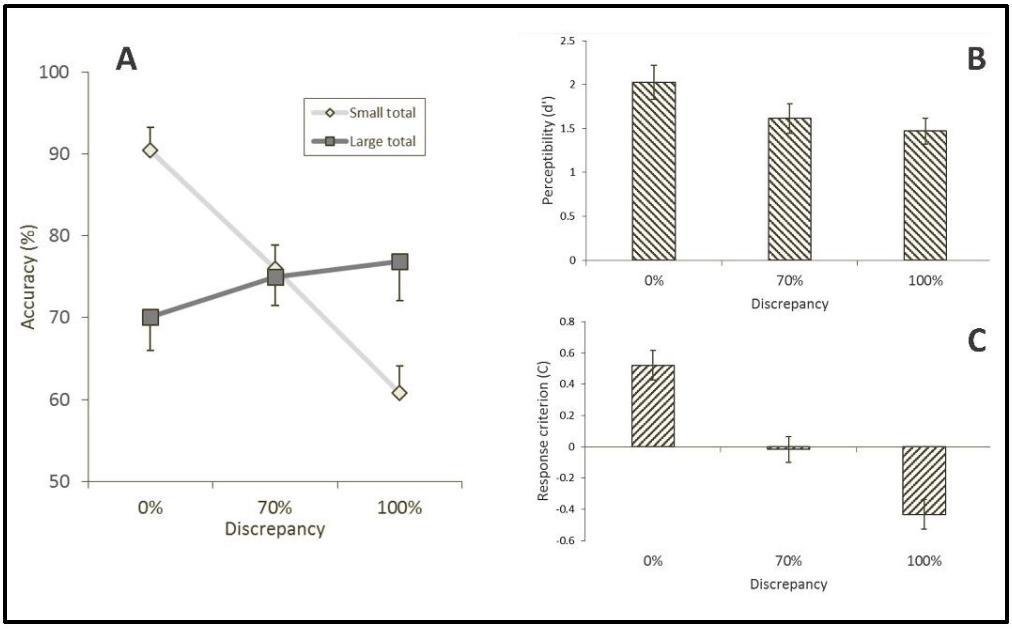


Figure 3.5. Accuracy, sensitivity, and bias along discrepancy in Experiment 2.

A. Participants' accuracy decreased with discrepancy when the discrepant pair had a smaller total intensity, but not when the discrepant stimulus had a greater total intensity. Both sensitivity (B) and criterion (C) were significantly modulated by the discrepancy between the two simultaneous stimuli in the pair. Error bars show standard error of the mean.

Secondly, we run another one-way (Discrepancy: 0%, 70%, and 100%) repeated measures ANOVA on the C values to test if participants' criterion also varied along discrepancy. Again analysis were Greenhouse-Geisser corrected. The effect of Discrepancy was highly significant ($F_{1.317, 25.021} = 60.907$, $p < 0.001$; η2 = 0.762). All the paired sample t-tests contrasts were highly significant ($p < 0.001$ in all comparison), showing that participants' criterion became significantly more liberal (i.e. higher number of "large" responses) passing from the 0% discrepancy condition (mean ± SD: 0.522 ± 0.42) to the 70% (mean ± SD: -0.17 ± 0.38) and the 100% (mean ± SD: -0.432 ± 0.42) discrepancy condition (see Figure 3.5C). Thus, as discrepancy between the two single intensities increased, the sensory perceptibility of the total intensity decreased and participants tended to judge every stimulation as a large total (i.e. overestimated the total), regardless of its actual overall physical intensity.

3.3.3 Experiment 3

Perceived intensity of discrepant and non-discrepant double tactile stimulations

First, as a sanity check, we tested whether the average of the three last reversal differed between low- and high-starting staircases. Paired t-tests analysis showed no statistical difference between this measurements ($p > 0.110$ in all comparisons), confirming a good convergence of the two staircases.

Hence, the values from ascending and descending staircases were averaged together and introduced in a 2 (Stimulation: single/double) x 2 (Intensity: small/large) repeated measures ANOVA to evaluate any difference in perceived intensity among conditions. We found a significant main effect of Intensity ($F_{1, 9} = 10.638$, $p = 0.010$; $\eta 2 = 0.542$), but no effect of Stimulation ($F_{1, 9} = 1.758$, $p = 0.218$) nor interaction between the factors ($F_{1, 9} = 0.468$, $p = 0.511$). In particular, regardless of the number of fingers stimulated, participants reported a higher perceived total intensity when a large stimulus was present in the stimulation (mean ± SD: 6.464 ± 2.04) compared to when the single or double stimulation was composed by the small stimulus/i (mean ± SD: 5.738 ± 1.98) (Figure 3.6). Therefore, when participants judged the total intensity of a double discrepant stimulation, their response was strongly biased towards the more salient stimulus of the pair, rather than relying on the total physical intensity actually delivered.

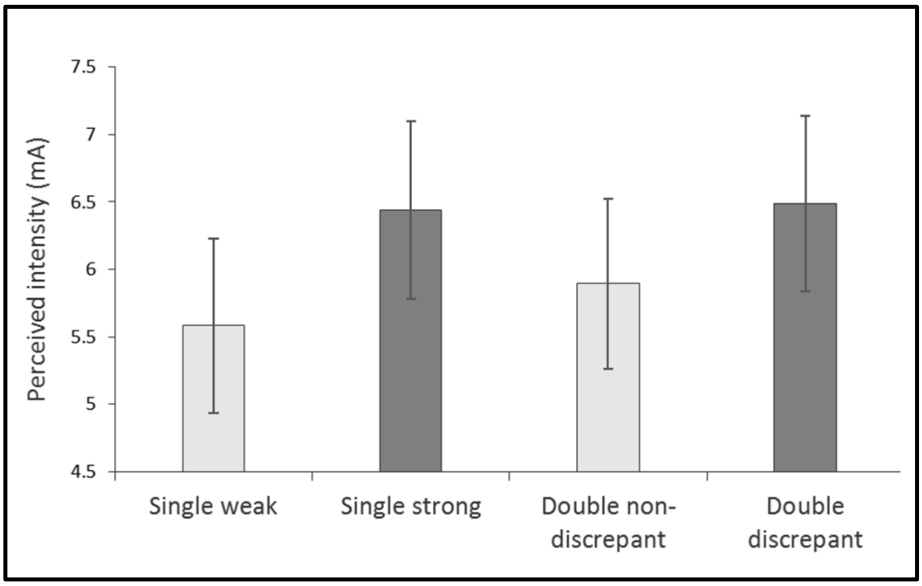


Figure 3.6. Perceived intensity among conditions in Experiment 3.

Participants perceived a higher total intensity when a large stimulus was present in the stimulation, compared to when the single or double stimulation was composed by the small stimulus/I, suggesting that the perception of double discrepant stimulation is strongly biased towards the more salient stimulus of the pair.

3.4 Discussion

The somatosensory system is constantly bombarded by a huge amount of information from the surrounding environment. Events reaching the receptors on the skin are generally multiple, simultaneous, and characterised by different levels of intensity. While psychology of perception has classically studied touch through the presentation of artificially isolated stimuli, here we investigated the process of somatosensory integration of double electro-tactile stimuli. Here, across three experiments, we confirmed and extended previous observations of nonlinear aggregation of multiple tactile stimulus intensities. First, the intensity of each single stimulus in a pair can be correctly estimated and can constitute a reliable information to be used for later stages of the processing (Experiment 1, catch trials). Importantly, the process of aggregation is not subordinate to the discrimination of events discrepancy, suggesting that salience is extrapolated via an automatic process which directly derive from stimulus intensity (Experiment 1, main trials). Second, when the discrepancy in intensity between two stimuli increases, participants' sensitivity to overall intensity decreases and their response criterion shifts toward a higher probability of "large" responses (Experiment 2). Finally, discrepant stimulations are perceived as stronger than equally intense non-discrepant stimuli, and the perception of total intensity of multiple stimulations strongly relies on the intensity of the most salient stimulus in the pattern (Experiment 3).

Single intensity detection

Results from catch trials in Experiment 1 clearly showed that regardless of the task performed, the magnitude of each single event was always correctly estimated. This finding indicates that judging the properties of the whole percept (either overall intensity or overall discrepancy) did not affect perception and retrieval of information about each single part. This is in evident contrast with previous reports about holistic perception in other sensory modalities. Poljac and colleagues (2012) demonstrated that the ability to detect colour changes in a pattern of scrambled dots dramatically drops when the dots can be integrated into a meaningful Gestalt, suggesting that the construction of a visual whole comes at the cost of reduced accessibility to information about its constituent parts. Moreover, Mathis and Kahan (2014) reported that holistic perception of Kanizsa figures reduces the identification of local-level elements such as edges. Similarly, studies on acoustic perception (Wile and Balaban, 2007; Schneider and Wengenroth, 2009) suggest that the perception of a holistic virtual pitch (an illusory tone derived by the nonlinear integration of multiple simultaneous pure tones) prevents the detection of changes in some of its components, giving rise to several illusory phenomena such as the *Shepard scale illusion* (Shepard, 1964), the *phantom fundamental* (Turner, 1977), and the *tritone paradox* (Deutsch, 1986). Although still in debate (Nelson, 1993; Cacciamani, Ayars, and Peterson, 2014), these findings are often quoted as evidence that when integral dimensions are processed as a whole, awareness of the constituent parts is reduced.

While increasing evidence suggests that grouping of multiple stimuli in a unitary Gestalt does also occur for somatosensory stimuli (Kitagawa et al., 2009; Chang et al., 2007; Carter et al., 2008; Serino et al., 2008; for a review see Gallace and Spence, 2011), the effect of judging the properties of a tactile whole on the perception of each part has not been directly investigated yet. In the catch trials of our Experiment 1, we unpredictably asked participants to report the intensity of a single event, while they were intent in a main task which required a holistic perception of multiple stimuli (overall intensity or overall discrepancy). If the effects described above for other modalities also occurred in the somatosensory system, grouping the events in a unitary percept in order to compare the pairs along integral dimensions such as intensity or discrepancy should have produced the loss of specific information regarding each stimulus. The absence of any main effect of task or interaction, and the accuracy in magnitude estimations showed by participants in Experiment 1 demonstrates that information about the single parts was not affected by the holistic judgements required by the tasks.

A crucial difference between our paradigm and previous studies about whole/part perception is that we asked participants to either judge single *or* total intensities in separate trials, rather than inquiring them about the intensity of the parts straight after the judgement on the total was made. This might have potentially brought to a situation in which participants switched very rapidly from a “holistic mode” to an “analytic mode” (Foard, and Nelson, 1984), instead of processing the two information in parallel. However, such a possibility seems unlikely for at least two reasons. Firstly, catch trials in Experiment 1 occurred in a completely unpredictable way and were rarer than main trials, where participants made judgements on the overall percept. A strategy based on attending both tasks simultaneously would have been overly effortful, and therefore it seems reasonable to think that participants kept a “holistic mode” throughout all the block. Moreover, studies using the *global-local task* in visual perception (Navon, 1977; Kimchi, 1992; for a review, see

Kimchi, 2015) show that global features have precedence over local features, such that perception of the whole usually recruits attentional resources more readily and automatically than perception of constituent parts (but see also Davidoff et al., 2008). Thus, our results show that the intensity of single touches in a pattern can be successfully retrieved in spite of the fact that attention is oriented towards the global characteristics of the percept, suggesting that the somatosensory system may be exempt from the global interference observed in other sensory modalities.

Crucially, another relevant implication of this observation is that the intensity of each single event in a double simultaneous stimulation is fully accessible and hence it could be used as a reliable input for further computations, namely, to compute the salience of each stimulus in the pair and assign weights accordingly. This, in turn, can provide support to the hypothesis suggested by Walsh and colleagues (2016) that nonlinear effects responsible for biased aggregation are based on the salience of each stimulus in the pattern.

Aggregation vs discrimination of double simultaneous stimulation

In the main task of Experiment 1 we asked participants to judge either the overall intensity or the overall discrepancy of double discrepant and non-discrepant stimulation. Our purpose was to compare participants' performance in each task to infer the nature of the processes underlying aggregation of multiple simultaneous inputs. Perception of total intensity could in fact rely on two alternative processes. One possibility is that aggregation is simply based on the identification and the *relative discrimination* of each single event in the pattern. Conversely, totalling of intensity could rely on an automatic module, independent from the precise differentiation between single events, and directly based, instead, on the salience of each stimulus.

Catch trials from Experiment 1 showed that information about single intensities is available, therefore, a comparator should be able to calculate the discrepancy between one stimulus and another (dashed lines in Figure 3.7). Consequently, the differential values obtained from the comparison between an event and the other could constitute the basis for the relative weighing of the stimulus itself for the successive summation. Crucially, this model implies that the differential value from each possible combination of two inputs in a multiple stimulation, is fully processed and, therefore, available. However, the results from the discrimination block in Experiment 1 show that participants' performance was surprisingly poor in judging which of two consecutive pairs had the largest amount of discrepancy between the single events composing it, suggesting that such information was in fact lacking or inaccessible to awareness. Total intensity can be perceived even when the single parts that compose it cannot be easily separated and discriminated. Another possibility is that the discrimination of single events is in fact possible, but the comparison between the differential values from two pair instead is not. Yet, such explanation seems unlikely. If the relative difference between the intensities of the two single events is the signal for the following weighing of each stimulus itself, then the system should also be able to determine and indicate in which of the two consecutive pairs the process resulted in the highest discrepancy.

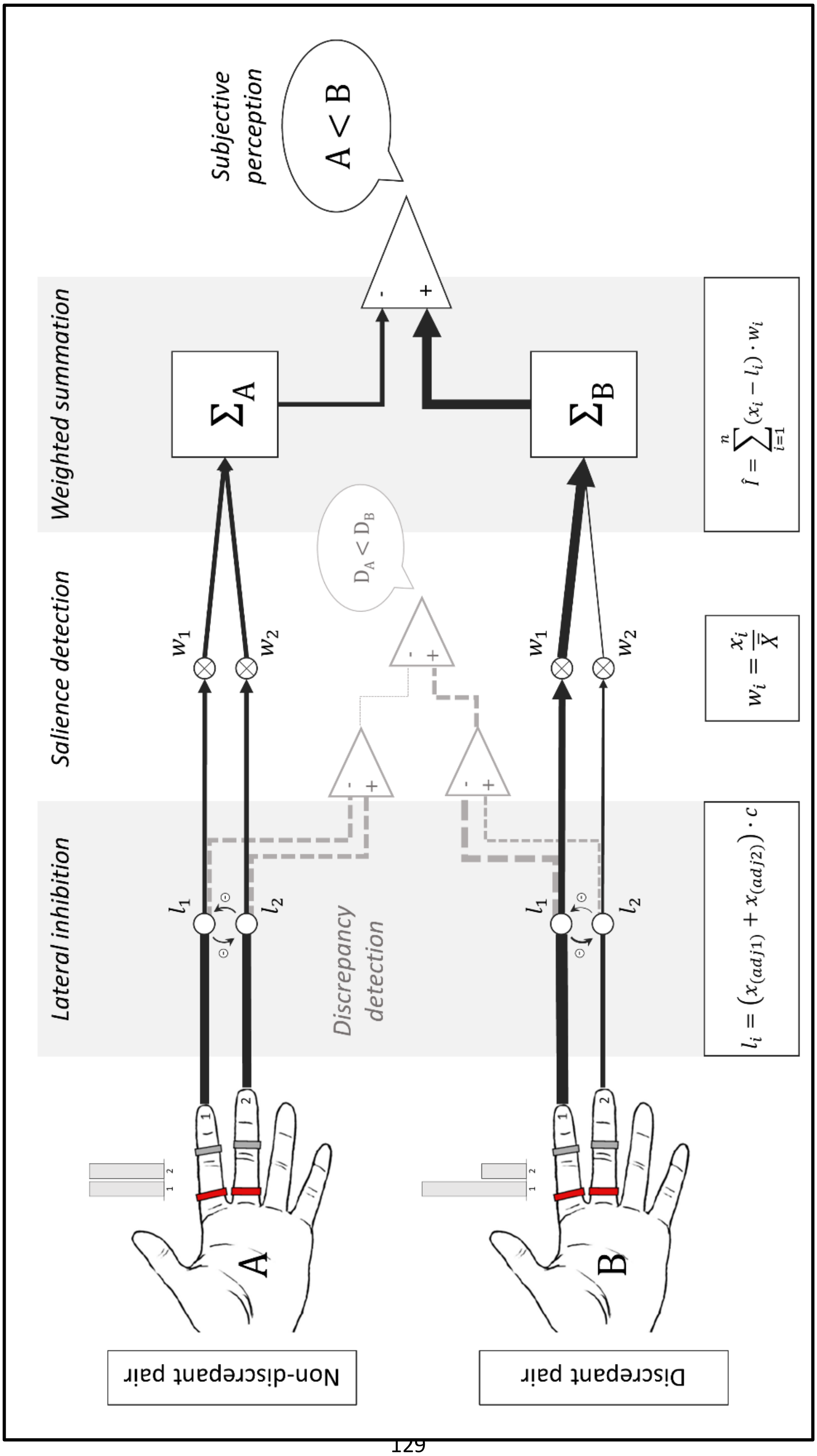

Non-discrepant pair
Discrepant pair
A
B
1
2
Lateral inhibition
l_1
l_2
Discrepancy detection
Salience detection
w_1
w_2
$D_A < D_B$
Weighted summation
Σ_A
Σ_B
Subjective perception
A < B
$l_i = \left(x_{(adj1)} + x_{(adj2)}\right) \cdot c$
$w_i = \frac{x_i}{\overline{X}}$
$\hat{I} = \sum_{i=1}^{n} (x_i - l_i) \cdot w_i$

Figure 3.7. Putative model of somatosensory summation of multiple discrepant and non-discrepant stimuli.

A. When non-discrepant multiple simultaneous somatosensory stimuli are aggregated in a total percept, the physical intensity delivered to each finger is first reduced by lateral inhibition (top left of the scheme). At this stage, the intensity of each stimulus is retrievable. Since salience in this condition (i.e. signal-to-noise ratio) is equal among the stimuli, the weight assigned to each of them is 1 (top centre of the scheme), and the weighted summation of the events only reflects the sub-additive effect of lateral inhibition (top right of the scheme). B. Multiple discrepant stimuli are also subject to lateral inhibition from the adjacent fingers. However, the amount of lateral inhibition is different among the stimuli, with the weak stimuli producing less inhibition of the strong stimuli (bottom left of the scheme). Single stimulus intensity of discrepant patterns after lateral inhibition also is accessible. Since the strong stimulus is larger than the average intensity of the multiple stimulation, its signal-to-noise ratio is detected as salience. Thus, the weight assigned to the strong stimulus is > 1, while, the weight of the weak stimuli is < 1 (bottom centre of the scheme). Therefore, the weighted summation of the discrepant pair is biased towards the strong stimulus in the pattern (bottom right of the scheme). As an output of the system, the comparison between equally-intense non-discrepant and discrepant pairs produce an overestimation of the discrepant pattern, driven by the salience of the strongest stimulus (far right of the scheme). The grey dashed lines (middle of the scheme) represent a hypothetical mechanism based on the detection of the discrepancy between each stimulus in a pattern. Such a process would require correct perception of the relative difference between each simultaneous stimulus first, and then among non-discrepant and non-discrepant pairs. However, our data rule out the existence of such a mechanism, as participants' accuracy in judging the total intensity of a tactile pattern, in Experiment 1, was significantly higher than that showed in judging the total discrepancy of the same pattern.

Lastly, memory for somatosensory stimuli is reportedly very short, lasting for about 700 ms (Harris et al., 2002). Since in the two alternative forced choices paradigm used in Experiment 1 there was one second interval between the first and the second pair of stimuli, one may argue that an alternative explanation for the scarce accuracy discrepancy detection might be ascribed to limited mnemonic resources. Although we cannot entirely exclude this possibility, it is important to note that the same delay was present in the aggregation block, where participants showed an accurate performance, making it difficult to support this hypothesis.

Therefore, the weighted summation of multiple inputs must be computed through perceptual mechanisms which are independent from the simple difference between stimuli, but yet related to their physical intensity.

Mechanisms underlying overestimation of multiple discrepant stimuli

Our findings from Experiment 2 and 3, in line with those from Walsh and colleagues' (2016), show that aggregation of multiple somatosensory intensities leads to an inaccurate subjective perception, where the total intensity of discrepant stimulation is overestimated. After ruling out explanations based on lateral inhibition and filling-in, Walsh and colleagues proposed that the overestimation of discrepant intensities is due to a perceptual peak bias, driven by stimulus salience. However, the mechanisms underlying the detection of salience and the subsequent weighted summation are still unclear.

One first question one may ask is whether such phenomenon represents a genuine perceptual process or a cognitive bias. That is, does overestimation of discrepant intensities reflect an inherent property of the somatosensory system, or it is, rather, a later, heuristic cognitive process which affects participants' reports of a correctly-processed information?

Peak-biased judgements have been described by social, affective, and cognitive psychology for a variety of situations, ranging from satisfaction ratings of simulated queues (Carmon and Kahneman, 1996), to recalling of baseball matches (Morewedge, Gilber, and Wilson, 2005) or vacations (Kemp, Burt, and Furneaux, 2008), judgements about business interactions (Miron-Shatz, 2009), and evaluation and memory of painful experiences (Kahneman, Fredrickson, Schreiber, and Redelmeier, 1993; Redelmeier and Kahneman, 1996). Therefore, it is extremely important to disentangle whether the overestimation of non-painful electro-tactile stimulations described here represents the extension of such a kind of heuristics to perceptual content, or, instead, it is a completely novel sensory mechanism showing some sort of super-additive processes occurring along the somatosensory pathway.

Results from our Experiment 2 provide a clear answer to this question. We used a well-established paradigm designed to set apart the genuine perceptibility of a given stimulation and the response style adopted by the individual (Green and Sweets, 1996). We found that as the discrepancy between the two stimuli increased, participants' sensitivity to overall intensity significantly dropped, showing nonlinear summation of multiple intensities. That is, participants indeed experienced discrepant stimulations as a different percept during, perceiving them as larger than non-discrepant pairs. Interestingly, the decrease in d' was mimicked by a significant change in response criterion, suggesting that when the discriminability of large/small totals was degraded by the increase in discrepancy, participants adopted a more liberal response style, increasing the probability to say that the stimulation has a "large" intensity.

The result about participants' chance in sensitivity is straightforward. Psychophysical conceptualisation of signal detection theory classically holds that if the effect of an experimental manipulation is truly perceptual, then it will necessarily be reflected in a change in d′ rather than a change in the measure of response bias (Witt, Taylor, Sugovic, and Wixted, 2015; Green and Swets, 1966; Tanner and Swets, 1954). However, a significant change in participants' bias does not necessarily means that the studied effect is cognitive in nature. In fact, as reported by Witt and colleagues (2015), in discrimination experiments such as our Experiment 2, signal detection theory cannot by itself determine the underlying source of the bias, be it perceptual or response based. Therefore, the change in participants' criterion in our experiment can perhaps give an insight on the direction of their perceptual experience: at increasing levels of discrepancy, all the presented stimulations – even the physically small totals – felt large, i.e. were overestimated.

Thus, although Experiment 2 suggests that overestimation of discrepant intensities depends on a genuine perceptual process, it remains to determine what kind of sensory mechanism could lead to such super-additive effect. In fact, the nonlinear interactions among multiple unimodal stimuli traditionally described in the literature refers to sub-additive phenomena, mainly linked to lateral inhibition. Lateral inhibition refers to the suppression of the activity of a sensory receptor produced by a concurrent stimulation occurring in the peripheral area of the same receptive field (DiCarlo, Johnson and Hsiao, 1998; DiCarlo, and Johnson, 1999, 2000). Although, lateral inhibition is likely to occur in our task, where adjacent fingers were simultaneously stimulated, it cannot explain results about the overestimation bias (see Walsh, Critchlow, Beck, Cataldo, de Boer, and Haggard, 2016), and further processes on top of it need to be identified.

Figure 3.7 schematically depicts a scenario in which, as in our tasks, the somatosensory system has to compare the total intensity of two different tactile patterns. Crucially, the overall physical intensity of the two pairs is equal, and only its distribution among the fingers varies, providing non-discrepant or discrepant conditions. When two simultaneous stimuli (*x1* and *x2*) are delivered on adjacent fingers, lateral inhibition will produce mutual reduction of both signals. A very simple way to describe this is

$$l_i = \left(x_{adj1} + x_{adj2}\right) \cdot c$$

where, for each stimulus, the physical intensity delivered to the adjacent fingers is multiplied to a constant value (*c*). Noticeably, in the case of the non-discrepant double stimulation, the amount of lateral inhibition will be equal for both stimuli, while in the case of the discrepant pair, the stronger stimulus will produce a stronger inhibition on – and will be less inhibited by – the weaker stimulus, enhancing the difference between the two intensities. Catch trials from Experiment 1 showed that, at this stage, the intensity of each event in the discrepant pair can be correctly detected and reported. Conversely, *discrepancy discrimination* between two simultaneous stimuli (grey dashed lines) is profoundly limited, laying just above the chance level, as showed by the main trials in Experiment 1. Furthermore, results about the comparison between the single weak stimulus and the double non discrepant pair in Experiment 3 are informative about the amount of lateral inhibition taking place in our task. We found that the perceived intensity of a non-discrepant double electro-tactile stimulation was only slightly larger than the perception produced by only one of the events composing it, and that this difference was not statistically significant. This suggests that lateral inhibition in our experiments was strong, attesting that a value of c was around 0.4-0.5.

The second stage of the process would require that the *salience* of each stimulus is detected and used for the weighted summation. Again, the main finding from Experiment 1 suggests that the simple relative difference between the intensity of each stimulus in the pair cannot be used at this stage as a valid salience signal, because it is inaccurate. Moreover, in line with Walsh et al.'s hypothesis, Experiment 3 shows that salience is strongly related to the physical intensity of the strongest stimulus in a patter. Indeed, the comparison between the perceived intensity of the single strong stimulus and the double discrepant pair d not differed significantly. Although, of course, absence of evidence does not constitute evidence of absence, and caution must be taken in interpreting null results, it seems at least quite remarkable that presenting a stimulus along with another amounting to almost 50% of its intensity did not produce a clear difference with the perceived intensity of the first stimulus alone.

A possible explanation of such results is that, after lateral inhibition, salience (w_i) is calculated in function of the signal-to-noise ratio between each single event and the average intensity of all the concurrent stimulations:

$$w_i = \frac{x_i}{\bar{X}}$$

Our skin, in fact, is continuously bombarded by an enormous amount of simultaneous information (e.g. the pressure from a chair, our clothes, one leg crossed over the other, etc.), and, therefore, a salient information (e.g. a colleague touching our shoulder) can be reasonably defined as that signal that stands out of the average intensity formed by the other concurrent, irrelevant, stimulations (noise). From such a definition it derives that, in the case of the non-discrepant pair, the weighting factor for each stimulus will obviously be always one, and, therefore, the summation of the two intensities can be computed without further adjustments. Crucially, in the case of the discrepant pair, instead, the stronger stimulus, being larger than the average of the double stimulation (i.e. more salient), will receive a weight bigger than one, leading to a boosting of its own intensity which will then bias the perception of the whole percept.

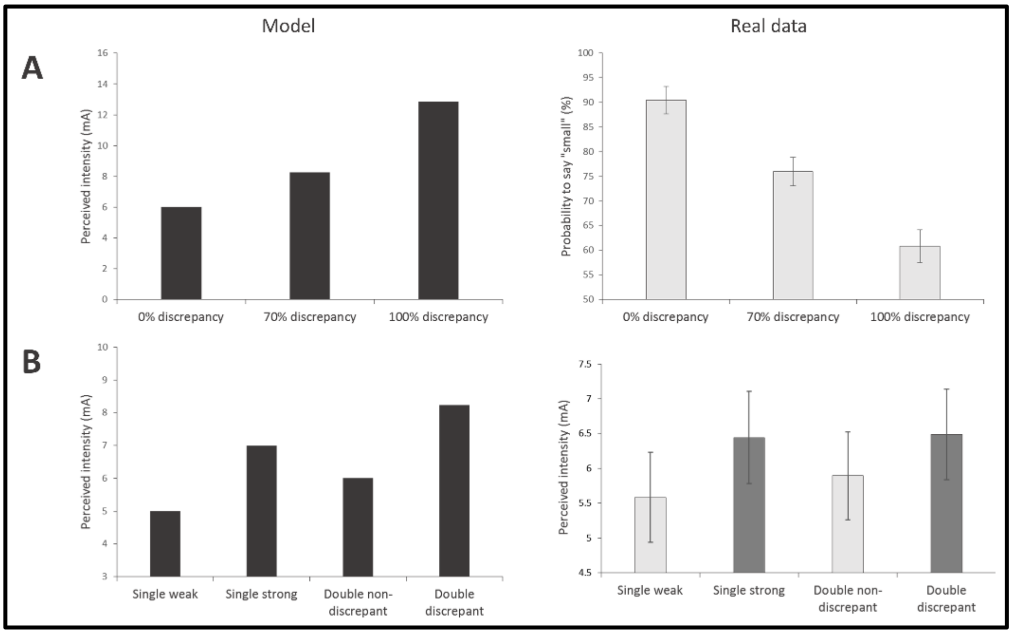


Figure 3.8. Comparison between the results predicted by the model and real data from Experiment 2 and Experiment 3.

A. Our model (top left) predicts that the perceived total intensity of double simultaneous stimulations is overestimated as the discrepancy between the two stimuli increases. In line with this prediction, data from our Experiment 2 (top right: average accuracy for both large and small totals) show that the probability to say “small” decreases as the discrepancy increases. B. The model (bottom left) also predicts that, because of lateral inhibition, non-discrepant double simultaneous stimuli are perceived just slightly bigger than each single stimulus composing it, and that, similarly, discrepant pairs are perceived just slightly bigger than the single strong stimulus in the pattern. Real data from our Experiment 3 (bottom right) confirm such prediction.

Finally, in a third stage, the estimation of the overall intensity of each pair can be computed according to:

$$\hat{I} = \sum_{i=1}^{n} (x_i - l_i) \cdot w_i$$

where the physical intensity of each event – net of lateral inhibition – is multiplied by its weight and summed up in the total percept.

Figure 3.8 shows, for speculative purposes, a comparison between the data derived by this model and the real data from our Experiment 2 and 3.

Conclusion

The present work investigated several different aspects of the processes underlying the perception of multiple discrepant simultaneous stimulations. Such kind of stimuli constitutes the rule, rather than the exception, of our daily interactions with the environment, and yet, to our knowledge this is one of the very first attempt of a systematic exploration of the mechanisms behind the integration of discrepant intensities in a single percept.

Across three experiments, we demonstrated that the presence of a stronger stimulus in a somatosensory pattern bias the perception of the total intensity of the pattern itself, confirming previous results from Walsh and colleagues (2016). Such bias results in a systematic overestimation of discrepant compared to non-discrepant stimulations. Crucially, this overestimation bias is a perceptual, rather than a cognitive phenomenon, and is based on processes which are independent from the aware detection of the discrepancy among the stimuli. Weighted summation of somatosensory intensities may depend on the physical intensity of each event, lateral inhibition, and perceptual salience, expressed by the signal-to-noise ratio between each stimulus and the average of all the simultaneous stimulations occurring at a given time. Finally, we proposed a simple model that can explain these findings all together, casting a light on the somatosensory integration of multiple discrepant inputs.

Chapter 4.

Thermal referral: evidence for a thermoceptive uniformity illusion without touch

Synopsis:

This Chapter presents a study on the spatial integration of multiple thermo-tactile and purely thermal stimuli, as it appears on *Scientific Reports* (Cataldo et al., 2016). We studied an illusion called thermal referral, where applying thermal stimuli on the ring and index fingers of one hand induces an illusory thermal sensation also on the middle finger. This illusion has been classically considered the result of cross-modal thermo-tactile interaction, reflecting a process of object recognition. In support of this interpretation, the illusion was reported to disappear when the middle digit was lifted off the thermal stimulator, suggesting that tactile stimulation is necessary. However, no study has investigated whether purely thermal stimulation might induce thermal referral, without any tactile object to which temperature can be attributed. We used radiant thermal stimulation to deliver purely thermal stimuli, which either were or were not accompanied by simultaneous touch. We found identical thermal referral effects in both the original thermo-tactile condition, and in a purely thermoceptive condition where no tactile object was present, suggesting that thermal referral could reflect low-level organization of the thermoceptive pathway, rather than a cognitive intermodal modulation based on tactile object perception.

4.1 Introduction

The somatosensory system comprises several sub-modalities, based on distinct peripheral receptor types. Sub-modality specificity is preserved in peripheral afferent fibres. However, complex central interactions between sub-modalities also occur, first within the spinal cord and then in the brain (Abraira and Ginty, 2013). Here we focus on interactions between touch and temperature. This interaction remains controversial because these sub-modalities have distinct cortical targets (primary somatosensory cortex and insula, respectively; Craig, Chen, Bandy, and Reiman, 2000), yet the perception of touch and temperature are strongly interdependent (Weber, 1996; Green, 1977; Ho, Watanabe, Ando, and Kashino, 2011). Indeed, somatic experiences often have a unitary thermo-tactile quality suggesting an obligatory cross-modal interaction: while holding a hot cup of tea, it is impossible to dissociate perceptually the touch of the cup from the warm sensation.

The Thermal Referral (TR) phenomenon is a striking demonstration of this thermo-tactile interaction (Green, 1977; Ho, Watanabe, Ando, and Kashino, 2011; Green, 1978). When innocuous warm thermal stimulators were applied to the ring and index fingertips of one hand, and a neutral-temperature stimulator to the middle finger, all three fingers felt warm. That is, the thermal sensation at the outer fingers was referred to the middle finger. Similar TR phenomena were found for cold stimuli. As a consequence, a pattern of physical stimulation that was tactually uniform, but thermally non-uniform, was illusorily perceived as thermally uniform (Ho, Watanabe, Ando, and Kashino, 2011). At the same time, the perceived overall intensity was reduced, relative to a condition where all three fingers were actually stimulated (Ho, Watanabe, Ando, and Kashino, 2011). According to a classic account of TR, the tactile system signals homogeneity, because the mechanical contact of finger and stimulator is common to all three fingers, while the peripheral thermal system signals heterogeneity, with different temperatures at each finger. In integrating these signals to provide a multisensory percept of the thermo-tactile object, tactile information is given a higher weighting than thermal information, so thermal signals specific to each finger are lost to perception (Green, 1977; Ho, Watanabe, Ando, and Kashino, 2011; Green, 1978). Ho and colleagues (Ho, Watanabe, Ando, and Kashino, 2011) recently proposed an account based on serial processing, rather than an integration of parallel temperature and touch signals. At a first stage, spatial summation (Hardy and Oppel, 1937; Stevens and Marks, 1971) tends to homogenize thermal percepts across multiple stimulated areas, producing an overall intensity percept proportional to the stimulated area. At a second stage, this intensity is then referred or attributed, on the basis of touch, to individual body parts. On this view, TR is a cross-modal phenomenon, in which tactile input on the middle finger drives the illusory perception of warmth.

Strong evidence for the role of touch in TR comes from reports that illusory thermal sensations disappeared when the middle digit was lifted off the thermal stimulator (Green, 1977). The actual state of the middle finger was thermally neutral with and without tactile contact, but the perceived temperature was warm during tactile contact, and thermally neutral without it. This result also seems to rule out explanations based merely on strong spatial summation within the thermoceptive system, since summation should ensure a continued perception of warmth, perhaps with some modest decrease depending on the strength of summation. These results suggested that tactile information is essential for TR.

However, to our knowledge, no study has tested whether purely thermal stimulation, without any tactile stimulation at all, can also induce TR. An affirmative result would cast doubt on the standard interpretation of TR as a cross-modal perceptual illusion driven by tactual object perception, and point instead to spatial interactions within the thermoceptive system. We accordingly developed a novel radiant thermal apparatus that allowed us to deliver either thermo-tactile or purely thermal stimuli. We replicated classical TR results regarding uniformity (experiment 1) and intensity of thermal perception (experiment 2) in a thermo-tactile condition. Crucially, we observed a purely thermoceptive version of TR in the absence of any tactile stimulation, which reproduced the features previously described for classical thermo-tactile TR. We also demonstrated that the thermoceptive version of TR cannot merely ascribed to poor thermal resolution (experiment 3).

4.2 Methods

Participants

Thirteen healthy right-handed participants (10 female, mean age ± SD: 23.8 ± 3.1 years) took part in experiment 1. One participant was excluded because of inability to follow instructions (see below). A group of twelve new participants volunteered in experiment 2 (10 female, mean age ± SD: 24.6 ± 3.9 years), and a further twelve new participants (9 female, mean age ± SD: 25.4 ± 5 years) volunteered in experiment 3. The sample size for each experiment (n = 12) was decided a priori on the basis of previous similar studies. The experimental protocol was approved by the research ethics committee of University College London. The study adhered to the ethical standards of the Declaration of Helsinki. All participants provided their written informed consent before the beginning of each experiment.

Radiant Thermal Stimulation

Figure 1 illustrates the experimental set-up used in the three experiments. Thermal radiant stimuli were delivered by a 125 mm diameter, 250 watt infrared light bulb. Three different stimulation intensities were delivered, by connecting the bulb to one of three dimmer. The switches were set at 0% (no stimulation), 40% (low intensity), and 100% (high intensity) of their range, respectively, and were not further adjusted during the experiment. These non-zero intensities were selected to produce transient increases in skin temperature that were higher than the thermal detection threshold of the hand (i.e., >1 °C; Stevens and Choo, 1998), lower than pain threshold (Hardy, Wolff, and Goodell, 1952; Harrison and Davis, 1999), but readily discriminable between all three levels. The participant's right hand was placed 11 cm above the infrared source, pronated on a moulded support. This support left the intermediate and distal phalanges of the index, middle and ring fingers exposed, while shielding the rest of the hand. In particular, the support blocked the radiant heat from reaching the thumb and the little finger. Two layers of 2 mm of thickness crystal glass were placed between the hand and the source. This allowed thermal radiant stimulation of the fingers, while isolating the fingers from potential air convection surrounding the infrared source. The upper glass was replaced after each trial to prevent it from overheating, and becoming an additional source. In the thermo-tactile condition, the upper glass sheet was raised until it contacted the glabrous skin of the index, middle and ring fingers, creating a 3 mm gap between the glasses, and providing further thermal isolation. To generate the neutral middle finger temperatures associated with TR, we placed a 4 × 12 cm aluminium shade between the two layers of glass, thus casting a heat shadow over the middle finger. Additional vertical aluminium spacers between index and middle fingers, and between middle and ring fingers prevented any radiant heat stimulation of the middle finger from above the upper glass. Accurate stimulus delivery was validated by measuring actual skin temperature in each condition of each experiment with a spot infrared thermometer (Precision Gold, N85FR Maplin, UK) (see below). We additionally used an infrared thermal camera (FLIR Silver SC5000 MWIR, FLIR systems, Oregon, USA) to quantify the effects of our thermal stimulation in one participant (who did not take part in any other experiment). The analyses focused on the spatial specificity of thermal stimulation, and its profile over time. These images confirmed that our apparatus could selectively warm some fingers, without inducing any substantial temperature changes of other adjacent fingers that were shielded from the radiant heat source (see Figure 2 for details).

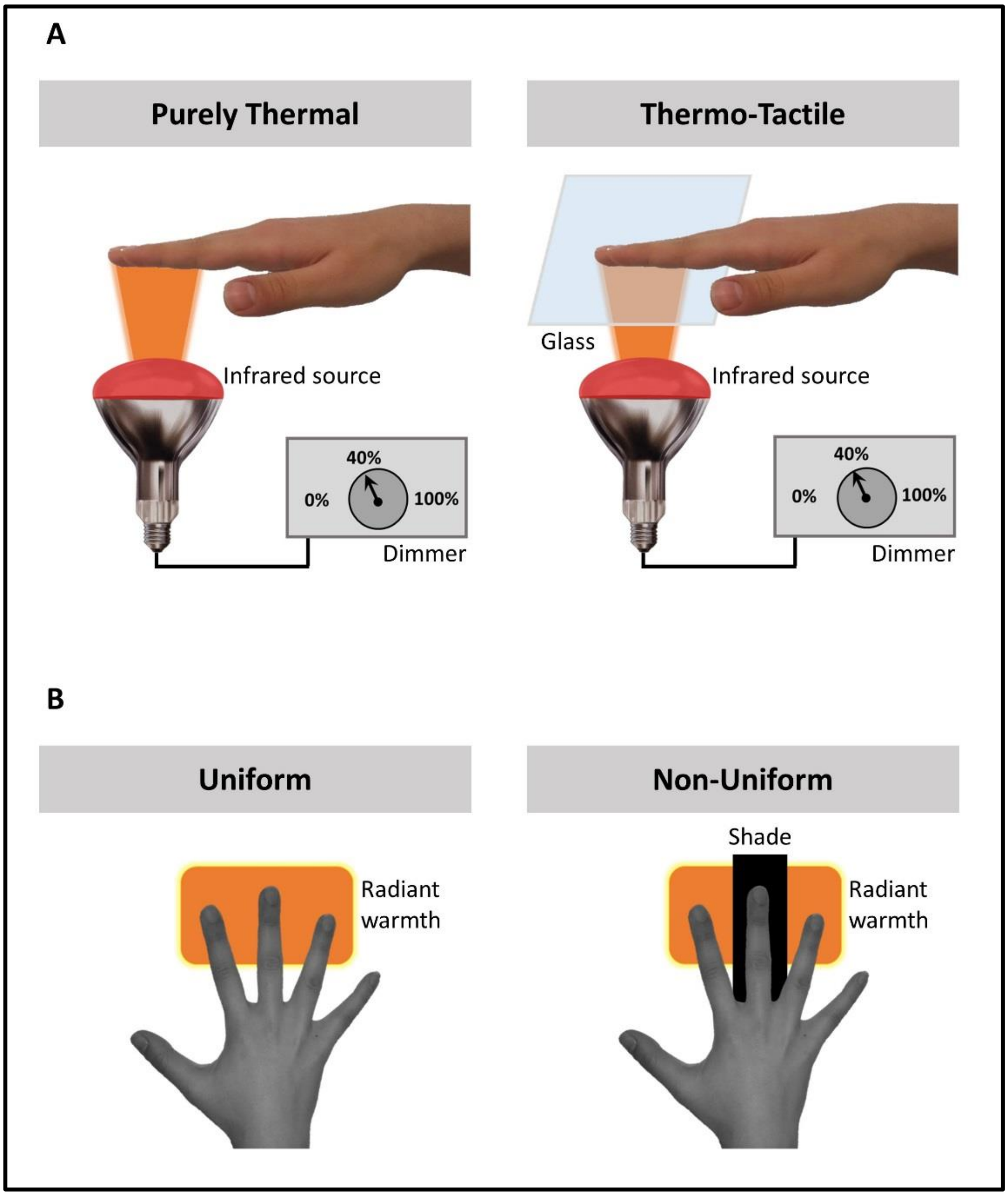


Figure 4.1. Experimental set up and conditions.

A. Thermal radiant stimuli were delivered by a 125 mm diameter, 250 watt infrared light bulb using three different stimulation intensities by connecting the bulb to one of three dimmer switches preset at 0% (no stimulation), 40% (low intensity), and 100% (high intensity). The participant's right hand rested above the infrared source. Intermediate and distal phalanges of the index, middle and ring fingers were exposed to the thermal stimulation. In the thermo-tactile condition, the fingers rested on a sheet of glass. B. To generate the non-uniform condition, an aluminium shade was placed between lamp and middle finger, to cast a heat shadow over the middle finger.

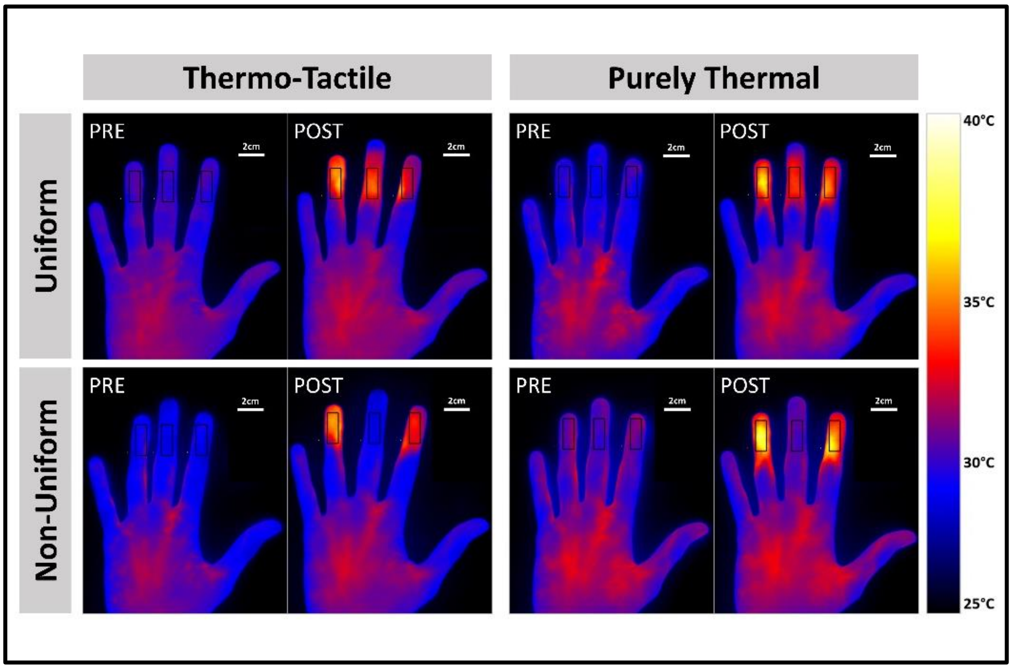


Figure 4.2. Thermographic images.

Thermal infrared imaging data recorded in a participant. A thermographic camera was used to film the entire experimental procedure. Two single frames were extracted, depicting the thermal profile of the hand immediately before and after warm radiant stimulation. A region of interest corresponding to the area of the skin exposed to the stimulation was marked on each finger. The change in temperature for each experimental condition was computed as the difference between post- and pre-stimulation mean temperature within each region of interest. Uniform pattern of stimulation (top row) induced an overall increase in temperature in all finger, with no differences between the middle finger and the outer fingers (middle: 4°C; outer fingers: 3.8°C, tactile conditions averaged). Conversely, the non-uniform warm-neutral-warm patter (bottom row) triggered a selective increase in temperature in the outer fingers, while the temperature of the shaded middle finger did not change (middle: 0.1°C; outer fingers: 4.5°C, tactile conditions averaged).

4.2.1 Experiment 1

Individual finger temperature perception task

Each participant completed two different tasks in a fixed order. The first task was a thermal perception task, which served both as a validation of the stimulation method and as perceptual calibration of thermoception on each finger. The second task aimed to replicate Ho and colleagues (2011) uniformity judgement method for investigating TR (see later).

One of three thermal radiant stimulation intensities (no stimulation, low intensity, high intensity) was delivered to the index, middle or ring finger of the right hand, in both a thermo-tactile and a purely thermal condition. At the beginning of each trial, the participant placed his right hand for 20 seconds in a 31 °C thermostatic water bath to set skin temperature at a constant baseline level. Skin temperature was measured by an infrared thermometer, and found to conform to the intended baseline (range: 28 °C–32 °C; mean baseline temperature ± SD: 29.9 °C ± 1 °C). Next, the experimenter dried the hand quickly, and placed it on the support. Radiant thermal stimulation was delivered to the target finger for 15 seconds based on pilot tests. This duration reliably increased skin temperatures, and also produced a clear detectable warmth sensation. Importantly, the stimulation was always below pain threshold. A sound signaled the end of the stimulation, after which the participant made a verbal response and the experimenter measured again skin temperature (post-stimulation). Participants were asked to rate the intensity of the thermal stimulation from 0 (no stimulation) to 10 (very hot). One stimulation at maximum intensity was given at the beginning of the experiment, and participants were instructed that experimental stimulations would always be below this level. This gave a functional anchor for the judgement scale. Each combination of three intensities, three fingers and two tactile conditions was repeated twice, giving 36 stimulations in total. Finger stimulated and intensity of stimulation were randomized within participant, while tactile condition order was counterbalanced between participants. Participants were blindfolded for the entire duration of the task.

Thermal uniformity perception

Uniformity judgement procedure was based on previous reports (Ho, Watanabe, Ando, and Kashino, 2011) and on the stimulation methods described above. Radiant thermal stimuli were delivered on the right index, middle and ring fingers, and participants judged the uniformity of the stimulation across all three fingers, by verbally responding “uniform”/“non-uniform”. In the non-uniform condition, a shade with two vertical spacers was interposed between the infrared lamp and the middle finger, while leaving the outer fingers exposed to the infrared light. In the uniform condition, a similar object composed by the two vertical spacers only, and no shade, was placed among the fingers, in order to match any auditory cue related to the application of the shade in the non-uniform condition. The low (40% of maximum) and high (100% of maximum) stimulation intensity levels of the previous task were used. Skin temperature was also recorded pre- and post-stimulation using an infrared thermometer.

Participants were asked to report whether the stimulation was uniform across all three fingers or not. Thermo-tactile stimulation conditions, and purely thermal conditions were both tested. Intensity (low/high) and spatial pattern (uniform/non-uniform) of stimulation were randomized within participant, while the order of tactile condition (thermo-tactile/purely thermal) was blocked counterbalanced between participants. Each stimulus was repeated five times, giving a total of 40 stimulations. For the entire duration of the task participants were blindfolded.

4.2.2 Experiment 2

Thermal intensity perception

In this experiment we measured the perceived intensity of the sensation resulting from TR. Previous studies reported a decrease in the overall perceived intensity in the thermo-tactile non-uniform patterns compared to spatially uniform patterns (Ho, Watanabe, Ando, and Kashino, 2011). This decrease was used as evidence that total thermal stimulation was redistributed across relevant tactile inputs. Here we investigated whether a similar reduction in the perceived overall intensity is present in the purely thermal TR.

The intensity perception task procedure was based on previous reports (Ho, Watanabe, Ando, and Kashino, 2011) and the stimulation methods described above. We quantified intensity perception using temperature matching (Ho, Watanabe, Ando, and Kashino, 2011; Kammers, De Vignemont and Haggard, 2010). In particular, we chose matching temperature as a dependent variable, because it gives continuous, quantitative data, is commonly reported in somatosensory sensations (Hunter, Dranga, Wyk, and Dostrovsky, 2015), has been reliably used before in matching tasks (Fruhstorfer, Harju, and Lindblom, 2003), and reflects the same continuous, underlying mechanism as thermal judgement. Participants were asked to place their right hand over a support, which allowed radiant thermal stimulation of the index, middle and ring fingers. Stimulation and temperature measurement were as in experiment 1. A 13 mm diameter thermode (Physitemp Instruments Inc, NTE-2A, New Jersey, USA) was mounted on a stand touching the participant's forehead. A chinrest ensured a constant contact and pressure between the thermode and the skin. The temperature of this probe was initially set at 30 °C. After 10 seconds from the beginning of the thermal radiant stimulation, the temperature of the forehead thermode was increased at +0.5 °C/s. Participants were instructed to report by a keypress when the forehead temperature matched the perceived temperature of the three stimulated fingers of the right hand. The radiant stimulation duration was set so that this was expected to occur after approximately 15 seconds, matching the stimulation durations in experiment 1.

Intensity (low/high) and spatial pattern (uniform/non-uniform) of stimulation were randomized within participant, while the order of tactile condition (thermo-tactile/purely thermal) was counterbalanced between participants. Each stimulus was repeated five times, giving a total of 40 stimulations. For the entire duration of the task participants were blindfolded and kept their forehead in contact with the thermode.

4.2.3 Experiment 3

Thermal spatial localisation

Localisation of thermal stimuli on the skin is reported to be poor (Cain, 1973; Simmel and Shapiro, 1969). Therefore, referred sensations in our experiments might potentially be driven by mislocalisation of thermal stimuli across the fingers, rather than by TR-like mechanisms. We therefore delivered radiant heat stimuli to a single finger, and investigated participants' ability to identify the stimulated finger.

The procedure was based on methods described above. Low and high intensity purely thermal stimuli were randomly delivered to the index, middle or ring finger of participants' right hand, without any tactile stimulation. Only one finger was stimulated during each trial. Pre- and post- skin temperature for the stimulated finger was recorded. After 15 seconds of thermal stimulation, participants verbally reported which finger was stimulated. Intensity (low/high) and position (index/middle/ring) of stimulation were randomized within participants. Each stimulus was repeated five times, giving a total of 30 trials. For the entire duration of the task participants were blindfolded.

4.3 Results

4.3.1 Experiment 1

Individual finger temperature perception task

We focused on whether the thermal radiant stimulation delivered was effective and reliable. First, we checked whether the radiant thermal stimuli produced a measurable increase in skin temperature. We computed the difference between post-stimulation and pre-stimulation skin temperature, and directly compared the temperature gain for no stimulation vs low intensity, and then for low vs high intensity stimulation. Clear differences in skin temperature were found for each finger in both thermo-tactile (no stimulation vs low intensity index: $t_{11} = -11.808$, $p < 0.001$; middle: $t_{11} = -7.132$, $p < 0.001$; ring: $t_{11} = -11.874$, $p < 0.001$; low intensity vs high intensity index: $t_{11} = -10.750$, $p < 0.001$; middle: $t_{11} = -2.643$, $p = 0.023$; ring: $t_{11} = -6.524$, $p < 0.001$), and in purely thermal condition (no stimulation vs low intensity index: $t_{11} = -8.165$, $p < 0.001$; middle: $t_{11} = -9.399$, $p < 0.001$; ring: $t_{11} = -7.697$, $p < 0.001$; low intensity vs high intensity index: $t_{11} = -2.101$, $p = 0.059$; middle: $t_{11} = -3.229$, $p = 0.008$; ring: $t_{11} = -5.386$, $p < 0.001$). Thus, our stimulation intensities produced monotonic increases in the skin temperature of each finger, as expected (Table 4.1).

		Index Finger			Middle Finger			Ring Finger		
		No	Low	High	No	Low	High	No	Low	High
Skin Temperature (°C)										
Thermo-	*M*	0.07	1.55	3.20	0.39	1.65	2.07	0.10	1.80	3.01
tactile	*SD*	0.52	0.52	0.61	0.70	0.62	0.71	0.67	0.57	0.48
Purely	*M*	0.04	1.58	2.03	-0.28	1.10	1.75	0.14	1.30	2.27
Thermal	*SD*	0.61	0.57	0.65	0.66	0.59	0.68	0.80	0.63	0.37
Magnitude Estimates (from 0 to 10)										
Thermo-	*M*	0.33	2.50	5.29	0.29	2.46	4.75	0.38	1.88	5.04
tactile	*SD*	0.39	1.17	1.48	0.45	0.78	1.27	0.43	1.26	1.71
Purely	*M*	0.50	3.21	5.67	0.50	3.25	5.25	0.25	1.67	3.25
Thermal	*SD*	0.85	1.20	1.74	0.43	1.66	1.75	0.34	0.72	1.16

Table 4.1. Individual finger temperature perception data.

Differences between post-stimulation and pre-stimulation skin temperature (degrees) and magnitude estimates (scale unit) in function of the radiant stimuli intensity. No= no stimulation; Low= low intensity; High= high intensity.

Next, we checked whether participants correctly perceived the different stimulations, by comparing magnitude ratings. Ratings increased with intensity for each finger both in the thermo-tactile (no stimulation vs low intensity index: $t11 = -6.191$, $p < 0.001$; middle: $t11 = -8.456$, $p < 0.001$; ring: $t11 = -3.761$, $p = 0.003$; low intensity vs high intensity index: $t11 = -7.131$, $p < 0.001$; middle: $t11 = -7.529$, $p < 0.001$; ring: $t11 = -6.980$, $p < 0.001$), and also in purely thermal condition (no stimulation vs low intensity index: $t11 = -7.288$, $p < 0.001$; middle: $t11 = -5.998$, $p < 0.001$; ring: $t11 = -6.425$, $p < 0.001$; low intensity vs high intensity index: $t11 = -5.463$, $p < 0.001$; middle: $t11 = -9.798$, $p < 0.001$; ring: $t11 = -5.777$, $p < 0.001$). Thus, varying intensity of stimulation induced concomitant variations in warmth perception, when each finger was stimulated individually (Table 4.1).

Uniformity judgement task

Our core scientific questions were 1) whether TR illusion was present in each of the thermo-tactile and purely thermal conditions and 2) whether the TR illusion differed in strength between these conditions.

First, a manipulation check assessed whether thermal shading was effective in influencing skin temperature of the middle finger. A 2 (Tactile condition: thermo-tactile, purely thermal) × 2 (Spatial pattern: uniform, non-uniform) repeated measures ANOVA on the difference between the middle finger and the average of the index and ring fingers skin temperature showed a significant main effect of Spatial pattern ($F_{1,\ 11} = 129.883$, $p < 0.001$; $\eta 2 = 0.922$), no significant effect of Tactile condition ($F_{1,\ 11} = 0.028$, $p = 0.871$), and no interactions between the factors ($F_{1,\ 11} = 0.004$, $p = 0.948$). The main effect arose because the difference between the middle finger and the other fingers was significantly higher in the non-uniform (mean ± SD: 2.0 °C ± 0.8 °C, tactile conditions averaged) than in the uniform stimulation condition (mean ± SD: 0.3 °C ± 0.8 °C, tactile conditions averaged), as predicted.

We then tested whether the TR was present in both thermo-tactile and purely thermal conditions. A signal-detection approach was used, based on previous studies (Ho, Watanabe, Ando, and Kashino, 2011). A hit was defined as a “uniform” response when the uniform thermal pattern was presented, while the false alarm was defined as a “uniform” response when the non-uniform thermal pattern was delivered by shading the middle finger. Sensory discriminability, d′ calculated as $z(pHIT) - z(pFA)$, was then estimated from the hit rate and false alarm rate. Performance in detecting non-uniformity was very poor in both thermo-tactile and in the pure thermal condition (Figure 3). Ten out of twelve participants in the thermo-tactile condition and nine out of twelve participants in the purely thermal condition showed a d′ lower than 1. Separate t-tests for each condition and intensity indicated that d’ scores were not significantly different from zero (thermo-tactile low intensity $t_{11} = -0.923$, $p = 0.376$; thermo-tactile high intensity $t_{11} = 0.091$, $p = 0.930$; purely thermal low intensity $t_{11} = 1.080$, $p = 0.303$; purely thermal high intensity $t_{11} = -1.085$, $p = 0.301$). Thus, participants were unable to detect thermal non-uniformity caused by middle-finger shading, confirming a TR illusion. A 2 (Tactile condition: thermo-tactile, purely thermal) × 2 (Intensity: low, high) repeated measures ANOVA was performed on the d’ values to compare the perceptual discriminability between thermo-tactile and purely thermal conditions (Figure 3). The analysis revealed no main effect of Tactile condition ($F_{1, 11} = 0.029$, $p = 0.867$), no main effect of Intensity ($F_{1, 11} = 0.44$, $p = 0.521$) and no interaction between factors ($F_{1, 11} = 2.182$, $p = 0.168$).

We therefore found no evidence that TR experience was modulated by touch.

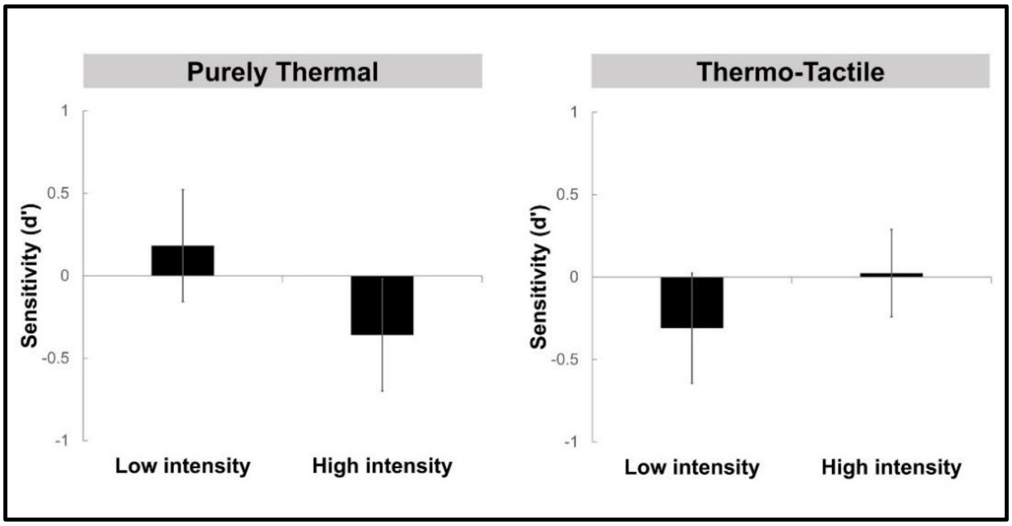


Figure 4.3. Thermal uniformity perception.

Sensitivity (d') measures in the purely thermal and thermo-tactile conditions. Performance was very poor in both experimental conditions, confirming a TR effect. No significant difference was found in sensitivity values between purely thermal and thermo-tactile conditions. Error bars show SE across participants.

4.3.2 Experiment 2

Thermal intensity perception

A manipulation check using a spot infrared thermometer confirmed that the thermal shading was effective at modulating skin temperature of the middle finger. A 2 (Tactile condition: thermo-tactile, purely thermal) × 2 (Spatial pattern: uniform, non-uniform) repeated measures ANOVA on the difference between the middle finger and the average of the index and ring fingers skin temperature confirmed a significant main effect of Spatial pattern ($F_{1, 11} = 63.075$, $p < 0.001$; $\eta 2 = 0.852$). No significant effect of

Tactile condition ($F_{1,\ 11} = 3.539$, $p = 0.087$), and no interactions between the factors ($F_{1,\ 11} = 0.209$, $p = 0.656$) emerged. The main effect of Spatial pattern arose because during non-uniform stimulation the difference between the middle finger and the other fingers was significantly higher (mean ± SD: 2.3 °C ± 0.6 °C, tactile conditions averaged) than in the uniform stimulation condition (mean ± SD: 0.4 °C ± 0.7 °C, tactile conditions averaged). In essence, this data confirmed in each subject the same pattern of results found in our more detailed stimulus validation using thermal imaging.

To analyse the overall intensity judgements, the perceived matching temperature in each condition was inserted in a 2 (Tactile condition: thermo-tactile, purely thermal) × 2 (Intensity: low, high) × 2 (Spatial pattern: uniform, non-uniform) repeated measures ANOVA (Figure 4). This analysis showed no main effect of Tactile condition ($F_{1,\ 11} = 0.631$, $p = 0.444$) but a significant main effect of both Intensity ($F_{1,\ 11} = 17.176$, $p = 0.002$; $\eta 2 = 0.610$) and Spatial pattern ($F_{1,\ 11} = 12.599$, $p = 0.005$; $\eta 2 = 0.534$). All interactions between factors were non-significant ($p > 0.258$). The main effect of intensity arose because, as expected, participants perceived high intensity of stimulation as significantly warmer (mean ± SD: 40.4 °C ± 4.6 °C, tactile and spatial pattern conditions averaged) than the low intensity of stimulation (mean ± SD: 38.7 °C ± 3.9 °C, tactile and spatial pattern conditions averaged). Crucially, the main effect of spatial pattern arose because a physically non-uniform pattern was perceived as significantly less intense (mean ± SD: 39 °C ± 4.3 °C, intensity and tactile condition averaged) than the physically uniform pattern (mean ± SD: 40.1 °C ± 4.3 °C, intensity and tactile condition averaged both in the thermo-tactile and the purely thermal condition). The perceived intensity was not significantly affected by touch.

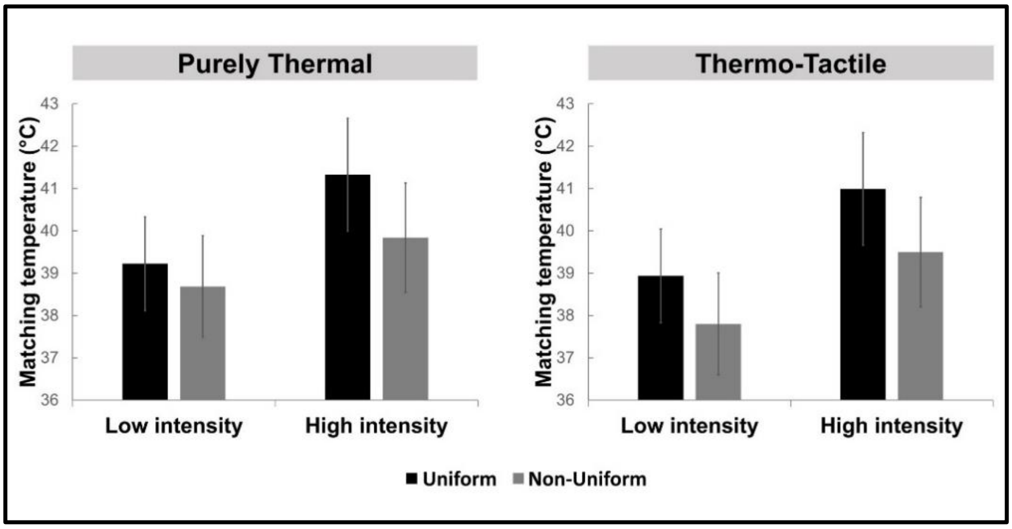


Figure 4.4. Thermal intensity perception.

Participant reported when the thermode on the forehead reached the same temperature as the overall thermal sensation across index, middle and ring fingers. Overall intensity of physically non-uniform stimulations (middle finger shade present) was judged less intense than uniform patterns. No significant difference was found between purely thermal and thermo-tactile conditions. Error bars show SE across participants.

4.3.3 Experiment 3

Thermal spatial localisation

First, we validated our method of stimulation, as in experiment 1, by computing the difference between post-stimulation and pre-stimulation skin temperature, and directly comparing the temperature gain for low vs high intensity, as for experiment 1. We confirmed clear differences in skin temperature between low vs high intensity (index: $t_{11} = -10.064$, $p < 0.001$; middle: $t_{11} = -12.377$; $p < 0.001$; ring: $t_{11} = -10.308$, $p < 0.001$).

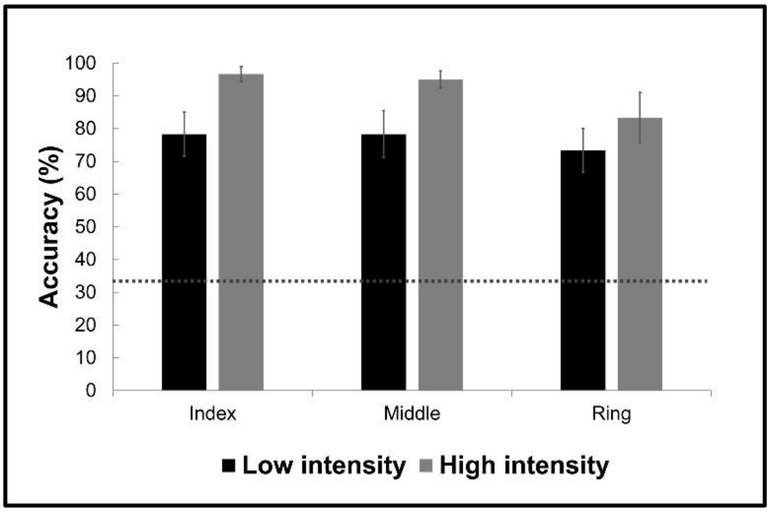


Figure 4.5. Thermal localisation.

Participant reported whether the thermal stimulation was delivered on the index, middle or ring finger. Overall accuracy is significantly different from chance level (indicated by a dashed line). Error bars show SE across participants.

		Reported finger		
		Index	Middle	Ring
Stimulated finger	Index	87.5 (1.3)	9.2 (1.0)	3.3 (0.5)
	Middle	2.5 (0.5)	86.7 (1.2)	10.8 (1.2)
	Ring	2.5 (0.6)	19.2 (1.8)	78.3 (2.1)

Table 4.2. Confusion matrix of the accuracy in the localisation task (Experiment 3).

For each finger stimulated, the percentage (and standard deviation across participants) of each response is given. Values on the diagonal are correct responses.

Next, we analysed accuracy of finger localisation judgements for each finger stimulated, and for each intensity. Localisation accuracy was always significantly better than the chance level of 33% (all $p < 0.008$ after Bonferroni correction for 6 tests). Accuracy rates, and a detailed breakdown of error types are shown in Figure 4.5 and Table 4.2. Thus, we conclude that our radiant heat stimuli could be localized reliably to individual fingers. Detailed analysis of the pattern of localisation errors showed that mislocalisation to adjacent fingers was more frequent than to non-adjacent fingers (Table 4.2).

4.4 Discussion

Here we describe for the first time a purely thermal TR, in the absence of any specific tactile stimulation: the sensation induced by purely thermal TR was indistinguishable from that induced by physically uniform stimulation, and also indistinguishable from the canonical tactile TR (experiment 1). The mechanisms underlying pure thermoceptive TR appear similar to those previously described for thermo-tactile TR (Ho, Watanabe, Ando, and Kashino, 2011). Alternative explanations based on poor localisation of thermal stimuli were rejected, since these radiant heat stimuli were localized rather accurately to individual fingers.

TR has been classically explained as a dominance of highly-weighted tactile information, over lower-weighted thermal signals in forming an integrated thermo-tactile percept. Evidence for this tactile-thermal integration comes from the fact that the illusory thermal sensation was reduced when the middle digit was lifted off the stimulator (Green, 1977).

That result suggested an important multisensory component in classical TR. We have demonstrated that thermal signals are sufficient to produce TR effects, and that tactile contact is not necessary. Further, we found no evidence that tactile contact modulates the TR effect. Our results suggest that the basic mechanism underlying TR may arise from within the thermoceptive system, rather than from interactions between thermoception and mechanoreception.

An alternative account of TR was given by Ho et al. (2011), based on serial processing of temperature and touch, rather than an integration of two parallel signals. Ho and colleagues (2011) proposed that, in a first stage, spatial summation tends to homogenize thermal percepts across multiple stimulated areas, producing an overall intensity percept proportional to the stimulated area. At a second stage, this intensity is then referred or attributed, on the basis of touch, to individual body parts – in this case the middle finger. Our results suggest that the first stage occurs within the thermoceptive system, and may be sufficient to explain our data.

Warm and cold thermoreceptors are fundamental in sensing external environmental temperatures in the innocuous range. The physiology of thermal processing is well known. When a purely thermal stimulus, as radiant warmth, is delivered to the skin, temperature-specific receptors in the skin are activated (Adair, 1999). In the case of our stimulations, where skin temperature was increased of about 3 °C from baseline, unmyelinated, low threshold C fibres projecting to the Lamina I dorsal horn were presumably activated (La Motte and Campbell, 1978). Then second order neurons transmit the information to the thalamus, which in turn projects to the cortex, primarily the insula (Craig, 2002). Additional classes of warmth receptors have also been identified (La Motte and Campbell, 1978; Treede, Meyer, Raja, and Campbell, 1995). However, these, like classical nociceptors respond only at higher temperatures (39–51 °C; La Motte and Campbell, 1978; Treede, Meyer, Raja, and Campbell, 1995; Dubin and Patapoutian, 2010), beyond the range studied here (30–35 °C).

When we touch an object, the sensations generated by thermal receptors are perceptually attributed to the object itself (Craig, 2002). Thus, although thermal perception is fundamentally interoceptive, the experiences it generates often have exteroceptive content. For example, we perceive the mug of tea as hot, though the receptors that drive this perception are, of course, located in the fingertips, not in the mug, and the thermal percept depends entirely on the fact that our fingers are in mechanical contact with the mug. The binding of sensory inputs to source objects is a ubiquitous feature of perception systems (Humphreys, 2001; Humphreys and Riddoch, 1987). The possibility that touch guides thermal object perception was first suggested by the foundational work of Ernst Weber (1996). Weber observed that, in the absence of touch, the skin felt similarly warm when heated either by blood from within the body or by a radiant thermal source from outside the body. Thus the brain uses tactile contact between the skin and an external object to attribute the warm sensation to the external object rather than to the body itself. Essentially the same argument is used in the classical account of TR (Ho, Watanabe, Ando, and Kashino, 2011). Attributing the thermal and tactile sensations on the three fingers to a common, spatially-extended source object triggers a powerful process of perceptual integration (Helbig and Ernst, 2007). In this integration process, the tactile sensations receive a relatively higher weighting than the thermal sensations. Tactile uniformity over-rides thermal non-uniformity, producing the TR illusion of a homogenous temperature. Green (1977) reported that lifting the neutral middle finger to break tactile contact abolishes TR. That is, a change in purely tactile input produced an illusory change in thermal perception. This result suggests that the homogeneity of tactile stimulation across the three fingers may explain the high weighting given to touch.

Importantly, these previous accounts assume that conscious perception occurs only subsequent to these processes of multisensory integration and object attribution. Conscious access to purely thermal sensation is precluded, because thermo-tactile percepts are assumed to be metameric: when participants are asked to judge thermal uniformity, they in fact report a multisensory thermo-tactile percept of the external object. Our results do not deny that source object attribution and multisensory integration play important roles in TR, but they do suggest that these mechanisms are not necessary. TR can equally occur in the absence of tactile inputs signalling an external object.

Since TR is possible without source object attribution, we can ask what features of the organisation of the thermoceptive pathway itself could underlie the effect. We consider four possibilities in turn: processing bandwidth, spatial resolution, thermal “filling-in” (Pessoa, Thompson, and Noe, 2001), and spatial summation (Hardy and Opel, 1937; Stevens and Marks, 1971).

First, our purely thermal TR could simply reflect limited attentional capacity (Lavie, 2005). People cannot perceive more than two touches in parallel (Gallace, Tan, Haggard, and Spence, 2008). Thermoception may be similarly limited. However, such bandwidth accounts cannot readily explain our results. First, our stimuli were delivered over an extended period of time, allowing participants enough time for allocating selective attention to each finger in turn. Second, a defining feature of attentional systems is that intense or salient stimuli nevertheless “break through” the limits of attention. When several stimuli are presented in parallel, a stimulus of lower or higher intensity than the others will pop out and automatically attract selective attention (Trisman and Gormican, 1988). If perceptual/attentional capacity explained our results, then non-uniformity detection should improve at higher thermal stimulation intensities, because the unstimulated middle finger should more readily pop out. In fact, we found a non-significant trend in the opposite direction, casting doubt on attentional explanations of our effect (Figure 3).

Second, purely thermal TR could reflect the thermoceptive system’s low spatial resolution (Cain, 1973; Simmel and Shapiro, 1969; Taus, Stevens, and Marks, 1975). Poor thermal spatial resolution would imply a single overall percept when three fingers are stimulated, losing information about local variation that underlies detection of non-uniformity. Classical studies support this view: indeed, people reported feeling warmth on the stomach when radiant heat was applied to the lower back (Cain, 1973). Pritchard (1931) commented that “*it is only when the … stimulus … involves deformation of the skin that accurate localisation is possible*”. The spatial resolution for non-contact radiant warmth was estimated between 4.5 cm and 15 cm on the forearm and around 14 cm on the back (Cain, 1973; Simmel and Shapiro, 1969). Our results show that localisation of radiant heat to a single finger was surprisingly accurate. One might argue that localisation can be inferred by the difference between the thermal intensities perceived on each finger. Indeed, people can accurately perceive discrepancies in thermal sensations across different fingers (Green, 1978). However, participants could only use differences in perceptual intensity to localise a thermal stimulus if they can (1) perceive that the fingers are not uniformly warm and (2) correctly identify which fingers feel warmer, and which feel less warm. Therefore, if people adopt intensity discrepancies to perform thermal localisation, they should, in principle, also be able to detect the uniformity of a pattern of thermal stimulation across the fingers. However, our results do not support this line of reasoning. We showed that participants could not perceive any non-uniform pattern when presented with a warm-neutral-warm pattern of stimulation, even though they could readily localize the same degree of warmth when delivered to a single finger. Thus, poor spatial resolution of warm sensations cannot readily explain our results. Specific perceptual mechanisms related to thermal patterns across multiple fingers appear necessary.

Another possible explanation of TR is based on a process known as “filling-in”. The warm input to the outer fingers would lead to filling-in a similar warm sensation at the middle finger, despite absence of thermal stimulation. In vision, percepts such as the Troxler effect (Martinez-Conde, MacKnik, and Hubel, 2004) are based on perceived homogeneity due to loss of local stimulus detail. Low-level and high-level theories have been proposed. According to low-level theories, early visual cortex neurons tuned to different dimensions, such as orientation and colour, may interact to produce neural activity in the absence of physical stimulation (Komatsu, 2006). According to high-level theories, a cognitive mechanism that assumes homogenous objects leads to a conceptual or symbolic extrapolation of detail from areas of stronger to weaker perceptual signal (Dennett, 1992). The latter account strongly recalls the attribution of multisensory inputs to a homogenous thermo-tactile source object in TR. Further, a thermal completion mechanism would predict that the physical intensity applied to the stimulated fingers is “copy-pasted” from the stimulated index and ring fingers to the non-stimulated middle finger, resulting in an unchanged, or at least not decreasing, percept of overall intensity (Ho, Watanabe, Ando, and Kashino, 2011). Our results do not support this “filling-in” hypothesis: the perceived overall intensity was significantly reduced in the non-uniform condition compared to the uniform condition.

Finally, spatial summation occurring within the thermoceptive system might readily explain our results. Classically, spatial summation is demonstrated by a decrease in the thermal detection threshold, or increase in suprathreshold intensity perception, when stimulating larger, rather than smaller skin regions. Spatial summation within the warm afferent channel is strong (Hardy and Oppel, 1937; Stevens and Marks, 1971). During TR, spatial summation would imply a stronger sensation of warmth in the physically uniform stimulation, in which three fingers are stimulated, than in the non-uniform stimulation, where only two are stimulated. Indeed, participants in Ho et al.’s (2011) thermo-tactile experiment perceived a lower overall intensity when the middle finger received no thermal stimulation (the TR condition), than when it was stimulated, consistent with the predictions of spatial summation. Our study confirmed this hypothesis. Participants perceived a lower overall intensity for non-uniform patterns compared to uniform patterns, even when stimulation was purely thermal. Classically, somatosensory neurons integrate all the inputs in their receptive field. Neurons with spatially–extended, multi-digit receptive fields could thus underlie spatial summation (Fitzgerald, Lane, Thakur, and Hsiao, 2006). Our result suggests that thermal referral effects are not dependent on tactile localisation, and may arise within the thermoceptive system. One may speculate that the thermoceptive system contains neurons with finger-specific receptive fields, which may then converge on higher-level neurons that summate their inputs, and thus have multi-finger receptive fields. Our result leads to the intriguing idea that localisation of a thermal stimulus occurs at the first level, where digit-specific information is available. In contrast, information about the overall pattern of thermal intensities, as in our uniformity judgements for example, occurs only at the second level, where digit-specific information is not available.

Most previous studies of TR involved thermo-tactile stimuli. When tactile stimuli are applied on the fingers of one hand, the tactile signals are initially processed separately. Next, the variability among the different fingers is computed. If variability is low, then a homogenous tactile object is assumed, and the tactile signals from the three fingers are combined. The thermal processing pathway lacks such a sophisticated object detection system. Rather, a degree of homogenization might operate automatically, and at an early processing stage, to produce a global representation, with little local detail. When both thermal and tactile signals are available, uniformity of stimulation across fingers is based on an integrated percept reflecting a unified average of both, rather than on a unisensory source. The relative weightings of tactile and thermal information in multisensory integration may explain the apparent discrepancy between Green's result (Green, 1977), and ours. In his experiment, raising the middle finger from the stimulator produced tactile signals of non-uniformity, which lead to a thermal percept of non-uniformity. In our shadow condition, the thermal conditions were identical to Green's middle-finger raised condition, but the tactile conditions were quite different. In particular, the non-homogenous tactile signals of Green's study were absent in our study. That is, homogeneity of tactile input appears essential for the illusion, although positive presence of a tactile object is not essential. TR requires either all stimulated fingers in contact or all stimulated fingers contact-free. We speculate that the thermal experience of traditional TR is exteroceptive and is attributed to an external object. Conversely, in our purely thermal TR, the thermal experience may be more interoceptive, and might be attributed to one's own body. This speculation could be directly tested in the future, by repeating our experiment using much lower levels of radiant heat, below the threshold for detecting an external heat source.

In conclusion, low-level mechanisms of spatial summation within the thermoceptive system seem sufficient to explain an illusion that had previously been interpreted as reflecting multisensory, cognitive processes of object perception.

Chapter 5.

Thermo-nociceptive interaction: inter-channel pain modulation occurs before intra-channel convergence of warmth

Synopsis:

This Chapter presents a study on the somatosensory interaction between pain and multiple thermal stimuli. In a paired conditioning-test stimulus paradigm, we manipulated the number and the position of thermo-tactile stimuli concurrently delivered with a CO2 laser pulse, to investigate the spatial properties of warmth-pain interaction and the level of somatosensory processing at which it takes place. To achieve this goal, we exploited the properties of thermal referral, described in Chapter 4, and spatial summation to modulate the thermal percept without changing the local state of the skin on the target site. We replicated the classical suppressive effect of warmth on pain processing. Crucially, we also found that inhibition of pain was independent from both the position and the number of thermal stimuli administered. This suggests that effect of warmth on Aδ nociceptors and pain is not strongly somatotopic, and that the inter-channel modulation of nociception by warmth occurs prior to, or independently of intra-channel summation of multiple thermal inputs.

5.1 Introduction

Whether pain is a specific sense, independent from the other sensory modalities, or rather the extreme of a continuum from normal to noxious stimulation has been matter of debate for philosophers and psychologists for a long time (Pearl, 2007; Moayedi and Davis, 2013; Dallenbach, 1939). Early theories on the organisation of the somatosensory system, such as the *Intensive Theory* (Erb, 1874; Goldsheider, 1894), and the *Central Summation Theory* (Livingstone, 1943), conceptualised pain as the mental experience occurring when the discharge activity induced by normal sensory events crosses a critical level of intensity. Concurring somatosensory inputs would converge and summate at spinal level, and the phenomenological experience of pain would arise only *after* this summative process, when the overall intensity approached potentially noxious levels associated with nerve and tissue damage (Goldsheider, 1894; Livingstone, 1943). Conversely, the *Specificity Theory* (Dubner, Sessle, and Storey, 1978) and the *Gate Control Theory* (Melzack and Wall, 1967 postulated that specific somatosensory inputs would interact with each other, rather than summate, in the dorsal horn of the spinal cord. In particular, according to the gate control theory, the interaction among different modalities (e.g. touch and pain) would occur through a gating mechanism in the substantia gelatinosa, whereas the transmission of nociceptive information would be inhibited by the activity of large (Aβ) fibers, and facilitated by the activity of small (Aδ and C) fibers (Melzack and Wall, 1967). In the last decades, the gate control theory has proven to be a valid model for the understanding of touch-pain interaction, receiving corroboration from ample experimental evidence about the suppressive effect of tactile stimulation on pain (Wall and Sweet, 1967; Higgins, Tursky, and Schwartz, 1971; Zoppi, Voegelin, Signorini, and Zamponi, 1991; Marchand, Bushnell, and Duncan, 1991; Kakigi and Shibasaki, 1992; Akyuz, Guven, Ozaras, and Kayhan 1995; Svensson, Hashikawa, and Casey, 1999; Watanabe, Svensson, and Arendt-Nielsen, 1999; Nahra and Plaghki, 2003, but see also Akparian, Stea, and Bolanowski, 1994).

However, a growing body of evidence suggests that the relation between pain and *thermoception*, instead, may elude an explanation based on such model for several reasons. First, the gate control theory is grounded on the assumption of *specificity* of somatosensory modalities. While the independence of touch and pain pathways is clear (Willis and Coggeshall, 2012; Craig, Chen, Bandy, and Reiman, 2000; Dubner, Sessle, and Storey, 1978; Sherrington, 1906; Burgess and Perl, 1967), evidence about *low-threshold thermal nociception* (LTN) (Green and Schoen, 2005; Green and Pope, 2003; Green and Akirav, 2010) shows that painful sensations can be elicited by stimuli that are well within the thermal, non-noxious range, suggesting a less defined specificity for thermal and nociceptive modalities, with some afferent fibers typically identified as warm fibers relaying both thermal *and* noxious information (Yarnitsky, 2008; Green, 2004; Green and Akirav, 2010; Christensen and Perl, 1970; Zhang, Davidson, and Giesler, 2006).

Second, touch-pain interaction is generally considered unidirectional. In line with the account of a gating system prioritising large afferent fibers, it has been proven that mechanical (Higgins, Tursky, and Schwartz, 1971; Mancini, Nash, Iannetti, and Haggard, 2014; Nahra and Plagki, 2003), electrical (Marchand, Bushnell, and Duncan, 1991; Akyuz, Guven, Ozaras, and Kayhan 1995), and vibrotactile (Zoppi, Voegelin, Signorini, and Zamponi, 1991; Kakigi and Shibasaki, 1992) stimuli inhibit pain, and only few studies have observed the opposite effect (Akparian, Stea, and Bolanowski, 1994). Conversely, thermo-nociceptive interaction has reportedly proven to occur in both directions. Suppression of thermal stimuli by pain is supported by early electrophysiological evidence that cortical responses from C fibers cannot be recorded during simultaneous activation of Aδ fibers (Bromm and Treede, 1987a,b; Margerl, 1999; Plaghki and Mouraux, 2003; but see also Hu, Cai, Xiao, Luo, and Iannetti, 2014; Plaghki, Bragard, Le Bars, Willer, and Godfraind, 1998). However, a growing number of behavioural (Casey, Zumberg, Heslep, and Morrow, 1993; Plaghki, Decruynaere, Van Dooren, and Le Bars, 2010) and electrophysiological (Truini, Galeotti, Cruccu, and Garcia-Larrea, 2007; Tran, Matre, and Casey, 2008; Nahra and Plaghki, 2005) studies have shown that innocuous thermal stimuli can markedly reduce both perception and cortical correlates of pain. For example, Truini and colleagues (2007) found that the cortical response to a nociceptive stimulation was significantly attenuated when it was preceded by a warm stimulus (Truini, Galeotti, Cruccu, and Garcia-Larrea, 2007).

Third, touch-pain interaction is somatotopically organised. Tactile inputs inhibit pain perception segmentally, but not when tactile and nociceptive inputs are delivered to different dermatomes (Kakigi, and Watanabe, 1995; Yarnitsky, Kunin, Brik, and Sprecher 1997; Watanabe, Svensson, and Arendt-Nielsen, 1999; Nahra and Plaghki, 2003). Moreover, even at intrasegmental level, the inhibition decreases linearly when the distance between the laser and tactile stimuli increases (Mancini, Nash, Iannetti, and Haggard, 2014). In contrast, the spatial organisation of thermo-nociceptive interaction is poorly understood, with psychophysical (Casey, Zumberg, Heslep, and Morrow, 1993; Price and McHaffie, 1988) and EEG (Tran, Matre, and Casey, 2008) studies investigating the spatial properties of thermo-nociceptive interaction showing more controversial results. In particular, despite one early work (Price and McHaffie, 1988) that reported no modulation of pain after thermal stimulation on remote body regions (ankle vs. foot/abdomen), Casey and colleagues (1993) found that magnitude estimation of noxious stimuli was reduced, although by different degrees, when thermal stimuli were presented on either adjacent or non-adjacent fingers (adjacent: 12-22%; non-adjacent: 10-13%). Moreover, in a recent study, Tran and colleagues (2008) found that the suppressive effect of C fibers on Aδ fibers was modulated by the physical intensity of the thermal stimulus, but did not vary according whether the two inputs were presented at intrasegmental, intersegmental, or contralateral stimulation sites (Tran, Matre, and Casey, 2008). They concluded, therefore, that C-Aδ interaction is mediated through a widely distributed, non-somatotopic mechanism.

Finally, observations from the *Thermal Grill Illusion* (TGI) (Thunberg, 1896; Craig and Bushnell, 1994, Craig, 2002; Marotta, Ferrè, and Haggard, 2015; Defrin, Benstein-Sheraizin, Bezalel, Mantzur, and Arendt-Nielsen, 2008) support the idea that more complex patterns of intra-channel summation and intermodal interaction take place in thermal-pain rather than touch-pain interaction. In TGI, presenting an alternating pattern of innocuous warm and cold stimuli induces a burning pain sensation (Thunberg, 1896; Craig and Bushnell, 1994). The classical account for this phenomenon postulates that, by default, nociception is inhibited by the cold pathway, but, under TGI conditions, cold information is inhibited in turn by the spatial summation of the surrounding warm stimuli (Craig and Bushnell, 1994, Craig, 2002). In other words, multiple warm stimuli would unmask pain by 1) summating with each other and 2) interfering with the cold pathway at spinal level. Interestingly, a recent study by Marotta and colleagues (2015) showed that TGI is not somatotopically organised, suggesting that both summation of warmth and inhibition of cold do not occur at spinal, but at supraspinal levels, *after* spatial remapping of warmth (Marotta, Ferrè, and Haggard, 2015). Therefore, a specific question about warmth-pain interaction that still need to be addressed, is whether the inter-channel integration between these two modalities occurs before or after intra-channel summation, as in TGI.

Overall, this body of evidence indicates that thermo-nociceptive interactions may require models very different from the gate control models for touch-nociceptive interaction. Here, we focussed on the interaction between warmth and pain. In particular, we used *spatial summation of warmth* to study the somatotopic organisation of warmth-pain interaction and the level of somatosensory processing at which it takes place. The thermoceptive system is strongly affected by spatial summation (Hardy and Oppel, 1937; Stevens and Marks, 1971; Marks and Stevens, 1973; Marks, 1974; Kenshalo, Decker, and Hamilton, 1967). The relation between temperature perception and physical warmth is described by a power function where the size of the exponent depends on the areal extent of the stimulus (Marks and Stevens, 1973). That is, other than by increasing the physical energy applied to the skin, perception of warmth can be enhanced by either extending the area of stimulation (Hardy and Oppel, 1937; Defrin and Urca, 1996; Kojo and Pertovaara, 1987 Machet-Pietropaoli and Chery-Croze, 1979), or increasing the number of thermal stimuli (Hardy and Oppel, 1937; Kenshalo, Decker, and Hamilton, 1967; Price, McHaffie, and Larson, 1989).

Interestingly, spatial summation can also give rise to the *mislocalisation* of the thermal percept, a phenomenon called *Thermal Referral* (TR) (Green, 1977, 1978; Ho, Watanabe, Ando, and Kashino 2011; Cataldo, Ferrè, di Pellegrino, and Haggard, 2016). In TR, applying warm stimulation on the index and/or ring finger of one hand produces the illusory perception of warmth on the (thermally neutral) middle finger (Green, 1977, 1978). Despite both increasing physical energy and spatial summation lead to the same perceptual experience (i.e. perceived enhancement of warmth on a target spot), each of this processes presupposes different neural mechanisms and occurs at different processing levels. Increases in the stimulus temperature over the non-noxious range (39-43°C) induce a monotonic increase in the cumulative number of impulses recorded from C fibers (LaMotte and Campbell, 1978; Darian-Smith, Johnson, LaMotte, Shigenaga, Kenins, and Champness, 1979; Duclaux and Kenshalo, 1980). Spatial summation of warmth, on the contrary, is a central neural phenomenon produced by the integration of thermal information at second- and third-order neurons in the spinal cord, and/or supraspinal levels (Herget, Granath, and Hardy, 1941; Stevens, Marks, & Simonson, 1974; Price, McHaffie, and Larson, 1989). Therefore, spatial summation of warmth and thermal referral constitute the ideal conditions for dissociating the perceptual from the physical content of thermoception, and can be used to individuate the level at which thermo-nociceptive interaction occurs.

In the present study, in two experiments assessing the psychophysical (Experiment 1) and electrophysiological (Experiment 2) correlates of pain, we systematically manipulated the position and the number of thermal stimuli delivered on participants' fingers to investigate 1) the somatotopic organisation of warmth-pain interaction, and 2) whether inter-channel convergence between these two modalities occur before or after intra-channel summation of warmth. We implemented a paired conditioning-test stimulus paradigm where we used CO_2 laser pulses to deliver painful stimuli on participants' middle finger while three contact-heat stimulators provided eight different thermal conditions: 1) no warmth (baseline), warmth on: 2) index finger, 3) middle finger, 4) ring finger, 5) index and middle fingers, 6) middle and ring fingers, 7) middle and ring fingers, 8) all fingers. This paradigm allowed us to make several predictions.

First, we expected that a warm stimulation on the middle finger (condition 3) would attenuate a concurrent painful input on the same finger by increasing participants' pain detection thresholds (Experiment 1), and by modulating magnitude estimation and neurophysiological correlates of pain (Experiment 2).

Second, we reasoned that finding an interaction between temperature and pain under thermal referral conditions (conditions 2 and 4, and condition 6) would clarify whether 1) warmth-pain interaction is based on a diffuse, non-somatotopic mechanism, or 2) warmth-pain interaction occurs at central levels, subsequent to spatial summation of the thermal stimulus.

Finally, if warmth-pain interaction is secondary to summation of warmth, enhancing the apparent intensity of warmth by increasing the number of simultaneous thermal stimuli, would produce a stronger suppression of pain. On the contrary, if thermo-nociceptive interaction occurs independently from spatial summation, varying the number of fingers exposed to warmth would not produce parametric changes in pain processing.

5.2 Methods

Participants

Ten healthy right-handed participants (3 female, mean age ± SD: 24.6 ± 4.2 years) took part in Experiment 1. The sample size of Experiment 1 was calculated a priori on the basis of previous similar studies on thermal-nociceptive interaction (Casey, Zumberg, Heslep, and Morrow, 1993; Churyukanov, Plaghki, Legrain, and Mouraux, 2012; Tran, Matre, and Casey, 2008). Fifteen new volunteers were recruited for Experiment 2 (10 female, mean age ± SD: 25.9 ± 4.3 years). The sample size for Experiment 2 (n = 14) was calculated a priori by means of a statistical power analysis based on data from a previous EEG pilot study using G*Power 3.1.9.2 software (Faul, Erdfelder, Buchner, and Lang, 2009). One participant was excluded from Experiment 2 because pain threshold could not be reliably established, and was replaced. Inclusion criteria for both studies involved the absence of any history of previous traumatic hand injury, absence of sensitive skin or skin conditions, abstention from analgesic medication for 24 hours prior the study, and abstention from caffeinated beverages for three hours prior to the study.

The experimental protocol was approved by the research ethics committee of University College London. Recruitment of participants and experimental procedures were conducted in accordance with the Declaration of Helsinki. All participants provided their written informed consent at the beginning of each experiment, after receiving written and verbal explanation of the purpose of the study.

Thermal stimulation of C fibres

Thermal stimuli were applied to the fingertips of the right hand by means of three Peltier-type thermodes (Physitemp Instruments Inc, NTE-2A, New Jersey, USA) in both experiments. The thermal probe has a smooth flat tip 13 mm in diameter and uses a Peltier semiconductor heat pump to provide variable, accurately controlled temperature stimuli above and below room temperature. The temperature range of the thermode extends from 0°C to 50°C with a ramping rate of ~2°C/s in the heating or cooling mode. The digital control unit incorporates proportional feedback to maintain accurate temperature control within ~0.1°C.

In both Experiment 1 and Experiment 2, three independent 13 mm diameter probes were fixed on a holding support placed underneath participants' right hand. To ensure full contact with the fingers, before the beginning of the experiment each stimulator was adjusted until it touched the glabrous skin of participants' index, middle, and ring fingers, at the level of the intermediate phalanges (see Figure 1). The level of maximal thermal stimulation presented in each trial was the same for all participants and consisted in a temperature of 36°C in Experiment 1 and 40°C in Experiment 2. Between trials, the temperature of each probe was set at a baseline level of 32°C.

Before the beginning of each experiment, participants went through a familiarization task where thermal stimuli were randomly applied on one or more fingers. Participants were asked to rate the thermal sensation felt on the middle finger only on a scale from 0 to 10 where 0 meant “no stimulation”, 1 “barely warm”, and 10 “very hot”.

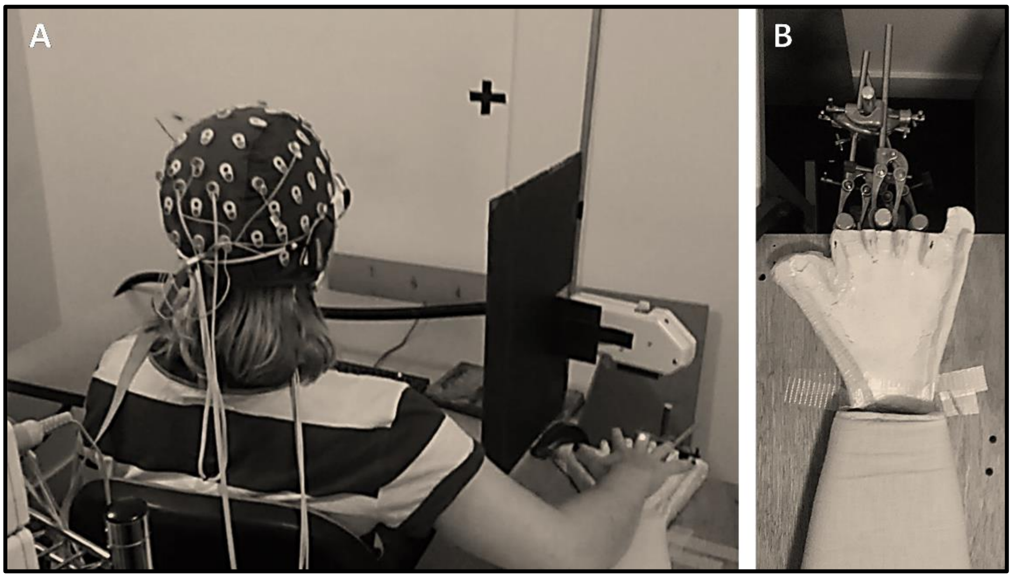


Figure 5.1. Experimental set up in Experiment 1 and Experiment 2.

A. Painful stimuli were delivered to the dorsum of participants’ right middle finger through a CO_2 laser pulse. B. Thermo-tactile stimuli were delivered by three 13 mm diameter Peltier-based thermodes applied at the level of the intermediate phalanges of right index, middle, and ring fingers. Participants kept their gaze on a fixation located centrally in front of them, and vision of the right hand and arm was blocked by means of a screen.

CO_2 Laser stimulation for Aδ activation

In both experiments, nociceptive stimuli were delivered on the dorsum of participants' right middle finger by a CO_2 laser stimulator (Laser Stimulation Device, SIFEC, Belgium), controlled by a computer. This device uses a closed-loop control of laser power by an online monitoring of skin temperature (Mor and Carmon, 1975; Meyer, Walker, and Mountcastle, 1976). The laser pulse (~100 ms) was transmitted via an optical fibre, and focused by lenses to a spot diameter of ~6 mm. A radiometer collinear with the laser beam detected the skin temperature at the site of stimulation, providing totally safe and reproducible noxious thermal radiant stimuli at a ramping rate of ~350°C/s (Jankovski, Plaghki, and Mouraux, 2013; Churyukanov, Plaghki, Legrain, and Mouraux, 2012). Using a wavelength of 10.6 µm, CO_2 stimulators ensure that the totality of laser power only penetrates the most superficial layers of the skin (Plaghki, and Mouraux, 2003; Hardy, Hammel, and Murgatroyd, 1956), where Aδ-fibre nociceptors are located (~100 µm; Bromm, and Treede, 1983), minimising any risk of tissue damage.

Participants rested their right hand pronated on a moulded support. The laser head was positioned above the hand, with the laser beam pointing on the dorsal aspect of the middle finger's intermediate phalanx (see Figure 1). A visible helium-neon laser spot was used to point the CO_2 laser to the target location. To ensure a consistent stimulus location across the experiment, the zone within which laser stimulation should fall was delimited by a ~12 mm diameter circle drawn on the dorsum of the middle finger. Extra care was taken during the testing to prevent any laser stimulation on the skin blackened by the ink, which could affect absorption of radiant heat (Leandri, Saturno, Spadavecchia, Iannetti, Cruccu, and Truini, 2006; Madden, Catley, Grabherr, Mazzola, Shohag, and Moseley, 2016). Participants wore protective goggles and were asked to maintain their gaze on a fixation cross centrally located in front of them. Vision of the right hand was blocked with a screen. Intensity, duration, and timing of the CO_2 laser stimuli were controlled by means of an ad-hoc MATLAB routine (The Mathworks, Natick, MA).

Prior to the beginning of each experiment, participants were familiarised with the laser stimuli. A series of trials was delivered at near- and supra-threshold intensity level (~46°C), and participants were asked to press a button with their left hand as soon as they felt any stimulation on the dorsum of the right middle finger and to rate the intensity of the laser stimulation on a scale from 0 to 10 where 0 meant “no pain”, 1 “slightly pinprick”, and 10 “the worst pain imaginable”.

Experimental design and statistical analysis

We used a within-subject design where participants’ Aδ radiant heat detection threshold (Experiment 1), magnitude estimation of pain (Experiment 2), and Laser Evoked Potentials (LEPs) (Experiment 2) were tested across eight different thermal conditions. The 8 conditions were designed to investigate systematically the effects of both spatial location and area of warm stimulation on nociception (see Figure 2). In condition 1, CO_2 laser pulses were delivered in absence of any thermal stimulation, providing a baseline measure of participant’s pain perception on the middle finger. In the remaining conditions, the site of thermal stimulation (index, middle, or ring finger; condition 2, condition 3, and condition 4) and the number of thermally stimulated fingers (one: conditions 2 to 4; two: conditions 5 to 7; or three: condition 8) were systematically manipulated (see Figure 2).

Behavioural and EEG data were analysed using STATISTICA software (version 8.0; StatSoft, Inc., OK, USA). Two separate sets of statistical analysis were run on warmth/pain perception (Experiment 1 and 2), pain thresholds (Experiment 1), and pain EEG correlates (Experiment 2) to investigate the spatial and summative properties of warmth-nociceptive interaction. The effect of spatial localisation of warmth was assessed through repeated measures ANOVAs on condition 1 (no thermal stimulation), condition 3 (warmth on the same finger), the average of condition 2 and 4 (warmth on index/ring finger; i.e. adjacent fingers t), and condition 6 (warmth on index and ring fingers; i.e. TR). Significant results were then examined by means of pairwise comparisons (Fisher's least significant difference test).

The effect of spatial summation of multiple simultaneous thermal stimuli was tested through a linear trend analysis, with weights −1, 0, and 1 comparing the conditions where warmth was applied on one (average of condition 2, 3, and 4), two (average of condition 5, 6, and 7), or three fingers (condition 8) (Mancini, Nash, Iannetti, and Haggard, 2014; Hays, 1994). Statistical tests were considered significant if $p < 0.05$. Non-significant results were further investigated through Bayesian analyses, using JASP (version 0.8.0.1; JASP Team 2016, University of Amsterdam). In particular, where necessary, we conducted Bayesian repeated measures ANOVAs or Bayesian one sample t-tests to determine whether our data supported the null hypothesis, or were due to insufficient statistical power (Rouder, Speckman, Sun, Morey, and Iverson, 2009; Weltzels, Grasman, and Wagenmakers, 2012).

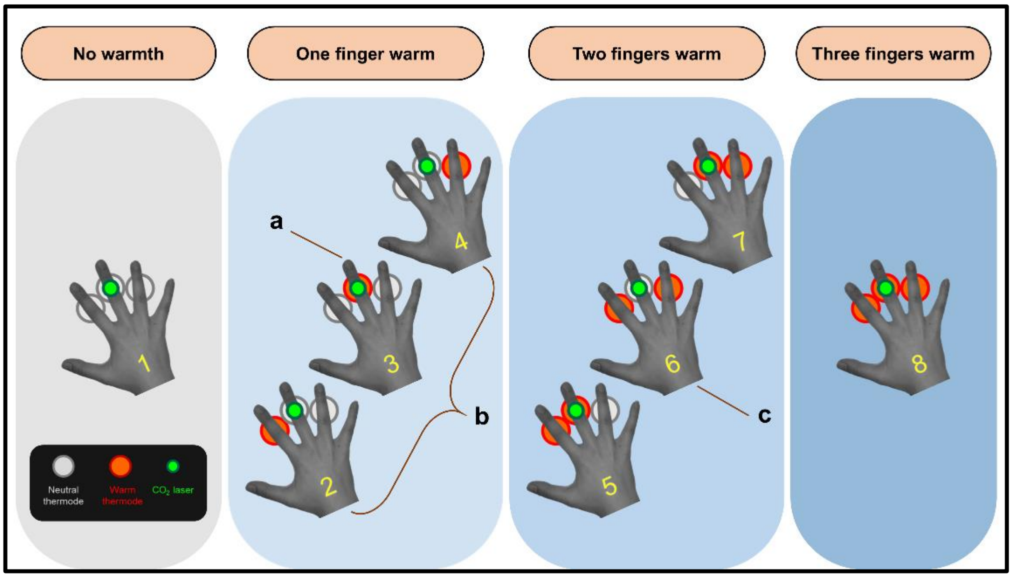


Figure 5.2. Thermo-nociceptive conditions in Experiment 1 and Experiment 2.

Pain processing of CO_2 laser pulses delivered on the dorsum of the middle finger was tested across eight different thermal conditions: 1) no warmth, warmth on 2) index finger, 3) middle finger, 4) ring finger, 5) index and middle fingers, 6) middle and ring fingers, 7) middle and ring fingers, 8) all fingers. In particular, this design allowed us to contrast pain correlates during no thermal stimulation with the conditions where concurrent warm and painful stimulation were delivered on the same finger (a), on the adjacent fingers (b), or under thermal referral (c). Moreover, the effect of numerosity of thermal stimuli on pain was tested when one (average of condition 2, 3, and 4), two (average of condition 5, 6, and 7), or three (condition 8) fingers were simultaneously stimulated through the thermodes.

5.2.1 Experiment 1

Psychophysical staircases for pain threshold

Adaptive staircase procedures provide a quick and reliable method to estimate perceptual thresholds (Cornsweet, 1962; Treutwein, 1995). Stimuli are presented in a series of ascending or descending trials. When the participant is first able to detect the stimulus on the ascending trial, the direction of the staircase is reversed and the intensity of the stimulus is decreased until it cannot longer be detected. Then the staircase is once again reversed and the procedure is repeated. The average of the last few reversals is taken as an estimation of the sensory threshold. To establish participants' Aδ-fibres pain threshold, here we used an adaptive psychophysical algorithm based on participants' reaction times (RT) to the CO_2 laser stimulation. Due to the different nerve conduction velocity of Aδ and C fibres (Campbell and LaMotte, 1983; Opsommer, Masquelier, and Plaghki, 1999; Bromm, and Treede, 1984), RT can be used to estimate the thermal detection threshold of heat-sensitive Aδ- and C-fibre afferents (Arendt-Nelsen and Bjerring, 1988; Mancini, Nash, Iannetti, and Haggard, 2014). In particular, in line with previous studies (Churyukanov, Plaghki, Legrain, and Mouraux, 2012; Jankovski, Plaghki, and Mouraux, 2013), we fixed a criterion of 650 ms to discriminate between C (≥ 650) and Aδ fibres (< 650).

At the beginning of the staircase, laser intensity was set at a temperature of 40°C. We choose such stimulation level because it is likely to be slightly above the thermal activation threshold of C fibres, and yet well below the threshold of heat-sensitive Aδ fibres (LaMotte and Campbell, 1978; Darian-Smith, Johnson, LaMotte, Shigenaga, Kenins, and

Champness, 1979; Churyukanov, Plaghki, Legrain, and Mouraux, 2012). Participants were asked to press a button as soon as they perceived any stimulation on the dorsum of the middle finger. The temperature of the following stimuli was adaptively changed according to participants' RT. If RT to the preceding stimulus were equal or longer than 650 ms, the temperature of the upcoming stimulus was increased until the first reversal. Conversely, if RT to a stimulus were shorter than 650 ms, the temperature of the upcoming stimulus was decreased. The step size of the staircasewas progressively reduced after each reversal, changing from 4°C, to 2°C, and finally 1°C.

Each stair-case ended after 15 trials. Typically, staircase procedures end when a fixed number of reversals is reached (Treutwein, 1995; García-Pérez, 1998). However, this implies that the number of trials and the duration of the staircase can be highly variable across conditions and participants, potentially producing different amount of mid-term sensitisation/habituation of the cutaneous and nervous structures underlying thermal and pain processing (Iannetti, Leandri, Truini, Zambreanu, Cruccu, and Tracey, 2004 Kleinböhl, Trojan, Konrad, and Hölzl, 2006). Consequently, to keep the duration of the experiment stable, we opted for a stopping rule based on a fixed number of trials. A total of 15 trials was chosen on the basis of a pilot test, which found that this number of trials was sufficient to obtain at least four reversal from each participant in each condition (n = 6; average number or reversals ± SD: 6.3 ± 0.8).

Procedure

The experiment took place in a temperature-controlled room at 23°C. Participants' superficial skin temperature of the hand dorsum was measured throughout the experiment by means of an infrared thermometer (Precision Gold, N85FR Maplin, UK) and it was kept between 28°C and 32°C (mean baseline temperature ± SD, Experiment 1: 30.6°C ± 1.4°C; Experiment 2: 30°C ± 1.4°C). Participants sat in front of a desk and rested their right hand on a moulded support placed in front of them. This support left the intermediate and distal phalanges of the index, middle, and ring fingers exposed to the thermal stimulators mounted beneath. CO_2 laser stimuli were delivered on the dorsum of the middle finger (see Figure 1). After signing the informed consent, participants were familiarised with the thermal and nociceptive stimulation (see above).

We used a paired conditioning-test stimulus paradigm where participants' pain threshold was separately assessed in eight blocks corresponding to the eight different thermal conditions described above. The order of the blocks was randomised across participants. To assure attention to the stimuli, a beep signalled the beginning of each trial. Before each trial, the temperature of the thermodes was set at 32°C. After the beep, the thermal stimulation ramped up to 36°C at a rate of ~2°C/s, and remained steady for the entire duration of the trial. After a random delay from the beginning of the thermal stimulation (between 4.5 s and 5.5 s), a 100 ms CO_2 laser pulse was delivered on the middle finger. Participants were asked to use their left hand to press a button as quickly as possible as soon as they felt any stimulation on the dorsum of the middle finger. After the key press, thermodes intensity returned to baseline, and participants were asked to perform separate magnitude estimations (ME) of both the thermal and the painful stimuli, providing a number on a scale from 0-10 corresponding to each sensation. The first rating was always associated with the thermal sensation perceived on the middle finger only (0 = “no stimulation”; 10 = “very hot”), while the second number reflected the pinprick sensation felt on the dorsum of the middle finger (0 = “no pain”; 10 = “the worst pain imaginable”). An inter-trial interval randomly varying between 10-15 s was set in order to prevent any possible effect of sensitisation or habituation of the thermoreceptors/nociceptors at the site of stimulation.

5.2.2 Experiment 2

EEG recording and LEPs analysis

Experiment 2 aimed to investigate the electrophysiological correlates of pain in the same thermal conditions described in Experiment 1. EEG data were acquired from the scalp at a sampling rate of 2048 Hz using an Active Two BioSemi EEG amplifier and ActiView software (Biosemi, Amsterdam, The Netherlands). Sixteen Ag-AgCl active electrodes were positioned on the scalp according to the 10-20 International System. Electrooculographic signals (EOG) for eye movements and eye-blinks monitoring were simultaneously recorded by means of four surface electrodes: left and right hEOG electrodes were placed on participants’ external canthi, while vEOG electrodes were placed above and beneath participants’ right eye. A fifth external electrode placed on the nose was used as reference. Electro-conductive gel was used to keep the impedance of all electrodes < 5 kΩ throughout the experiment.

Participants were asked to keep their eyes open, maintaining their gaze on a central fixation cross located in front of them, to focus on the stimuli delivered on their right hand, and to relax their muscles.

EEG data were processed using EEGlab (Delorme and Makeig, 2004), an open source toolbox for analysis of averaged and single-trial EEG dynamics, running on MATLAB. Continuous, raw data for each participant in each block were recorded and stored on ActiView, and successively imported on EEGlab for off-line analysis. Data were resampled to 250 Hz, and then bandpass filtered between 1 Hz and 30 Hz cut off all the frequencies unrelated with cortical processes. Large artefacts were detected through visual scrutiny and rejected before further processing. EEG epochs were extracted from the continuous data using a window analysis time of 3000 ms (from -1000 ms to 2000 ms relative to the CO_2 laser pulse). The mean signal immediately preceding the laser stimulus (from -500 ms to 0 ms) was set as baseline and removed from each epoch. Artefacts originating from eye-blinks and ocular movements were identified and pruned by means of Independent Component Analysis (ICA) (Delorme and Makeig, 2004; Jung, Makeig, Westerfield, Townsend, Courchesne, and Sejnowski, 2001; Makeig, Jung, Bell, Ghahremani, and Sejnowski, 1997). ICA is a computational method for separating a multivariate signal into independent non-Gaussian subcomponents. For each participant we manually selected and rejected all the independent components representing artefacts or non-cortical processes, such as eye movements or facial muscle activity. The criteria for the identification of muscular artefacts were based on each component’s scalp topography, power spectrography, inter-trial coherency, and intra-trial time course.

After the pre-processing, Laser-evoked potentials (LEPs) data analysis were computed on the signal recorded at the vertex (electrode Cz in the 10-20 system). LEPs consist of several transient responses that are time locked and phase locked to the onset of laser stimuli (Mouraux and Iannetti, 2008). For each participant, epochs from each specific experimental condition were averaged and time-locked to the onset of the CO_2 laser pulse. Then, the main negative (N2 wave) and positive (P2 wave) vertex components associated with LEP were manually identified and selected on the basis of their latency and polarity, for each participant and in each condition. In particular, N2 and P2 components were defined as the most negative and positive biphasic deflections between 150 ms and 500 ms after stimulus onset (Hu, Cai, Xiao, Luo, and Iannetti, 2014; Iannetti, Hughes, Lee, and Mouraux, 2008). Comparison analysis between conditions were performed on the amplitude of the group-level average waveforms.

Procedure

The setting, apparatus, and experimental design of Experiment 2 were based on the methods described for Experiment 1. We used the same paired conditioning-test stimulus paradigm and the same eight thermal conditions described above to test N2 and P2 amplitudes. The main difference between experiments was in the dependent variables.

Participants were seated in a comfortable chair in a quiet, temperature-controlled room, and were familiarized with the thermal and laser stimuli before the beginning of the experiment. In a pre-phase, the same psychophysical staircase procedure described above was used here to calculate participants' pain threshold in absence of thermal stimulation. This ensured that the CO_2 laser intensity in the main phase of the experiment was perceptually comparable among participants. Laser temperature of the first trial of the staircase was again set at 40°C, and the intensity of the following trials adaptively changed according to participants' RT. However, a different stopping rule was used here. After the third reversal, any intensity producing an Aδ-like response (RT < 650 ms) was repeated three times. The participant's pain threshold was defined as the laser temperature inducing two out of three consecutive Aδ-like responses. After pain thresholds were established, the EEG cap was mounted and the experiment began.

Participants completed eight blocks composed of 16 trials each. In each block the eight different thermal condition described for Experiment 1 (see Figure 2) were presented twice, in a fully randomised order, giving a total of 128 trials. A beep signalled the beginning of each trial. Then, the thermal stimulation for the specific condition ramped up from a baseline level of 32°C to a target intensity of 40°C (~2°C/s), and remained steady for the entire duration of the trial. After a variable delay (5-6 s), a 100 ms CO_2 laser pulse was delivered to the dorsum of participants' right middle finger.The intensity of the laser stimulation for each participant was set at the individual pain threshold +6°C, and was kept fixed throughout the entire experiment. No motor response was required, to prevent motor cortex activation during LEP recording. Participants were asked to focus on both warmth and pain stimuli while fixing a fixation cross placed in front of them. After 3 s, a further beep occurred, and participants rated the intensity of thermal and laser stimulation providing a number from 0 to 10 for each sensation (see above). The inter-trial interval varied randomly between 12 and 27 s, and the position of the laser beam on the finger was slightly changed between each trial, to prevent sensitisation and habituation of the receptors.

5.3 Results

5.3.1 Experiment 1

Magnitude estimates of warmth

We analysed magnitude estimates of warmth on the middle finger as a sanity check, to ensure that thermal stimulation was reliably perceived as predicted in each experimental condition. First, we ran a repeated measures ANOVA to test perception of warmth in the four relevant spatial conditions (no thermal, same finger, adjacent fingers, thermal referral; see above). We found a highly significant effect of position of warmth on participants' magnitude ratings ($F_{3,\ 27} = 21.273$, $p < 0.001$; η2 = 0.703). Pairwise comparisons showed that all thermal conditions were significantly different from the "no thermal stimulation" condition ($p \leq 0.005$ in all comparisons) (see Figure 5.3A). In particular, compared with no warmth (condition 1, mean ± SD: 0.1 ± 0.3), participants reported higher magnitude estimation when the same (condition 3: 2.8 ± 1.3), or adjacent (conditions 2 and 4: 2.2 ± 1.7) fingers were stimulated. Crucially, also classical thermal referral induced significantly higher ratings of warmth (condition 6: 3.6 ± 1.9). Magnitude estimates did not differ among the three thermal conditions ($p \geq 0.096$).

Second, the presence of spatial summation with increasing number of thermal stimuli was tested through a linear trend analysis on single (average of conditions 2, 3, and 4), double (average of condition 5, 6, and 7), and triple simultaneous finger stimulation (condition 8) (see Figure 5.2). The analysis showed a significant monotonic increase in warmth perception along with the number of fingers stimulated ($t_9 = 5.097$, $p < 0.001$; 95% CI: 0.76, 1.57; Cohen's dz = 2.062). In all participants, ME of warmth was lower during conditions in which only one finger was stimulated (2.4 ± 1.5) and parametrically increased when two (3.6 ± 1.4) and three fingers (4.1 ± 1.8) were simultaneously stimulated (see Figure 5.4A).

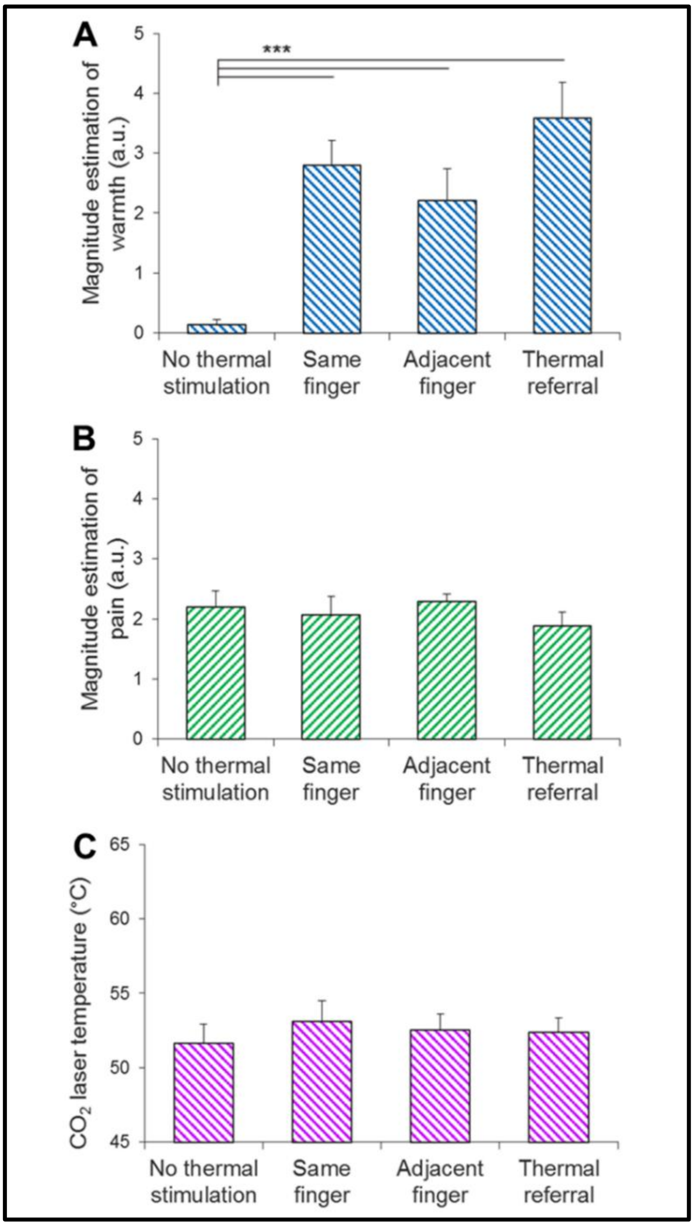


Figure 5.3. Effect of site of thermal stimulation on warmth and pain perception in Experiment 1.

A. Magnitude estimation of warmth. Compared with no thermal stimulation, participants perceived higher intensities of warmth in each thermal condition. B. Magnitude estimation of pain. Pain perception did not vary across conditions, confirming that the perceptual clamping induced by the psychophysical staircase implemented was effective (see text). C. Pain threshold. Participants' pricking detection thresholds were not affected by any of the thermal conditions. Error bars represent the standard error of the mean.

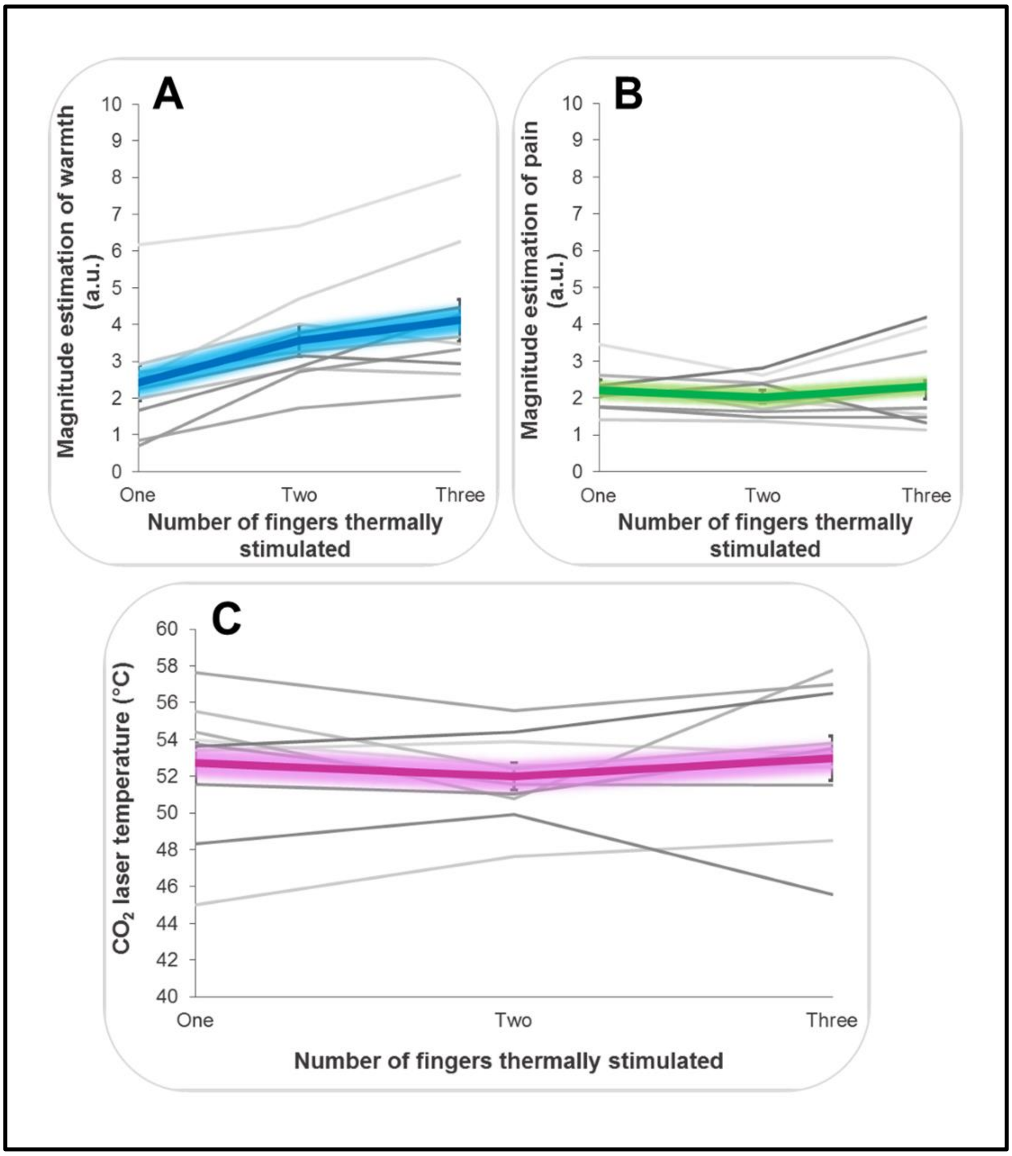


Figure 5.4. Effect of number of thermal stimuli on pain in Experiment 1.

A. Magnitude estimation of warmth. Increasing the number of fingers thermally stimulated induced a monotonic increase in the apparent intensity of warmth on the middle finger, as intended. B. Magnitude estimation of pain. Again, pain perception did not vary across conditions, confirming the effectiveness of our psychophysical thresholding method (see text). C. Pain threshold. Participants' pricking detection thresholds did not vary when single, double, or triple simultaneous stimulations were provided. Grey lines represent data from single participants. Coloured lines represent the average across participants. Error bars and shading of coloured lines represent the standard error of the mean.

Thus, participants were able to correctly perceive single warm stimulations delivered on the middle finger. Moreover, when a single adjacent finger was stimulated, participants reported illusory sensation of warmth on the middle finger, suggesting thermal referral for single stimulation (Green, 1978). Importantly, participants also perceived classical thermal referral when both the index and ring fingers were simultaneously stimulated. Although the thermal state of the middle finger was neutral in each of these conditions, all participants reported higher perception of warmth during thermal referral compared with no thermal stimulation. Finally, as the number of stimulated fingers increased, perception of warmth on the middle finger also showed a monotonic increase, as expected.

Magnitude estimates of pain

Experiment 1 was specifically designed to measure differences in pain thresholds through the psychophysical method of staircases. For this reason, in this experiment magnitude estimates of pain were used as a manipulation check, to verify the reliability of the staircase procedure implemented, rather than as the key dependent variable of interest. As mentioned above, psychophysical staircases are adaptive methods where the physical intensity of a stimulus is adjusted to a specific perceptual threshold. Therefore, in this experiment we expected our adaptive algorithm to produce uniform pain perception across all the experimental conditions.

Magnitude ratings of CO_2 laser stimuli ranged from 0.6 to 2.3, and were generally on the lower side of the scale (mean ± SD: 2.2 ± 0.8), confirming that pain perception was kept around pinprick detection threshold level. The repeated measures ANOVA on the four relevant spatial conditions (see above) was far from statistical significance ($F_{3, 27} = 1.529$, $p = 0.230$) (see Figure 5.3B). To determine whether the data offered support for the null hypothesis, we additionally ran a Bayesian repeated measures ANOVA (Rouder, Speckman, Sun, Morey, and Iverson, 2009; Weltzels, Grasman, and Wagenmakers, 2012). The result was strongly in favour of the null hypothesis, showing that the data were twice as likely to occur under the null model than under the alternative model ($BF_M = 0.478$; $BF_{01} = 2.092$, error = 0.457%).

Similarly, the linear trend analysis of ME of pain along increasing number of thermal stimuli was also non-significant ($t_9 = -1.469$, $p = 0.176$) (see Figure 5.4B). The Bayesian factor analysis for one sample t-test was again in favour of the null hypothesis, showing that the data were 1.4 times more likely to occur under the null model ($BF_{01} = 1.408$; error < 0.001%). This indicates that the data are not under-powered, and that they provide substantial evidence for the null hypothesis.

These preliminary analyses confirmed that the psychophysical staircases were effective in selecting laser energies that produced comparable pain perception across the different warmth stimulation conditions.

Psychophysical staircases

The frequency distribution of the reaction times was clearly bimodal, with our cut-off of 650 msec effectively separating participants' responses into two categories (see Figure 5.5) with peak average at 549 ms and 1271 ms, respectively. This confirmed that our psychophysical staircases were effective in eliciting Aδ fiber- and C fiber-like RTs, supporting the reliability of our procedure.

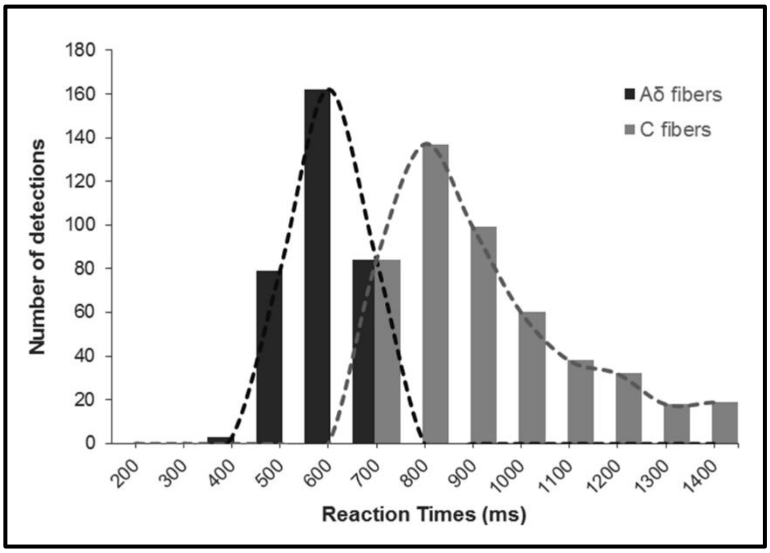


Figure 5.5. Frequency distribution of the RTs in the psychophysical threshold procedure implemented in Experiment 1.

RTs to brief CO_2 laser pulses applied on the dorsum of participants' right middle finger showed a clear bimodal distribution, suggesting that the 650 ms criterion used for the selective activation of Aδ fibers in the pricking detection threshold procedure was compatible with the conduction velocity of (myelinated) Aδ fibers and (unmyelinated) C fibers.

However, pain thresholds varied greatly across participants and conditions, with CO_2 laser intensity ranging from 44.3°C to 58.3°C (mean temperature ± SD: 52.3°C ± 3.7°C). Unexpectedly, neither the repeated measures ANOVA on spatiality ($F_{3,\ 27} = 0.670$, $p = 0.578$) (see Figure 5.3C), nor the linear trend on numerosity of warm stimuli ($t_9 = -1.101$, $p = 0.299$) reached statistical significance (see Figure 5.4C). Importantly, the Bayesian analyses on both tests showed that our data were amply powered for detecting an eventual effect of spatiality and/or numerosity on pain threshold, supporting the null hypothesis by a probability ratio of 4:1 ($BF_M = 0.198$; $BF_{01} = 4.057$, error = 1.222%) and 2:1 ($BF_{01} = 1.955$, error < 0.001%), respectively.

Thus, pain thresholds were not modulated by any of our thermal conditions, and no behavioural evidence of thermo-nociceptive interaction was observed in the present experiment.

5.3.2 Experiment 2

Magnitude estimates of warmth

Results on magnitude estimates of warmth replicated the findings of Experiment 1. The repeated measures ANOVA on temperature ratings in the different spatial conditions was highly significant ($F_{3,\ 39} = 38.690$, $p < 0.001$; η2 = 0.748) (see Figure 5.6A). All pairwise comparisons were significant ($p < 0.001$) except the contrast between “warmth on the middle finger” and thermal referral conditions ($p = 0.560$). In particular, compared with no thermal stimulation condition (condition 1: 0.5 ± 0.6), participants rated perceived warmth on the middle finger significantly higher when thermal stimuli were presented 1) on the same finger (condition 3: 2.8 ±

1.5), 2) on adjacent fingers (conditions 2 and 4: 1.9 ± 0.9), or 3) or simultaneously on index and middle fingers (TR) (condition 6: 3.0 ± 1.2). Moreover, classical thermal referral was stronger than thermal referral induced by single stimuli on adjacent fingers and did not differ from physical stimulation applied on the middle finger.

The linear trend analysis on warmth intensity ratings during single (average of conditions 2, 3, and 4), double (average of condition 5, 6, and 7), and triple finger stimulation (condition 8) showed that perception of warmth on the middle finger parametrically increased along with the number of thermally stimulated fingers ($t_{13} = 7.675$, $p < 0.001$; 95% CI: 1.52, 2.70; Cohen's $d_z = 2.051$). Thermal stimulation on the middle finger was perceived lower when one finger was stimulated (2.2 ± 1.0) and linearly increased when two fingers (3.4 ± 1.3) and three fingers (4.3 ± 1.8) were simultaneously stimulated (see Figure 5.9A).

Thus, thermal stimulation was reliable and provided the expected results on mislocalisation and spatial summation of warmth.

Magnitude estimates of pain

In Experiment 1 we used psychophysical staircases to manipulate the physical intensity of pain. Consequently, pain perception was balanced across the different experimental conditions by adjusting CO_2 laser intensity. Conversely, in Experiment 2 we kept CO_2 laser intensity fixed within participants, and analysed magnitude estimates of pain as a dependent variable of our thermal manipulation.

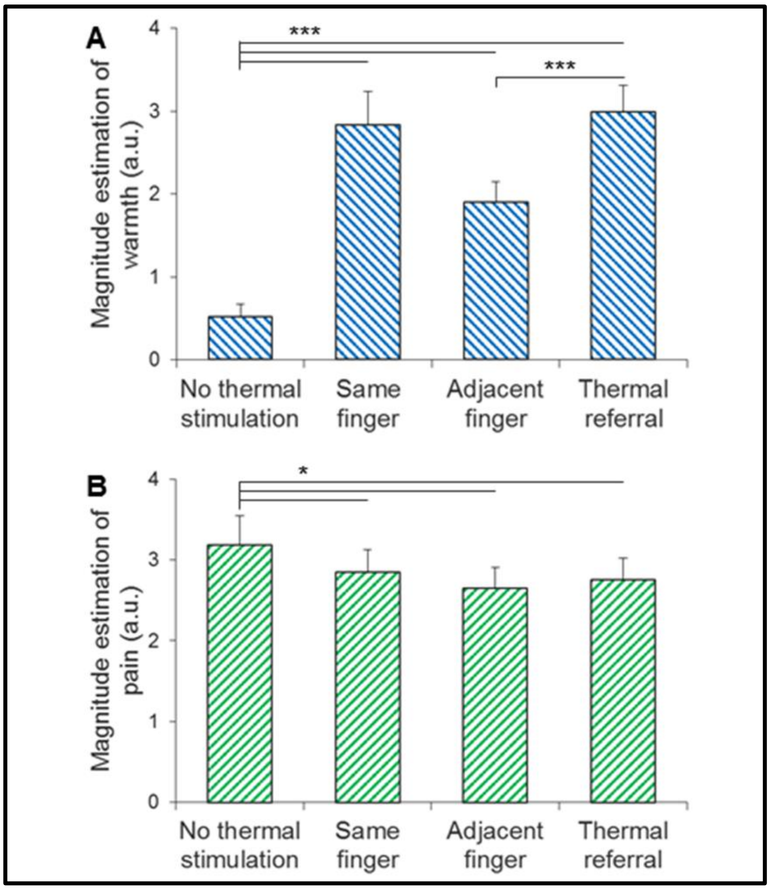


Figure 5.6. Effect of site of thermal stimulation on warmth and pain perception in Experiment 2.

A. Magnitude estimation of warmth. Compared with no thermal stimulation, participants perceived higher intensities of warmth in each thermal condition. B. Magnitude estimation of pain. Pain perception was significantly reduced in all thermal condition, compared with no thermal stimulation. However, the site of thermal stimulation did not affect the suppressive interaction. Error bars represent the standard error of the mean.

The repeated measures ANOVA on the different spatial conditions was significant ($F_{3,\ 39} = 5.165$, $p = 0.004$; $\eta2 = 0.284$) (see Figure 5.6B). Baseline pain perception on the middle finger (condition 1: 3.2 ± 1.3) was significantly reduced by any concurrent thermal stimulation ($p \leq 0.026$ in all comparisons). In particular, in 10 out of 14 participants, magnitude estimates of pain decreased in average of 10.5% when warmth was concurrently delivered on the same finger (mean ± SD: 2.9 ± 1.0). Eleven out 14 participants also showed a significant reduction of pain (16.8% in average) when warmth was delivered on the adjacent fingers (2.6 ± 1.0). Pain was also reduced of 13.6% in average in 10 out of 14 participants during classic thermal referral (2.8 ± 1.0). Other pairwise comparisons were non-significant ($p \geq 0.172$) (see Figure 5.9B).

To investigate the effect of spatial summation of warmth on pain perception, we again performed a planned linear trend comparison on the conditions where single (average of condition 2, 3, and 4), double (average of conditions 5, 6, and 7) or triple (condition 8) thermal stimulations were applied to the fingers (see above and Figure 5.8). No linear trend was found ($t_{13} = 0.342$, $p = 0.738$). This suggests that increasing the number of simultaneous thermal stimulation did not affect subjective perception of pain (one finger: 2.7 ± 1.0; two fingers: 2.7 ± 0.9; three fingers: 2.5 ± 1.0) (see Figure 9B). We also applied Bayes factor analysis and found that the null hypothesis was 3.5 times more likely that the alternative hypothesis ($BF_{01} = 3.518$, error < 0.001%), suggesting that the absence of a linear trend among conditions with increasing number of thermal stimuli was not simply due to a lack of statistical power.

To summarise, warmth had an inhibitory effect of on pain perception, irrespectively of the site of thermal stimulation. Interestingly, although pain was attenuated by the illusory perception of warmth produced by TR, the concomitant presentation of multiple thermal stimuli did not produce any further modulation of the thermo-nociceptive interaction.

Laser Evoked Potentials (LEPs)

Latency grand averages (across participants and conditions) for N2 and P2 components (mean latency for N2 wave ± SD: 262.4 ms ± 40.3 ms; P2: 390.3 ms ± 55.1 ms) were consistent with previous reports on LEPs (Valentini, Chakrabarti, Aglioti, and Iannetti, 2012; Hu, Cai, Xiao, Luo, and Iannetti, 2014; Truini, Galeotti, Cruccu, and Garcia-Larrea, 2007) (see Figure 5.7).

Concomitant warmth stimulation had a modulatory effect on N2 (F3, 39 = 3.030, p = 0.041; η2 = 0.189), but not on P2 component (F3, 39 = 0.080, p = 0.971) (see Figure 5.8). The Bayesian repeated measures ANOVA on P2 amplitude data confirmed that the probability of the null result merely reflected a lack of power was extremely low (BFM = 0.104; BF01 = 9.596, error = 0.673%). Dissociation of effect on N2 and P2 has been reported previously (Tran, Matre, and Casey, 2008). The peak amplitude of N2 wave in the baseline condition, without thermal stimulation was delivered, was significantly higher than all the other thermal conditions. In particular, compared with no thermal stimulation (-15.2 μV ± 7.3 μV), N2 amplitude was significantly reduced when a concomitant thermal stimulus was presented on the same finger (-11.1 μV ± 4.1 μV, *p* = 0.007). This modulation was very consistent across participants, as shown by a mean suppression of 22.2% of N2 amplitude in 11 out of 14 participants. N2 was reduced by 27.8% in 12 participants out of 14 also when warmth was applied on the adjacent fingers (-11.9 μV ± 3.5 μV, *p* = 0.028). A marginally significant drop of 22.8% in N2 amplitude was also found in 10 participants out of 14 during classical thermal referral (-12.3

μV ± 5.0 μV, *p* = 0.051). All the other comparisons were far from statistical significance (*p* ≥ 0.427).

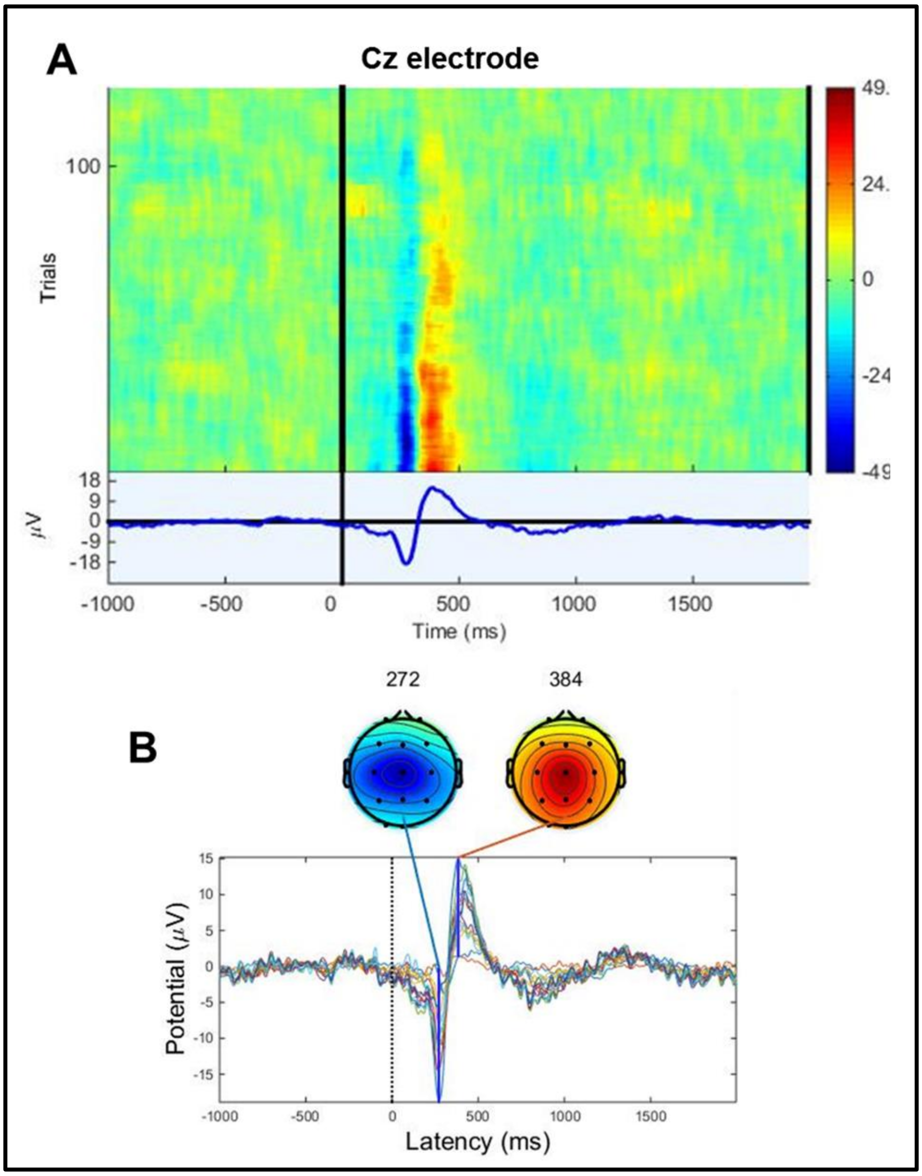


Figure 5.7. N2-P2 complex in a representative participant in Experiment 2.

A. Inter-trial coherence and LEP grand average. The N2-P2 complex recorded from Cz electrode was clearly detectable in almost every trial. B. N2 and P2 topographies and latencies. Both LEPs components showed scalp distributions and peak amplitudes coherent with previous studies on nociception induced through CO_2 laser pulses on the hairy skin of the hand.

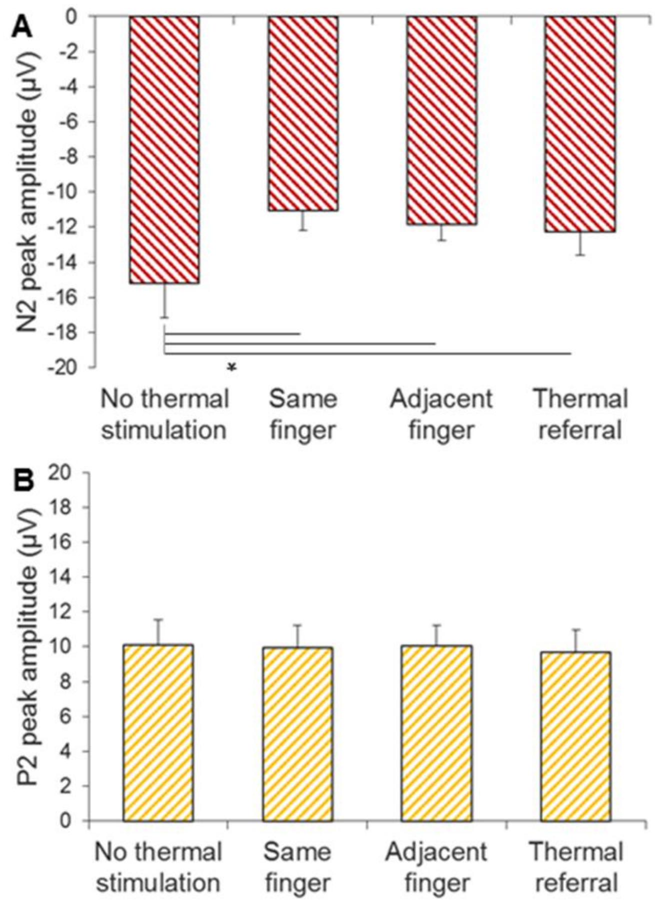


Figure 5.8. Effect of site of thermal stimulation LEPs components in Experiment 2.

A. N2 wave. Peak amplitude of N2 component was significantly reduced in all thermal condition compared with no thermal stimulation condition. However, warmth suppressed Aδ fibers cortical response irrespectively from the site of stimulation. B. P2 wave. P2 component was not affected by any of the experimental conditions. Error bars represent the standard error of the mean.

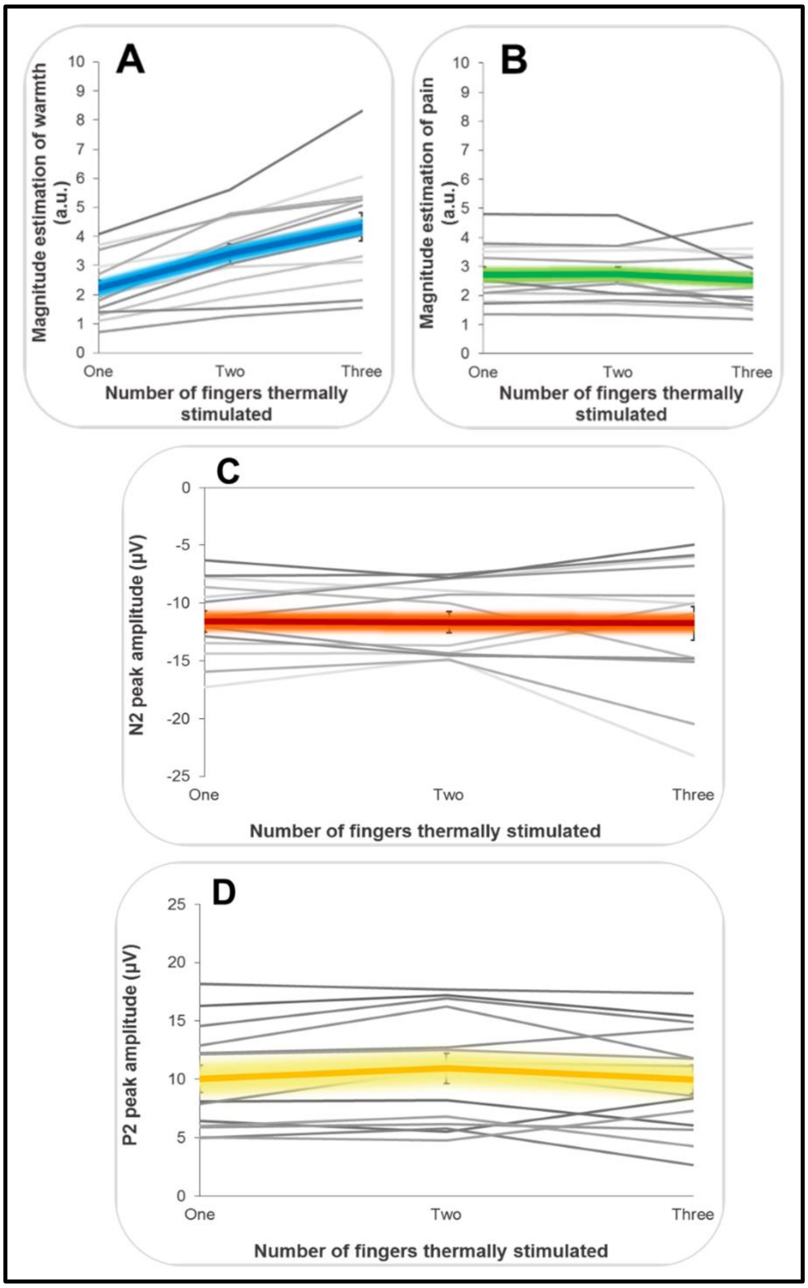


Figure 5.9. Effect of number of thermal stimuli on pain in Experiment 2.

A. Magnitude estimation of warmth. Increasing the number of fingers thermally stimulated induced a monotonic increase in the apparent intensity of warmth on the middle finger. However, neither perceptual (B) nor electrophysiological (C and D) correlates of pain were affected by the number of simultaneous thermal stimulations. Grey lines represent data from single participants. Coloured lines represent the average across participants. Error bars and shading of coloured lines represent the standard error of the mean.

N2 and P2 amplitudes during single (average of condition 2, 3, and 4), double (average of conditions 5, 6, and 7) or triple (condition 8) thermal stimulations were inserted in two separate linear trend analyses to assess the effect of numerosity of thermal stimulation on LEPs. In both cases, the amplitude of pain-related components did not show any linear trend ($p \geq 0.874$ in both tests), and values for N2 (one finger: -11.6 μV ± 3.4 μV; two fingers: 11.7 μV ± 3.5 μV; three fingers: 11.7 μV ± 5.5 μV) and P2 (one finger: 10.0 μV ± 4.4 μV; two fingers: 10.9 μV ± 4.8 μV; three fingers: 10.0 μV ± 4.5 μV) were strikingly similar across the different thermal conditions (see Figure 10B and Figure 10C). The Bayes factor analysis was again strongly in favour of the null hypothesis, showing that the probability of a linear trend was more 3.5 times less likely than the null hypothesis for both LEP components (N2: $BF_{01} = 3.662$, error = 0.001%; P2: $BF_{01} = 3.683$, error = 0.001%).

Overall, the modulation of N2 amplitude across all thermal conditions closely reflected participants' subjective perception of pain. Applying concurrent warm stimuli attenuated perception and electrophysiological correlates of pain, regardless of the spatial position. However, neither N2 nor P2 LEP components showed a significant linear trend at increasing number of thermal stimuli simultaneously presented.

5.4 Discussion

In the present study, we manipulated the number and the position of thermal stimuli concurrently delivered with a CO_2 laser pulse, to investigate the spatial properties of warmth-pain interaction and the level of somatosensory processing at which it takes place. To achieve this goal, we exploited, seemingly for the first time, the properties of thermal referral and multiple simultaneous thermal stimulation, two thermal phenomena based on spatial summation, which are known to modulate the thermal percept without changing the local state of the skin on the target site. We replicated the classical suppressive effect of warmth on pain processing. Crucially, we also found that inhibition of pain was independent from both the position and the number of thermal stimuli administered. This suggests that effect of warmth on Aδ nociceptors and pain is not strongly somatotopic, and that the modulation of nociception by warmth occurs prior to, or independently of intra-channel summation of multiple thermal inputs. Our results are multifaceted, but clear.

First, the internal validity of the study is confirmed by the data on magnitude estimation of warmth in each of our thermal conditions. Magnitude estimates were largely independent of warm stimulus location, heavily dependent on warm stimulus numerosity, and demonstrated the illusory mislocalisation of thermal sensation (i.e. thermal referral). Therefore, by carefully controlling participants' warmth perception, our paradigm allowed us to make clear predictions about the relation between pain and both physical and perceptual content of thermoception.

Second, in line with previous reports (Casey, Zumberg, Heslep, and Morrow, 1993; Plaghki, Decruynaere, Van Dooren, and Le Bars, 2010; Truini, Galeotti, Cruccu, and Garcia-Larrea, 2007; Tran, Matre, and Casey, 2008; Nahra and Plaghki, 2005), our data from Experiment 2 showed that a concurrent thermal stimulus induced a significant attenuation of both subjective (magnitude estimates) and objective (LEPs) measures of pain.

Crucially, the inhibitory effect of warmth on pain was comparable when warmth and laser were delivered to the same finger, and when they were delivered to adjacent fingers. In fact, an equal, or even higher amount of attenuation of pain was present in the conditions where participants experienced TR, reporting warmth on the middle finger in absence of any physical stimulation on that site. These results can be explained by two alternative mechanisms. On the one hand, they may represent a central processing of warmth-pain interaction, occurring on top of spatial summation and after full perceptual analysis of the thermal stimulus. On the other hand, they may support the idea of a diffuse, non-somatotopic integrative mechanism, completely independent from the perceptual content of thermoception.

To disentangle between these two alternative possibilities, we made a clear prediction based on our manipulation of multiple simultaneous thermal stimuli. We expected that if pain processing is secondary to full perceptual computation of temperature, enhancing the apparent intensity of warmth by increasing the number of stimulated fingers, should produce a stronger inhibitory effect on pain. On the contrary, if thermo-nociceptive interaction occurs independently from spatial summation, our thermal numerosity manipulation would not produce any change in pain processing. Our linear trend analysis clearly showed that while *thermal* perception was strongly affected by the number of simultaneous stimuli presented, neither perceptual nor electrophysiological correlates of pain followed this trend. Summation of warmth did not influence the degree of pain suppression.

Spatial organisation of warmth-pain interaction

Previous works have investigated the spatial gradient of thermo-nociceptive interaction (Price and McHaffie, 1988; Casey, Zumberg, Heslep, and Morrow, 1993; Tran, Matre, and Casey, 2008). These studies generally converge on the interpretation that the warmth-pain interaction is non-somatotopic. A somatotopic organization would require that stimuli applied to the same fingers interact more than stimuli applied to different fingers. For example, Tran and colleagues (2008) systematically manipulated the site of thermal stimuli presented during concomitant electrical pain stimulation. Their data showed that C fibers conditioning of Aδ fibers-mediated cortical response was equally effective at intrasegmental, intersegmental, and even contralateral stimulation sites (Tran, Matre, and Casey, 2008), suggesting a *diffuse*, rather than spatially-dependent interaction mechanism. Similarly, in our study we did not observe any difference in the modulation of pain when the thermal and noxious stimuli were presented on different fingers. As a consequence, a strictly peripheral account of warmth-pain interaction can be ruled out. However, a central integrative mechanism occurring *after* the full perceptual processing of both signals is equally unlikely.

In our Experiment 2, a linear increase in apparent intensity of warmth with number of stimulation sites did not produce a proportional linear decrease in LEP amplitudes. This suggests that the interaction between warmth and pain is strong, but is binary rather than proportional in nature. Combined together, these results indicate that the inter-channel interaction between warmth and pain must be mediated through a widely distributed, non-somatotopic mechanism, independent from the intra-channel convergence or summation of thermal inputs.

Spatial summation and thermal referral during warmth-pain interaction

In Experiment 2 we found that pain was attenuated during thermal referral conditions. However, this finding can be might be due either to scarce spatial dependency of warmth-pain interaction, or to the illusory percept induced by the illusion.

Several studies have investigate the nature of thermal referral (Green, 1977, 1978; Ho, Watanabe, Ando, and Kashino 2011; Cataldo, Ferrè, di Pellegrino, and Haggard, 2016). According to the classical account, when a thermo-tactile stimulus is applied on the fingers of one hand, the uniformity (low variability) between the multiple simultaneous tactile stimuli would trigger the representation of a single, homogenous object. Then, based on the prior that single objects have uniform temperature (at least on the area interested by the touch of three adjacent fingers of one hand), a cognitive, top-down mechanism would “fill-in” the thermal information about the middle finger with the content of the surrounding fingers (Dennet, 1992). In contrast with this interpretation, recent studies (Ho, Watanabe, Ando, and Kashino 2011; Cataldo, Ferrè, di Pellegrino, and Haggard, 2016) have ruled out explanations based on high-level process of object attribution. In particular, Cataldo and colleagues (2016) have shown that thermal referral can be induced using purely thermal stimulation, without any tactile object to which temperature can be attributed. This finding was interpreted as the evidence that thermal referral relies on the spatial summation mechanisms occurring within the thermoceptive system. Hence, thermal referral most likely results from the convergence of finger-specific thermal information on higher-level neurons with spatially–extended, multi-digit receptive fields, which summate their thermal inputs (Cataldo, Ferrè, di Pellegrino, and Haggard, 2016; Fritzgerald, Lane, Thakur, and Hsiao, 2006).

Interestingly, Cataldo and colleagues (2016) also postulated that detection and localisation of a thermal stimulus would occur at the first level, where digit-specific information is available, while information about the overall pattern of thermal intensities, as in thermal referral, would occur only at the second level, where digit-specific information is not available (Cataldo, Ferrè, di Pellegrino, and Haggard, 2016).

From this point of view, the modulation of pain during thermal referral we observed in our Experiment 2 may be interpreted as the evidence that warmth-pain interaction also occurs at this second stage, after the single thermal inputs have converged and summed in a holistic percept. However, this interpretation implies a very straightforward prediction about the manipulation of numerosity of thermal stimuli implemented in our study. If warmth-pain interaction occurs on top of spatial summation, the stronger thermal signal resulting from the convergence of multiple, compared to single stimuli should produce a stronger suppression of nociceptive information. Tran and colleagues (2008) have shown that Aδ-mediated cortical response is significantly more attenuated by a 50°C, rather than a 37°C, C fiber conditioning stimulus, suggesting that the *physical intensity* of the thermal stimulus is taken into account for the processing of pain. If the *perceived intensity* of a thermal pattern had the same inhibitory effect on pain, an increase in the overall apparent warmth intensity should produce a similar monotonic reduction of pain signal.

The results from our Experiment 2 are strongly against this possibility. Based on the assumption of spatial summation, we fitted a simple model of a linear relation between the number of fingers thermally stimulated and pain levels. For both our measures of pain, the probability for our data to be explained by a linear trend were amply far from statistical significance (magnitude estimates of pain: p = 0. 738; LEPs: $p \geq 0.874$). In particular, both magnitude estimates and LEPs of pain showed remarkably similar values along the three thermal conditions. Although caution is generally required in drawing conclusions from null results, our findings are unlikely to reflect a lack of power for two reasons. First, before data collection we conducted a power analysis using the effect size of a previous EEG pilot study to calculate *a priori* the sample size required to obtain a statistical power of at least 0.8 (1 - β error probability). Second, we also tested the probability of the null versus the alternative hypothesis *a posteriori*, by means of Bayesian analysis. In all the non-significant results from the linear trend analyses, the data were always about 3.5 times more likely to occur under the null than the alternative model, supporting the idea that in fact, warmth-pain interaction was not modulated by the increase of apparent warmth induced by spatial summation.

Dissociation between correlates of pain and pain thresholds

Overall, warm stimuli modulated both the perceptual and neurophysiological measures of pain tested in Experiment 2, but not the pinprick detection thresholds measured in Experiment 1. Pricking detection threshold and tolerance pain thresholds are commonly used as dependent variables in studies assessing the effect of specific experimental manipulations on pain processing (Berkley, 1997; Rolke, Baron, Maier, Tölle, Treede, Beyer, and Braune, 2006; Robin, Vinard, Vernet-Maury, and Saumet 1986; Bendtsen, Jensen, Olesen, 1996; Pickering, Jourdan, Eschalier, and Dubray, 2002). However, the psychophysical method most commonly adopted for the study of warmth-pain interaction is the subjective magnitude estimation, assessed through verbal ratings or visual analogue scales (Price and McHaffie, 1988; Casey, Zumberg, Heslep, and Morrow, 1993; Nahra and Plaghki, 2005; Truini, Galeotti, Cruccu, and Garcia-Larrea, 2007; Tran, Matre, and Casey, 2008; Hu, Cai, Xiao, Luo, and Iannetti, 2014). While a dissociation between LEP correlates and subjective perception of pain has already been observed (Truini, Galeotti, Cruccu, and Garcia-Larrea, 2007), only two studies, to date, have used psychophysical staircase procedures to investigate the effect of an adapting temperature on pain thresholds (Plaghki, Decruynaere, Van Dooren, and Le Bars, 2010; Churyukanov, Plaghki, Legrain, and Mouraux, 2012). Interestingly, the results from these studies are in open contrast with each other. On the one hand, Plaghki and colleagues (2010) found that the threshold for pricking pain elicited by CO_2 laser stimuli was largely invariant with regard to the baseline skin temperature, but was instead strongly modulated by the transient thermal change produced by an infrared heat stimulation. Increasing the skin temperature of a large surface area by an average of ~8°C resulted in an increase of pain threshold of about ~4°C (Plaghki, Decruynaere, Van Dooren, and Le Bars, 2010). On the other hand, Churyukanov and colleagues (2012) observed the opposite pattern of results. They found a highly significant positive relationship between Aδ fibres threshold and the skin temperature measured before the onset of the trial, but no effect of increasing the skin temperature by +4°C or +8°C prior to applying a CO_2 laser pulse on the same spot. This discrepancy was explained as a possible effect of temporal dynamics and spatial extension of the thermal stimulus (Churyukanov, Plaghki, Legrain, and Mouraux, 2012). While the rise time of warm stimuli in Plaghki et al. (2010) was very slow (~2.5°C/s) and the stimulation area very large (whole hand; ratio between warmth and pain: ~50:1), the stimulation provided by Churyukanov and colleagues (2012) had a very quick ramping rate (~8°C/s), but stimulated only a very small surface area (6 mm diameter; ratio between warmth and pain: 1:1).

The thermal stimulation used in our experiments differed in many aspects from that described in either of these studies. First, we kept room temperature under control (~23°C), and we carefully measured participants' skin temperature throughout the entire duration of both experiments in order to keep it at a stable level. We expected, and obtained, very little variation in participants' baseline skin temperature (Experiment 1, mean ± SD: 30.6°C ± 1.4°C; Experiment 2: 30°C ± 1.4°C), consequently, any eventual modulation of subjective and objective measures of pain in our data can be ascribed to the preceding thermal conditioning stimulus only. Second, whereas both previous studies have used radiant heat sources for thermal stimulation (namely infrared lamp and CO_2 laser), we used thermo-tactile stimulators. Yet, this difference cannot explain our null results in Experiment 1. Inhibition of pain during thermo-tactile stimulation has been already demonstrated, apart from our

Experiment 2, also in other previous studies (e.g. Nahra and Plaghki, 2005; Truini, Galeotti, Cruccu, and Garcia-Larrea, 2007). Moreover, if anything, concurrent tactile stimulations would have induced a stronger inhibition of pain (see above), yet we did not find any significant difference between our thermal conditions and the baseline. Third, the temporal and spatial properties of our thermal stimuli laid somewhere in between those described above. Our Peltier-based thermodes had a slow ramping rate (~2°C/s), as in Plaghki et al. (2010), but a relative small contact surface area (13mm in diameter; ratio between warmth and pain: ~2:1), similarly to Churyukanov et al. (2012). Crucially, our main manipulation interested the extent of the stimulation area, therefore, if the size of the thermal stimulus is responsible for the different results between Plaghki et al. (2010) and Churyukanov et al. (2012), we should observe in our data an increase in pain threshold when three (ratio warmth-pain: ~4:1) versus one (ratio warmth-pain: 1:1) finger/s are stimulated. Conversely, the average CO_2 laser temperature reached in the two conditions differed by as little as 0.3°C, with a SD of 3.7°C, and the linear trend analysis on threshold values was far from statistical significance ($p = 0.299$).

The reliability of our staircase procedure was confirmed by the bimodal nature of RT responses, and by fact that in the same experiment participants' perceptual judgements of pain were low (mean ± SD: 2.2 ± 0.8) and uniform across conditions ($p = 0.230$), showing that pain perception was kept at pricking detection threshold, as intended. Moreover, our sample size was decided *a priori* on the basis of previous similar studies, and, most importantly, the Bayes factor analysis performed on the linear trend supported the null over the alternative hypothesis. This makes it very unlikely that our null results are due to a lack of statistical power. Finally, although thermal stimulation in Experiment 1 (36°C) was less intense than that in Experiment 2 (40°C), participants' magnitude estimation of warmth was very similar, and showed exactly the same pattern of modulation in both cases. Therefore, we hypothesize that a dissociation between pricking detection thresholds and perceptual and electrophysiological correlates of pain may exist. Further investigation is needed to address this question more specifically.

Mechanisms underlying warmth-pain interaction

Different theories have been proposed, so far, to explain the interaction between thermoceptive and nociceptive systems. Early electrophysiological studies have focussed on the observation that cortical responses to C fibers cannot be recorded if a concomitant Aδ fibers stimulation is provided (Bromm and Treede, 1987a; Treede, Kief, Hölzer, and Bromm 1988; Treede, Rolf-Detlef, Lorenz, and Baumgärtner, 2003; Kakigi, Inui, and Tamura, 2005; but see also Hu, Cai, Xiao, Luo, and Iannetti, 2014). This effect has been interpreted as the possibility that the two electrophysiological responses derives from the same cortical generators, and that, therefore, a *refractory period* impedes the simultaneous concurrence of both signals (Magerl, Ali, Ellrich, Meyer, and Treede, 1999; Kakigi, Tran, Qiu, Wang, Nguyen, Inui, and Hoshiyama, 2003; Plaghki and Mouraux, 2002). Although refractoriness can explain the inhibitory effect of Aδ over C fibers-evoked responses, this theory has been criticised after the first reports that, conversely, a preceding C fiber pulse does not completely abolish the perception of a subsequent Aδ stimulus, as an on/off mechanism would predict (Mouraux, Guerit, and Plaghki, 2004; Truini, Galeotti, Cruccu, and Garcia-Larrea, 2007; Tran, Matre, and Casey, 2008). A “revised” version of *relative refractoriness* has been suggested by Truini and colleagues (2007), where the ratio of energy per unit time regulates the availability of the common generators to elicit an evoked response to the second pulse. In particular, based on their data showing that high-intensity stimulations produce a stronger inhibitory effect on either systems, the authors proposed that the Aδ-C interaction is based on a *first come, first served* principle, where only the earliest signals can induce cerebral responses (Truini, Galeotti, Cruccu, and Garcia-Larrea, 2007; Garcia-Larrea, 2004). From this perspective, LEPs would then reflect the output of a network detecting rapid input changes relative to a preceding state. A similar conclusion about Aδ fibers being *change detectors*, rather than pure level detectors, was drawn by Churyukanov and colleagues (2012), who postulated that the threshold for Aδ fibers input does not rely exclusively on the physical energy applied on that system, but also on the background C fibers input coming from the skin surrounding the stimulated area.

Our findings do not deny an interpretation of Aδ-C interaction being based on the detection of the relative energy density conveyed by the two volleys. Rather, they extend it in at least two regards. First, we showed that a strictly *peripheral* mechanism of change detection, where the firing of Aδ fibers and its interaction with C fibers only depends on the skin temperature at the stimulation site, is not likely. During our thermal referral conditions, the thermal state of the finger stimulated with CO_2 laser pulse was neutral, and it is reasonable to assume that the C fibers surrounding the noxious stimulus were silent. Nonetheless, we observed the same, or even a bigger amount of signal suppression in this conditions. Therefore, sensory mechanisms located at higher levels than those detecting the relative firing rate between afferent fibers must be responsible for this effect. Second, while spatial summation of warmth would be the most plausible explanation of our first finding, the evidence that manipulating the apparent intensity of warmth did not further affect attenuation of pain suggests that a strictly *central* modulation of the interaction is equally unlikely (see Figure 5.10).

Early studies on animals have shown the existence of *wide dynamic range neurons* (WDR) in the dorsal horn of the spinal cord (Le Bars, Dickenson, and Besson, 1979a,b; Mendell, and Wall, 1965; Handwerker, Iggo, and Zimmermann, 1975; for a review see Le Bars, 2002). These neurons have the property to be multimodal, responding to input coming from all the somatosensory sub-modalities, and are often indicated as a likely substrate of the analgesia induced by touch (Mancini, Nash, Iannetti, and Haggard, 2014; Le Bars, 2002). Moreover, these multireceptive neurons have also been studied in terms of their involvement in processes of spatial summation of pain (Bouhassira, Gall, Chitour, and Le Bars, 1995; Gall, Bouhassira, Chitour, and Le Bars, 1998, 1999). In particular, most of these cells are strongly inhibited by noxious inputs applied on a remote part of the body. This phenomenon has been described with many different terms, such as *Diffuse Noxious Inhibitory Control* (DNIC) (Le Bars, Dickenson, and Besson, 1979a,b; Villaneuva and Le Bars, 1994), *Heterotopic Noxious Counter-Stimulation* (HNCS) (Price and McHaffie, 1988; Cormier, Piché, and Rainville, 2013; Rustamov, Tessier, Provencher, Lehmann, and Piché, 2016), c*ounterirritation analgesia* (Piché, Arsenault, and Rainville, 2009; Willer, Bouhassira, and Le Bars, 1999). However, to standardize terminology, it has been recently proposed to use *diffuse noxious inhibitory control* to refer to the lower brainstem-mediated inhibitory mechanism observed in animal studies, and *Conditioned Pain Modulation* (CPM) to describe the human behavioural correlates (Yarnitsky, 2010; Yarnitsky Arendt-Nielsen, Bouhassira, Edwards, Fillingim, Granot, and Wilder-Smith, 2010; Nir and Yarnitsky, 2015; Davis, 2013).

Conditioning pain modulation is described as a specific nociceptive mechanism, often summarised in the principle 'pain inhibits pain'. However, our results on warmth-pain interaction appear to be remarkably similar to a CPM mechanism in at least two aspects. First, several studies of DNIC in animals (Le Bars, 2002; Le Bars, Dickenson, and Besson, 1979a,b; Villaneuva and Le Bars, 1994) and CPM in humans (for a review see Yarnitsky, 2010 and Yarnitsky Arendt-Nielsen, Bouhassira, Edwards, Fillingim, Granot, and Wilder-Smith, 2010) in the last decades consistently showed that the inhibitory effect of 'pain on pain' does not appear to be organised somatotopically, but applies across the whole body. Second, and more importantly, Granot and colleagues (2008) also demonstrated that once the analgesic effects on a test pain stimulus were evoked by a required degree of conditioning painfulness, their magnitude was not further affected by increased conditioning pain levels (Granot, Weissman-Fogel, Crispel, Pud, Granovsky, Sprecher, and Yarnitsky, 2008). In other words, spatial summation of pain did not affect the analgesic effect of a first noxious stimulus. The authors therefore postulated that conditioning pain modulation is a phenomenon that reaches a ceiling effect and a quick saturation, such that even low amount of conditioning pain is sufficient to induce analgesia. In particular, according to Granot and colleagues (2008): *“ascending activity in the spinal pain tracts is sufficient, upon arrival in the brainstem, to activate the descending modulation response, regardless of whether the final cortical experience induced by that barrage is painful or not*”.

Our finding that pain is not affected by the apparent magnitude of conditioning warmth is strikingly in line with this hypothesis, suggesting that the analgesic effect of warmth on pain does not have a direct proportional relationship with the magnitude of perceived warmth. Therefore, although conditioning pain modulation has been described as a specific mechanism only occurring within the nociceptive pathway (Le Bars, Dickenson, and Besson, 1979a,b; Granot, Weissman-Fogel, Crispel, Pud, Granovsky, Sprecher, and Yarnitsky, 2008), our results seem to suggest that the interaction between warmth and pain may occur through a very similar non-somatotopic mechanism where the convergence *between* modalities is independent from the convergence and summation taking place *within* each channel (see Figure 5.10).

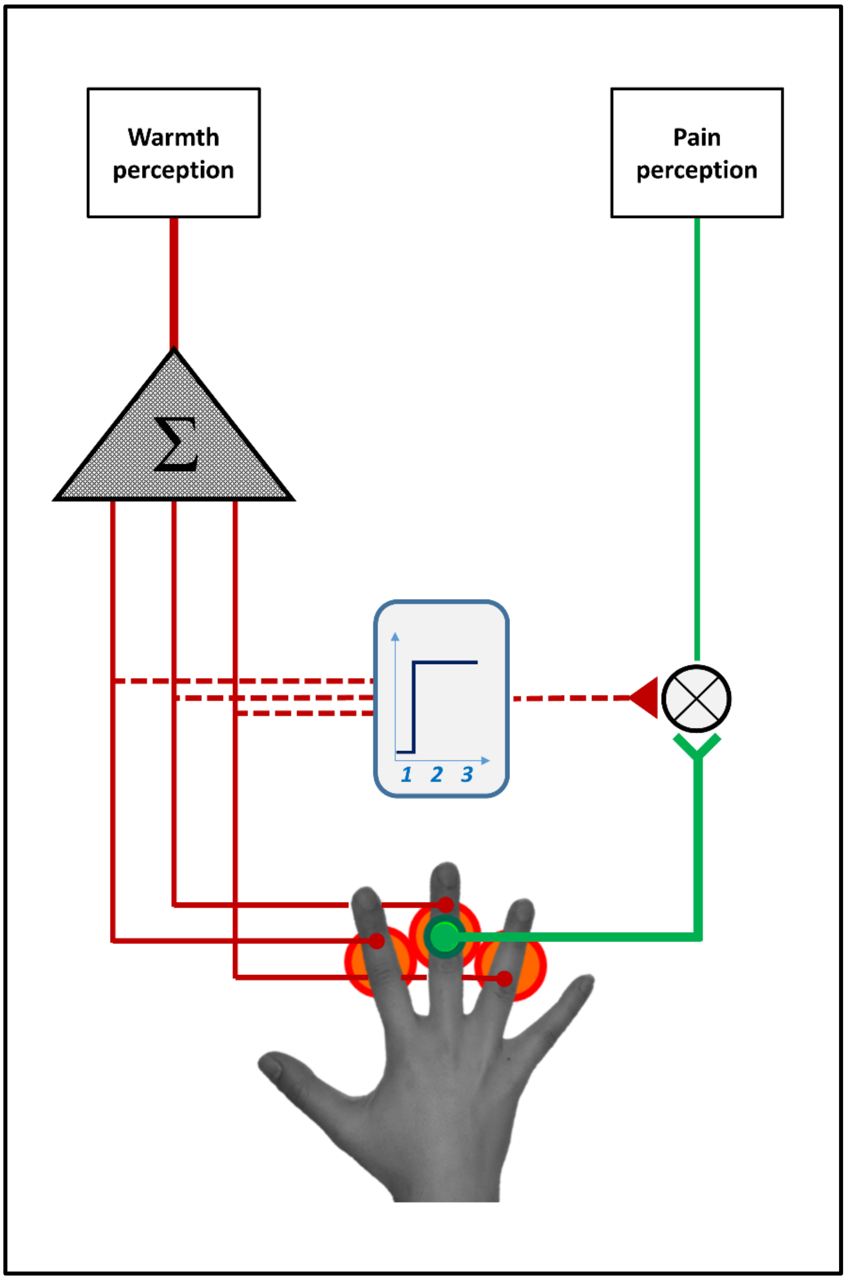


Figure 5.10. Schematic model of warmth-pain interaction.

Results from Experiment 2 suggest that the inter-channel interaction between warmth and pain occurs before of, or independently from intra-channel convergence and summation of warmth.

Chapter 6.

General discussion and conclusion

Synopsis:

This Chapter presents a recap of the main findings of the experimental works presented in the thesis. Section 6.2 focusses on the nonlinearity observed in the perception of intensity of *unimodal* multiple somatosensory stimuli. Section 6.3 summarise the results about the *cross-modal* interactions studied in this work. Section 6.4 gives an overview of the different processing levels at which uni- and cross-modal interactions take place in the somatosensory system. Lastly, Section 6.5 provides the final remarks.

6.1 Introduction

The core goal of this thesis is to shed a light on the mechanisms underlying the integration of multiple simultaneous stimuli, within and between different sub-modalities of the somatosensory system. In particular, across four studies and twelve different experiments, this work investigated the perceptual characterisation of patterns throughout the three exteroceptive somatic senses. The review of the existing literature presented in Chapter 1 revealed that most of the well-characterised properties of perceptual processing described for single events do not apply to a context of multiple simultaneous somatosensory stimulation. Well-known processes underlying detection, localisation, discrimination, and magnitude estimation of *single* somatosensory stimuli are not sufficient, by themselves, to formulate accurate predictions on how *multiple* simultaneous stimuli are integrated along the somatosensory pathways.

First, in Chapter 2 and Chapter 3 we investigated, seemingly for the first time, the perception of *total intensity* of discrepant and non-discrepant somatosensory patterns. We found that when discrepant tactile, cold, or warm stimuli were integrated in a holistic percept, their overall intensity was strongly biased toward the most salient stimulus in the pattern. As a consequence, discrepant patterns composed by smaller physical intensities were in fact perceived as stronger than uniform patterns with equal or even larger physical intensity.

Then, in Chapter 4 we assessed participants' ability to localise thermo-tactile and purely thermal stimuli delivered in isolation, or in uniform and non-uniform patterns. We found that the accuracy in reporting the location of a single thermo-tactile or purely thermal stimulus on the fingertips was surprisingly high (nearly 90%). In contrast, when participants were presented with a non-uniform warm-neutral-warm pattern, their ability to identify the thermal state of the middle finger was completely abolished. Since its discovery in 1977, such phenomenon, namely thermal referral, has been explained as the result of a high-level, cross-modal interaction between thermal and tactile inputs. However, using thermal radiant stimulation, we demonstrated for the first time that the illusory homogenisation of multiple complex patterns in uniform sensations is a purely thermoceptive property.

Finally, in Chapter 5 we exploited the knowledge about convergence and summation of multiple simultaneous thermal stimuli gained in Chapter 4 to investigate the nature of thermo-nociceptive interaction. In particular, we asked whether nociception and pain are parametrically modulated by the number of thermal stimuli simultaneously applied to different fingers. Evidence for a dose-dependent relation, with pain perception linearly decreasing as the number of thermal stimuli increases, would support a high-level, centrally regulated process, whereby thermo-nociceptive interaction occurs *after* intra-channel convergence and summation of warmth. Our psychophysical and electrophysiological data were clearly against this hypothesis, showing that pain modulation by warmth is regulated by an "on/off" mechanism, where attenuation of pain occurs regardless of the position and number of thermal stimuli concurrently applied to the body.

6.2 Nonlinear summation of unimodal somatosensory patterns

All the studies presented in this work have addressed, from different points of view, the topic of perceived magnitude of somatosensory stimuli. Perceived intensity is considered a relatively simple dimension of somatosensation and it is therefore often manipulated in psychophysics to allow reliable quantitative comparisons between specific experimental conditions (Bensmaia 2008). We have confirmed and extended previous results about the exquisite precision of both the tactile (e.g. Weinstein, 1968; Mountcastle, 2005) and thermoceptive (Nathan and Rice, 1966; Simmel and Shapiro, 1969) systems, showing high accuracy in detecting the amount of physical energy introduced into the system when *single* stimuli are presented. In different experiments, participants proved to be able to correctly rate the intensity of single electro-tactile stimuli, as measured through verbal magnitude estimation (Experiment 1 in Chapter 3), or psychophysical method of limits (Experiment 3 in Chapter 3). Moreover, the same was true for the thermoceptive system as well, with participants showing high accuracy in judging the intensity of single thermo-tactile and purely thermal stimuli (Experiment 1 in Chapter 4).

However, when participants were asked to judge the *total* intensity of multiple stimuli, we observed a series of remarkable effects both in the tactile and thermal domain. We found a highly replicable overestimation of discrepant over non-discrepant electro-tactile patterns (Experiments 1 and 2 of Chapter 2, and Experiments 2 and 3 of Chapter 3). Moreover, we replicated the same effect for warm and cold stimuli (Experiment 4 in Chapter 2), suggesting that such a bias may be a general principle underlying spatial integration in the whole somatosensory system.

6.2.1 Overall intensity in the tactile domain

Across seven experiments, we conducted a number of different manipulations to unveil the nature of the overestimation of discrepant electro-tactile stimuli. First, we found that the peak-biased summation operates within a single brain hemisphere (Experiment 3 in Chapter 2), producing overestimation of discrepant pairs when the stimuli are presented on the same hand, but not when they are on different hands. Nonetheless, the effect did not show a strict somatotopic organisation, since there was no difference between judging the total intensity of adjacent and non-adjacent fingers (Experiment 1 in Chapter 2).

Second, we demonstrated that such peak bias effect is a genuine perceptual phenomenon (Experiment 2 in Chapter 3), with discrepancy affecting both participants' sensitivity and response criterion during overall intensity judgements. In particular, we postulated that the *salience* of each stimulus in a discrepant pattern could be the signal triggering overestimation of overall intensity in a perceptual process similar to the peak bias (Fredrickson and Kahneman, 1993) occurring in affective judgements.

Third, in line with the bulk of evidence from the existing literature, we found that lateral inhibition (DiCarlo, Johnson, and Hsiao, 1998; DiCarlo and Johnson, 1999, 2000) played a crucial role in the sub-additive interactive effects observed during multiple simultaneous stimulations, with double tactile patterns being perceived as just slightly larger than each of the stimuli forming the pair (Experiment 3 in Chapter 3). Yet, simple extinction of the weaker stimulus in the pattern could not explain our effect, as participants correctly reported occurrence and intensity of the weak stimulus (Experiment 1 in Chapter 2), and even their perception of total intensity was modulated by weak stimuli of different intensities (Experiment 2 in Chapter 2).

Lastly, judgements of overall intensity were significantly more accurate than judgements of overall discrepancy (Experiment 1 in Chapter 3), suggesting that the process of somatosensory aggregation is not subordinated to the discrimination of events discrepancy. Altogether, these results led us to develop a simple model of the weighted summation of multiple discrepant and non-discrepant somatosensory stimuli (Chapter 3). Such model takes into account lateral inhibition, discrepancy, and salience, and postulates that specific weights for each single input are assigned on the basis of the signal-to-noise ratio between the stimulus itself and the average of all the simultaneous events.

6.2.2 Overall intensity in the thermal domain

If Experiment 4 in Chapter 2 shows that all the conclusions drawn so far for discrepant electro-tactile patterns do clearly apply to the cold and warm channels as well, further considerations have to be made for somatosensory integration in the thermoceptive system. As mentioned earlier in this thesis, the perceived intensity of a thermal stimulus shows a strong dependence on the surface area of skin that is stimulated (e.g. Hardy and Oppel, 1937; Stevens and Marks, 1971; Marks and Stevens, 1973; Marks, 1974). Accordingly, when temperature is held constant, but the surface area is increased by increasing the number of thermal probes, strong spatial summation boosts the apparent magnitude of the stimulus (Hardy and Oppel, 1937; Defrin and Urca, 1996; Kojo and Pertovaara, 1987).

In this work, spatial summation has been investigated both for its peculiar effect on the mislocalisation of thermal events during thermal referral (Chapter 4), and for providing the ideal conditions to explore the dissociation between sensation and perception of warmth (Chapter 5). For example, in Experiment 2 of Chapter 4 we found that, in spite of the illusory uniform sensation induced by thermal referral, participants correctly perceived the overall intensity of three simultaneous thermal stimuli as larger than that derived by only two stimuli. Similarly, in both experiments of Chapter 5, we found a clear linear increase in participants' magnitude estimate of warmth along with the number of stimulated fingers.

Thus, if on the one hand multiple tactile stimulations are strongly affected by lateral inhibition, on the other hand, multiple thermal stimuli are instead automatically aggregated by spatial summation. However, nearly all the classical studies about lateral inhibition and spatial summation have only used paired stimuli of equal intensity (e.g. Hoechstetter, Rupp, Stančák, Meinck, Stippich, Berg, and Scherg, 2001, Severens, Farquhar, Desain, Duysens, and Gielen, 2010; Kenshalo, Decker, and Hamilton, 1967; Price, McHaffie, and Larson, 1989; but see also Gandevia, and McKeon, 1983). In our experiments, we introduced an intensity discrepancy between paired stimuli, so that one was noticeably larger than the other. This led to nonlinear effects which produced similar outcomes on both modalities. On top of lateral inhibition, the perception of discrepant tactile patterns was boosted by the salience of the strong stimulus. Similarly, discrepant thermal patterns were also overestimated, despite the fact that spatial summation generally promotes aggregation.

Therefore, our effect of overestimation of discrepant patterns seems to overcome the apparent dissociation between the most typical perceptual processes occurring in different modalities of the somatosensory system.

6.3 Interaction between different somatosensory sub-modalities

As mentioned in Chapter 1, the organisation of the somatosensory system is extremely complex, with the bodily senses comprising several sub-modalities, each responsible for a range of different sensations. In fact, for a long time scientists have been puzzled by the apparent duality of somatosensation, characterised by a highly specialised peripheral receptors and ascending pathways, and still providing our phenomenological experience as a unified “somatosensory scene”. The coldness of a glass, the wetness of a sponge, or the burning heat from a baking tray appear to be intrinsic properties of the object we are touching, rather than separate sensations. In all these cases, it feels quite impossible to dissociate the tactile content from the secondary sensation associated with it. And yet, the activity in the mechanoreceptors, per se, does not distinguish between any of this case.

The answer to this apparent contrast has to be found in a number of interactions across different sub-modalities, taking place at different stages of the sensory processing (e.g. Abraira and Ginty, 2013). The somatosensory system seems to have an inherently multisensory nature, such that the perceptual outcome of alternative forms of tactile stimuli is not necessarily strongly related to what actually occurs on the skin surface, but rather, it derives from the central neural processing of those signals.

In this thesis, the somatosensory integration of information coming from different somatosensory sub-modalities has been investigated in two different studies addressing thermo-tactile (Chapter 4), and thermo-nociceptive (Chapter 5) interactions.

6.3.1 Thermo-tactile interactions

In Chapter 4, we focussed on the interactions between touch and temperature. These two sub-modalities are particularly emblematic, because, besides having completely distinct receptors and pathways, they also project to different cortical targets (Craig, Chen, Bandy, and Reiman, 2000). Yet the perception of touch and temperature are strongly interdependent (Weber, 1996; Green, 1977; Ho, Watanabe, Ando, and Kashino, 2011). For example, the classical view of thermal referral as a thermo-tactile phenomenon, was grounded on the observation that lifting the middle finger off the stimulator abolished the illusion (Green, 1977, 1978; Ho, Watanabe, Ando, and Kashino, 2011).

We found, instead, that thermal referral also occurred during purely thermal stimulation, and that a concurrent uniform tactile sensation did not have any modulatory effect on it. This suggests that the thermoceptive system plays a more active role than previously hypothesised in the interaction. We propose that low-level mechanisms of spatial summation can produce the mislocalisation of complex thermal pattern. Nonetheless, the fact that homogeneity of tactile input (i.e. all fingers in contact, or none) is essential, also demonstrates that although touch does not trigger the illusion, as previously postulated, it does strongly interact with the thermal sensation and can *disrupt* the illusion. In fact, when the illusory uniformity generated by the thermoceptive system is contrasted by tactile discontinuity, the higher weight given to touch in the somatosensory system overrides the thermal sensation.

6.3.2 Thermo-nociceptive interactions

Chapter 5 has investigated the interaction between warmth and pain. The relation between thermal and nociceptive information has not received as much attention as the classical touch-pain interaction (e.g. Melzack and Wall, 1967; Zoppi, Voegelin, Signorini, and Zamponi, 1991; Watanabe, Svensson, and Arendt-Nielsen, 1999; Nahra and Plaghki, 2003), and therefore it remains still poorly understood (Bromm and Treede, 1987a,b; Plaghki, Decruynaere, Van Dooren, and Le Bars, 2010; Tran, Matre, and Casey, 2008; Nahra and Plaghki, 2005).

Our results about the independence of pain processing and pain perception from the number and the position of concurrently delivered thermal stimuli provide a critical insight about the level at which thermo-nociceptive takes place. First, we showed that a strictly peripheral mechanism depending only on the local temperature of the skin is not likely. This is demonstrated by the fact that during thermal referral we observed the same, or even bigger amount of pain suppression, even if the thermal state of the finger stimulated with CO2 laser pulse was in fact neutral. However, we also showed that a strictly central modulation of the interaction is equally unlikely (Experiment 2 in Chapter 5). After the modulation of pain by warmth had been established, manipulating the apparent intensity of warmth by increasing the number of thermal stimuli did not further affect the thermo-nociceptive interaction. Therefore, our results seem to suggest that the interaction between warmth and pain may occur through a non-somatotopic mechanism taking place before the convergence and summation of warmth.

6.4 Processing levels of unimodal and cross-modal interactions

When multiple simultaneous somatosensory stimulations reach the skin, the interaction between each input can occur at several processing levels, from the local area of the skin affected by the stimulation, to the different relay of the somatosensory pathways, from the neural organisation of primary sensory areas, to the perceptual, associative areas. Moreover, the outcome of perception is also affected by attentional and memory limitations, as well as experience and expectations.

First, because skin itself has its own mechanical properties, the very first step of sensation (i.e. the transduction of physical intensity in action potentials) is already given by the physical interaction between the skin and the object. Despite the fact that our studies have mostly employed electrical and radiant stimuli, mechanical stimuli constitute the vast majority of our interactions with the environment. Due to the mechanical properties of the skin, the spatial gradient of skin deformation induced by a single stimulus impressed e.g. on the hand, is already considerably wider than the stimulus itself (Taylor and Lederman 1975; Tregear 1966). Clearly, when a more complex stimulus (i.e. an everyday object), is applied on the hand, the skin would show much more complex patterns of physical deformation. Moreover, it has been shown that when a stimulus makes contact with our body, the deformation of the superficial layer of the skin gives rise to traveling waves also beneath the surface of the skin (Moore, 1970; von Békésy, 1955). Such traveling waves excite far mechanoreceptors, and consequently, perception of mechanical patterns undergo to further blurring.

Second, the ascending pathways were traditionally considered as mere relay stations, with a direct correspondence between the input recorded by the afferent fibers, and the output conveyed to the cortex (e.g. Mountcastle, 1967). While this observation is still generally confirmed for the elaboration of single stimuli, growing evidence suggests that complex interactions within and between somatosensory sub-modality occur already *before* reaching the cortex. For example, animal studies have shown that cross-whisker suppression (the equivalent of lateral inhibition in mice) occurs in the absence of cortical activity (Higley and Contreras, 2007). In particular, according to the authors of the study, *"the suppression arises from local circuit operations at multiple levels of the subcortical afferent pathway and is amplified by the nonlinear transformation of synaptic input into spike output in both the thalamus and cortex"* (Higley and Contreras, 2007). Moreover, as previously mentioned, studies on the funnelling illusion support the idea of *early* interactions between multiple somatosensory stimuli. For example, Chen and colleagues (2003) used optical imaging in area 3b of the primary somatosensory cortex during funnelling illusion, and showed that simultaneous stimulation of two fingertips produced a single focal cortical activation between the single fingertip activation regions. Thus, neuronal activation in early cortices already represents the perceived, rather than the physical location of peripheral stimulation.

Third, although this evidence suggests that preliminary interactions take place at sub-cortical levels, the neural organisation of somatosensory cortices clearly plays another important role in the integration of multiple unimodal or cross-modal inputs. For example, Lamme (2006) proposed a “recurrent neural processing hypothesis of perceptual awareness”, where three consequentially evolving events are needed to achieve perception. First the physical energy of the stimulus induces an initial “feedforward sweep” of information throughout a sensory pathway. Second, the information is fully elaborated by primary and secondary cortices, where local recurrent processes provide the repeated exchange of information between later (higher) and earlier (lower) areas. Finally, the percept is not reportable until the recurrent activation spreads executive areas (Lamme 2006). Using dynamic causal modelling of event-related potentials in electroencephalography, Auksztulewicz and colleagues (2012; Auksztulewicz, and Blankenburg, 2013) found the first evidence that such hypothesis can be generalised to touch perception. Later processing between contralateral S1 and SII cortices in ‘feedforward-feedback loops’ predicted both stimulus detection and metacognitive confidence ratings of subjective perception.

Next, the properties of a pattern might nonetheless be neglected as a consequence of insufficient attentional capacities. For example, the classical theory proposed by Neisser (Spelke, Hirst, and Neisser, 1976; Nessier and Beklen, 1975) postulate that at some central level of sensory processing a bottleneck occurs where the rate of sensory information reaching that level exceeds its processing capacity. Therefore, individuals’ attention must either divided (Forster and Eimer, 2005; Posner, 1978), or focussed on a limited subset of the sensory field at the expense of the unselected part of the pattern.

Finally, even if all critical information about a stimulus pattern were to successfully reach awareness without any previous interaction, the integration of multiple stimuli and sensations in a holistic percept would be still affected by the past experience and the general expectation about the world. A very compelling evidence that pattern perception is limited by such higher-level processes comes from early studies of congenitally blind patients whose vision was restored after cataract removal (Gregory and Wallace, 1963; Valvo, 1971). Despite almost all the lower-level of visual processing were perfectly effective, functional use of vision was completely lacking, and even detrimental for their behavioural performances. Therefore, at least part of the perceptual ability to integrate multiple stimuli appears to develop with experience or to require continued stimulation for normal functioning (Kirman, 1973).

6.5 Conclusion

The physical reality surrounding us is overly complex for the limits of our senses and our attentional capacities. In this thesis, we argue that the somatosensory system can overcome its bandwidth limitations by synthesizing complex patterns into uniform and coherent percepts, based on the most salient information available.

Whenever we touch (or we are touched by) a *single* stimulus, we are able to perceive its properties with an astonishing richness of details. For example, when we swipe one finger on the surface of a fruit, we are able to perceive an irregularity in its texture as wide as a few micrometres. However, when we grasp the same fruit in our hand, our sensorial and attentional bandwidth limitations make impossible to perceive each point of contact with the same clarity and fidelity. That is, whenever we make contact with *multiple* stimuli simultaneously, our exquisite discriminative precision is lost. Yet, this loss of information has the great advantage to provide us with a synthetic, uniform, and holistic percept of the object, which in turn makes the interaction with the object possible.

The studies presented in this thesis have investigated some of the main aspects involved in the perception of composite somatosensory patterns, shoving that the most salient information in a pattern is taken as a proxy of the overall intensity (Chapter 2 and 3) and location (Chapter 4) of the stimulation. Furthermore, we have also investigated somatosensory integration among different sub-modalities (Chapter 4 and 5).

Overall, our findings suggest that nonlinear integration of multiple somatosensory stimuli may be an efficient way to synthesise reality in order to deal with the bandwidth limitations of the somatosensory system.

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Appendix A

A.1 Apparatus for thermal referral without touch.

Figure A.1.

Photographs showing the posture of the hand, and radiant heat from below. In this condition, the middle finger is shaded, and the index and ring fingers are stimulated.

A.2 Middle finger shading: manipulation check.

To address whether touching the middle finger against the glass caused important changes in temperature which could undermine our results, we measured the skin temperature of the shaded middle finger at regular intervals beginning before the first onset of stimulation. We conducted separate tests for thermo-tactile stimulation, and for purely thermal stimulation. This test aimed to establish whether the shaded middle finger was indeed thermally neutral, as intended. Skin temperature was recorded in three participants (2 female, mean age ± SD: 32 ± 2.7 years) before stimulation, then every 3 seconds during the radiant heat stimulation and immediately after. To make the recordings, the hand was briefly removed from the radiant heat source. The duration of the stimulation was set at 15s, as in the other experiments. A video of the procedure can be found here:

https://drive.google.com/folderview?id=0B0l7EuZ4rWeQUGNNUjRYNFB2QXc&usp=sharing

Results confirmed our previous findings: the shade ensured that no radiant heat stimulation was delivered, so finger temperature did not increase with exposure (see Figure A2). Second, the temperature of the middle finger appears rather stable over time. More importantly, the minimal fluctuations involved are almost identical in the thermo-tactile and purely thermal condition. The effect of touching the glass increased the temperature of the shaded middle finger by around 0.25 degrees (figure 2), in comparison to a purely thermal, non-tactile condition. This effect was present, throughout the 15 s stimulation period. In contrast, the effect of thermally stimulating the middle finger (shaded/non-uniform – uniform conditions in experiment 1, p. 9) was very much greater, at 1.7 degrees. Therefore, it is most unlikely that temperature fluctuations specifically due to touch can explain our findings.

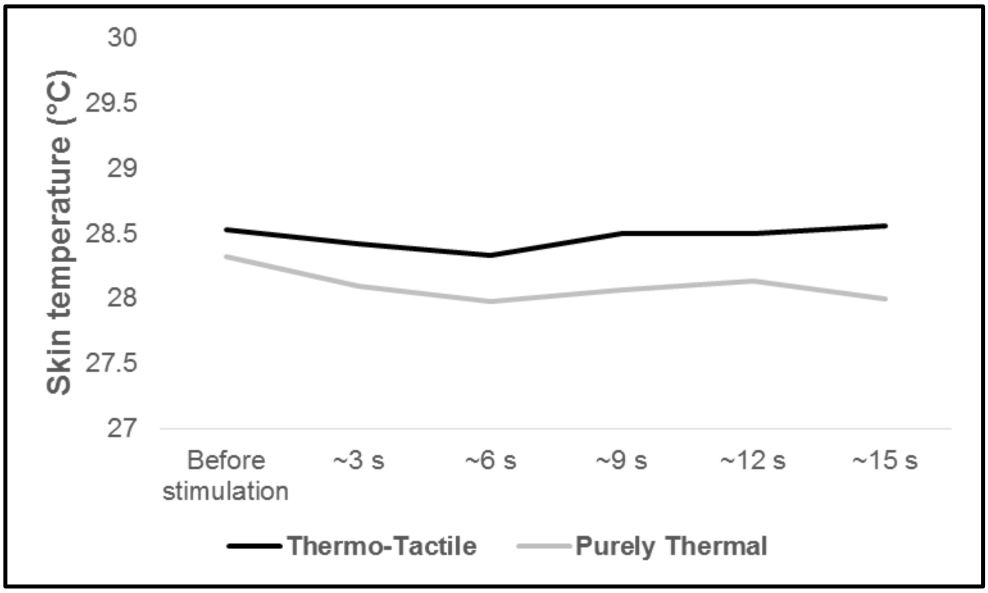

Figure A 2. Continuous recording of middle finger skin temperature.

A.3 Dynamic thermal imaging.

We also performed dynamic imaging of the entire experimental procedure using thermal infrared cameras. The video traces for each experimental condition are here:

https://drive.google.com/open?id=0B17i-PmCh1ZHWmxIMkdTTnNjMVk

The video clearly shows that (i) the radiant stimulus was effective in increasing skin temperature, (ii) there was not spread of radiant warm on the whole hand, and (iii) the shield successfully prevented the middle finger to be stimulated.

Appendix B

B.1 Bayesian factor of linear trend analysis.

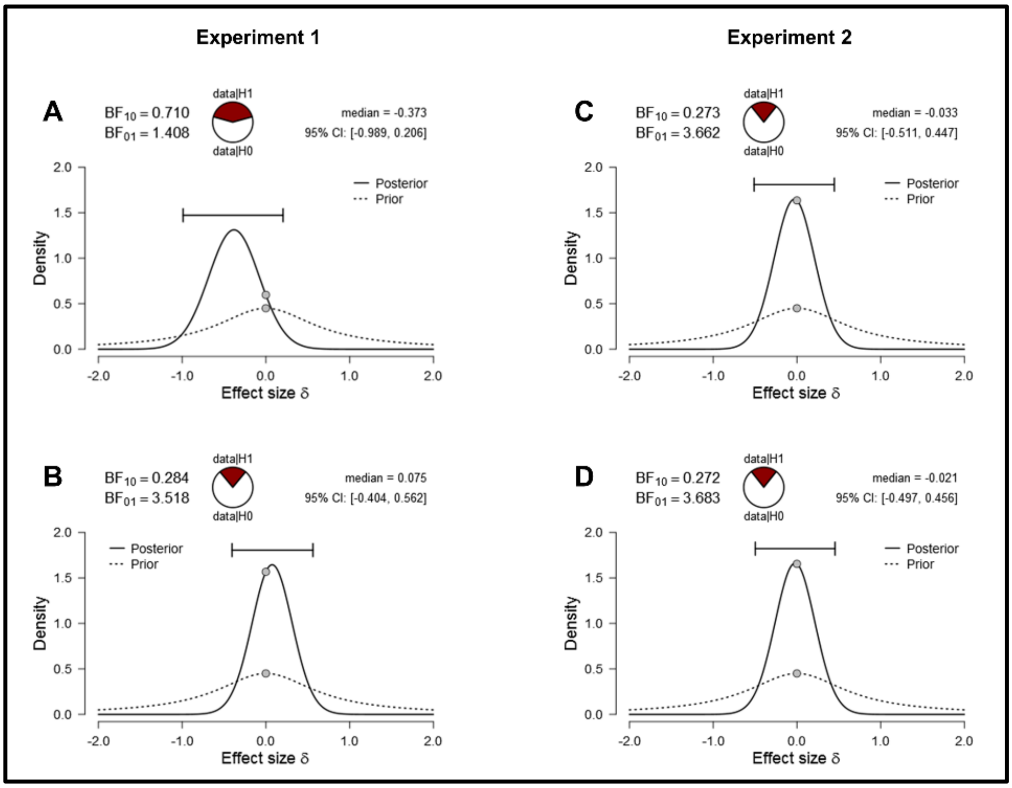

Figure B.1. Bayes factor of linear trend analyses in Experiment 1 and Experiment 2

Bayesian analysis on the null results of linear trend analyses of pain in both Experiment 1 (A and B) and Experiment 2 (C and D) strongly supported the null versus the alternative hypothesis.