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Running Title: Spatial configurations in pain perception

Transforming the thermal grill effect by crossing the fingers

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Summary

The relation between pain perception and spatial representation of the body is poorly understood. In the thermal grill illusion (TGI), alternating non-noxious warm and cold temperatures cause a paradoxical, and sometimes painful, sensation of burning heat [1]. Here we combined thermal grill stimulation with crossing the fingers to investigate whether nociceptively-mediated sensation depends on the *somatotopic* or *spatiotopic configuration* of thermal inputs.

We stimulated the index, middle and ring fingers, when the middle finger either was or was not crossed over the index, to generate *warm – cold – warm* patterns in either somatotopic or spatiotopic co-ordinates. Participants adjusted a temperature delivered to the other hand until it matched their perception of the cold target finger (index or middle) (figure 1a). We found significant temperature overestimation when the target was central within the spatial configuration (*warm-cold-warm*), compared to when the target was peripheral (*cold-warm-warm*). Crucially, this effect depended on the spatiotopic configuration of thermal inputs, but was independent of the finger posture, and was present for both index and middle target fingers. That is, the thermal grill effect for the middle finger was abolished when the middle finger was crossed over the index to adopt a spatiotopically peripheral position, while the same effect was newly generated for the index finger by the same postural change. Our results suggest that the locations of *multiple* stimuli are remapped into external space as a group. Nociceptively-mediated sensations depended not on the body posture per se, but rather on the external spatial configuration formed by the pattern of thermal stimuli in each posture.

Highlights

- The contribution of spatial body representation to pain perception is still unclear.
- We measured how crossing the fingers influences the thermal grill model of pain.
- Thermal grill effects depended on configurations of stimuli in spatiotopic, not somatotopic patterns

Results and Discussion

An alternating pattern of innocuous warm and cold stimuli on the skin induces a burning, potentially painful, sensation termed *thermal grill illusion* (TGI). According to one theory, spatial summation of warm stimuli leads to inhibition of a cold pathway at a spinal level. Since the cold pathway normally inhibits nociceptive afferents at a thalamocortical level, inhibiting the cold pathway unmasks a hot, burning quality of nociceptive sensation, in skin regions that are in fact exposed to cold [1]. The thermal grill has proved a valuable experimental model of pain, notably because it activates nociceptive brain pathways without tissue damage.

Several previous studies link the *level* of pain to *location* of stimulation in external space. For example, a noxious stimulus on the hand was rated as less intense when the hands are crossed, compared to uncrossed [2]. Interestingly, such modulations of external spatial location did not influence early, nociceptive-specific processing, but only later, non-sensory specific processes [2]. Spatial aspects of the thermal grill have been investigated previously [3], but these investigations focussed on the skin areas stimulated by one warm and one cold probe, and on the spacing between them. Spatial features of thermal grill effects might, in principle, be different from spatial modulations caused by crossing the hands. First, the thermal grill depends on *several* thermotactile stimuli, whereas previous crossed-hands experiments investigated a *single* noxious stimulus. Second, highly mobile body regions like the fingers may involve an additional level of spatial organisation, because the *internal spatial relations between stimuli*, such as their sequential spatial order, can also be reconfigured, without major shifts in egocentric spatial location, and without crossing the midline.

We applied a thermal grill stimulus on crossed and uncrossed fingers, and explored how these changes in spatial configuration altered the thermal grill effect. In Aristotle's illusion, a single object held between two crossed fingers is experienced as two objects. According to the standard interpretation, this reflects failure to remap finger inputs into external space, in contrast to the rapid,

efficient remapping for crossed hands. Stimuli on crossed fingers are processed as if the fingers were still uncrossed [4], suggesting that multi-digit tactile perception is somatotopic, rather than spatiotopic. This interpretation would suggest no modulation of thermal grill sensations when crossing the fingers, because inputs to the crossed fingers are not remapped to their new spatial locations, unlike inputs to crossed hands [2]. Conversely, modulation of thermal grill sensations by finger posture would require a re-evaluation of both the neural representation of fingers, and the role of these representations in thermoception, possibly including pain.

We stimulated the index, middle and ring fingers of the right hand in four different conditions, defined by the factorial combination of finger posture (uncrossed or crossed fingers), and the thermal distribution across the three fingers. The thermal distribution was selected to make a *warm – cold – warm* pattern in either somatotopic or spatiotopic co-ordinates (Figure 1b). Either the index or the middle finger was designated as the target finger, where sensation should be judged. The dorsum of the target finger always received cool stimuli, from a 14° C thermal probe (see supplemental figure 1). The other two non-target fingers, rested on a thermal plate, whose temperature could also vary (see later). The thermal grill produces unusual sensations, with a characteristic quality of heat [5], often described as “burning” [6]. It is sometimes described as painful (around 50% of cases in one recent study [5]). We quantified the effect by asking participants to judge the temperature of the probe on the target finger dorsum. We chose perceived temperature as a dependent variable, because it gives continuous, quantitative data, is commonly reported in nociceptive sensations using thermal grill stimulation [1, 6], has been reliably used before in matching tasks [7], and reflects the same continuous, underlying mechanism as pain judgement [5]. Moreover, temperature matching avoids the methodological difficulties, notably suggestion effects, that occur when applying verbal labels such as ‘pain’ to the unusual sensory quality of thermal grill stimuli [8].

To obtain a quantitative estimate of thermal grill effects using temperature matching, we applied an identical thermal probe to the left hand, at the homologous location to the probe on the target finger of the right hand. The posture of the left hand was adjusted to match the posture of the right hand on the same trial, with fingers either uncrossed or crossed as appropriate. The temperature of the left-hand matching probe was gradually swept up or down, and the participant indicated when its temperature was felt to match that of the target finger. The signed matching error was recorded. A positive error indicated that the target finger felt hotter than veridical (i.e., overestimation). Crucially, in the uncrossed position, if the middle finger is the target, it is located between the two warm fingers. Conversely, if the index finger is the target, it is located peripheral to the two warm fingers. In the crossed position, these spatial configurations are reversed (Figure 1b).

Participants were tested in two sessions (See Supplemental Experimental Procedures). First, in a baseline condition, we tested temperature matching for uncrossed and crossed fingers while the non-target fingers of the right hand received a neutral (30°) temperature, below that normally used to induce thermal grill illusions. Participants could accurately match temperatures in this condition, irrespective of target finger, and independent of crossed/uncrossed posture (all main effects and interactions, $p > 0.306$, cf [9]). Crucially, the baseline condition provides a control for several factors that might potentially influence temperature estimation, including discomfort, arousal, any possible motor activity used to maintain finger posture, general difficulty in localising or attending to the to-be-judged location, placement of the thermode for effective stimulation, and interference or facilitation of thermoception due to self-touch between fingers. In the second session, the temperature of the non-target fingers was increased to the warm level (43° C) that conventionally produces the thermal grill illusion. The stimulus values of 43° C/14° C for the non-target and target fingers respectively were based on a previous study of thermal grill effects on the fingers [7]. Pilot testing confirmed that these values indeed produced the unusual quality of noxious burning sensation on the cold target finger that characterises the thermal grill, and that neither the cold nor

warm stimuli were painful when tested individually. We also confirmed that this sensation was associated with reliable overestimation of target finger temperature.

Finally, we performed an additional control experiment in a new group of participants, to assess whether crossed finger posture and spatial configuration of thermal inputs had any effects on low-level thermal perception on the target finger. The finger postures were as in the main experiment, but thermal stimulation was applied only to the dorsum of the target index or middle fingers. The threshold for detecting cold and warm stimuli were measured in separate tests, based on standard Quantitative Sensory Testing protocols.

The data for each session in the main experiment are shown in supplementary tables 1 and 2. We subtracted temperature matching errors at baseline from those in the thermal grill session, to obtain a quantitative measure of the thermal grill effect. A 2x2 repeated measures ANOVA on this measure showed a main effect of finger ($F_{1,15} = 8.168$, $p = 0.012$, $\eta^2_P = 0.353$, $\eta^2 = 0.093$), no effect of posture ($F_{1,15} = 0.214$, $p = 0.650$, $\eta^2_P = 0.014$, $\eta^2 = 0.002$) and, crucially, a significant interaction between finger and posture ($F_{1,15} = 7.113$, $p = 0.018$, $\eta^2_P = 0.322$, $\eta^2 = 0.178$) (Figure 1c). Simple effects testing to explore the interaction showed a strong temperature overestimation for the middle target finger in the uncrossed posture, which was significantly reduced in the crossed posture ($t_{15} = -2.167$, $p = 0.047$, Cohen's $d = 0.596$). The index finger showed the opposite pattern: no temperature overestimation in the uncrossed posture, but a significantly increased overestimation in the crossed posture ($t_{15} = 2.289$, $p = 0.037$, Cohen's $d = -0.528$). Interestingly, the overestimation for the middle finger in the uncrossed position did not differ significantly from the overestimation for the index finger in the crossed position ($p > 0.05$). Further, the effects of finger crossing on temperature estimation for index and middle fingers were almost identical in magnitude (mean 3.09 degrees for middle, 2.95 degrees for index), though clearly opposite in sign. The magnitudes did not differ significantly ($p > 0.05$) although caution is clearly required in interpreting these null results.

Applying an identical ANOVA to the warm and cold detection experiment showed no significant effects (all $p > 0.1$). In particular the crucial interaction between target finger and finger

posture were far from significant ($p=0.537$, $p=0.743$ for cold and warm respectively), suggesting that our postural modulations of TGI were unlikely to arise from changes in low-level thermal perception (see supplementary table 4). The lack of any thermoceptive modulations in both the control experiment, and in the baseline condition of the main experiment, therefore suggest that the key result in figure 1c reflects a spatial modulation of the specific warm-cold-nociceptive *interaction* that produces the TGI, and not a modulation of unimodal thermal sensations per se. Finally, the stability of warm and cold thresholds across crossed and uncrossed postures strongly suggests that our main TGI results cannot be due to difficulties in delivering effective stimulation in the crossed posture.

This pattern of interaction could be clearly interpreted: the thermal grill effect was strong when the target finger was located centrally in *spatiotopic* coordinates, in between the non-target fingers. In contrast, when the target finger was located at the outside edge of a spatiotopically-defined distribution of fingers, the effect was significantly reduced. Previous studies have reported thermoceptive and nociceptive effects that are specific to particular fingers [9], or specific to particular body postures [2]. However, the effect reported here depended only on spatial *configuration* and was independent of which finger served as target, and also independent of whether the finger posture was crossed or uncrossed. That is, the nociceptor-mediated sensation depended on the external spatial relations between multiple thermotactile stimuli.

Previous investigations [2] found analgesic effects of crossing the hands across the midline. However, altered embodiment or altered self-location alone did not produce analgesia [10]. This was interpreted as reflecting conflict between somatotopic/hemispheric and spatiotopic/external frames of reference. However, spatial conflict alone cannot explain our data. We found that crossing the fingers could either decrease or increase the thermal grill effect, depending on the spatiotopic thermal *configuration* of fingers thereby produced. The TGI effect did not depend on finger posture per se, but on creation of a spatial sequential order of warm-cold-warm stimulation.

An explanation based on conflict between reference frames alone would require implausible ad hoc assumptions to account for the importance of this ordered pattern.

Instead, our data are more parsimoniously explained if the level of nociception depends on *spatiotopic thermal configuration*. This contrasts with previous reports of Aristotle's illusion suggesting that tactile perception on the fingers was organised only somatopically, without remapping into spatiotopic frames of reference [4]. Our finding of strong spatiotopic configurational effects in thermal grill situations suggests finger stimulations are, in fact, remapped into external space. Further, we designed our stimulation so that mere confusion between fingers [11, 12], or regarding stimulus locations could not easily account for our results. First, we applied thermotactile stimulation to the *dorsum* of the target finger, but to the *pads* of the non-target fingers, to prevent confusion or mislocalisation. Second, the to-be-judged target stimuli differed from the other stimuli both in the tactile location stimulated, and in temperature. Finally, any tactile mislocalisation effects caused by crossing the fingers should be common to baseline and thermal grill conditions. Our data strongly suggest a spatiotopic and configural organisation underlying the thermal grill effect.

The digits display two levels of spatial organisation. First, each finger can be moved independently to a range of locations in external space [13]. Second, the fingers have a specific sequential order relative to another. Accordingly, patients with finger agnosia have difficulty in "relating the fingers to each other in correct spatial sequence" [14]. Some external space motions can completely reconfigure the normal spatial order of the fingers, as in our crossed posture. Our result suggests that the relative spatial order of the digits, not only their location in space, may be relevant to multisensory thermotactile interactions.

Ho and colleagues [15] reported a thermoceptive "filling-in" effect when one finger in a group of three received a different temperature from the other two. In their task, participants identified the "odd-one-out" finger. Their participants tended to perceive a single, relatively homogenous temperature, despite temperature variation across fingers, suggesting that thermal

information is automatically combined across multiple points of contact on a single, spatially-coherent source object [15]. A similar effect has been described in TGI conditions [16]. However, the thermotactile patterns we used could not readily be produced by a single object. Our data may reflect a role of spatial configuration of the *body* [17], rather than spatial properties of objects.

The “unmasking” theory of Craig and Bushnell attributes the TGI phenomena to spatial summation of warm inputs, and resulting inhibition of cold signals [1] (Figure 2a). These processes were initially hypothesised to occur at spinal level [1]. However, later studies showed TGI-like effects across dermatome boundaries, suggesting that spatial summation also occurs centrally [3]. A recent neuroimaging study identified the thalamus as the neural correlate of the TGI effect [19]. Our spatial configuration effects are consistent with suprasegmental spatial organisation, in which multiple thermotactile stimuli, rather than just a single location, are remapped to produce an ordered nociceptive space (Figure 2b-e). Summation of warm inputs, and inhibition of the cold pathway would occur *after* spatial remapping, thus unmasking nociception at spatially intermediate locations.

Most experimental pain studies involve a *single* stimulus. This may explain why the body’s spatial configuration is rarely investigated in pain studies. Our results suggest that thermal interactions could involve spreading activation across a hypothetical neural map of external space. When two warm stimuli surround the cold stimulus, both the warm signals spread. The central cold stimulus is doubly inhibited, there is strong unmasking of nociception, and a strong thermal grill effect (Figure 2b and 2e). This mechanism can also explain reduction of TGI in the crossed middle finger and uncrossed index finger conditions (Figure 2c and 2d). In this configuration, adjacent warm signals again strongly summate, but the cold input is spatially distant from the peak of summated warm activation. This results in less inhibition of cold inputs, and therefore less unmasking of nociception, and a reduced TGI effect. This “broadcast” model is based on spreading activation and summation of multiple stimuli that are established features of subcortical

[20] and cortical [21] neural maps. Our effect clearly operates in external spatial coordinates, while previous summation mechanisms have been described in receptor-based, somatotopic coordinates. However, neurons with external spatial tuning have been widely reported in several brain areas [17, 22].

What implications do our findings have for pain? Our stimulation produced the characteristic nociceptor-mediated sensation of burning pain found with several other TGI stimuli [1, 7, 8, 16]. However, we preferred not to ask participants to *judge* pain explicitly, for methodological reasons. In any given stimulation instance, an individual participant may or may not describe the evoked sensation as ‘pain’ [6]. Thus, we urge caution in relating TGI studies generally, and our temperature estimation data in particular, to pain. Nevertheless, the scientific literature shows clear links between chronic pain and both aberrant somatosensory cortical activity [23], and spatial distortions of body representation [24]. Crossing the hands is known to reduce levels of both chronic [25], as well as experimental [2] pain. Our data show that spatial relations between body sites with different afferent input can influence nociceptively-mediated thermal sensation. Other sensory systems, including vision, audition and touch, exhibit Gestalt-like configurational and spatial grouping phenomena, but the potential role of such phenomena in nociception has received little attention. We therefore speculate that changes in posture to alter the spatiotopic configurations provided by affected and unaffected body regions could influence chronic pain.

Author contributions

A.M., E.R.F. and P.H. designed research; A.M. performed research; A.M analyzed data; and A.M., E.R.F. and P.H. wrote the paper.

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Figure Legends

Figure 1. Experimental conditions and results

(a) General overview of the experimental apparatus. (b) In the baseline session, cold stimuli (blue circles) were applied on a target finger (middle and index), while these two fingers were either uncrossed or crossed. The non-target fingers received neutral temperature stimulation (pink circles). In the thermal grill session, cold stimuli (blue circles) were applied as in the baseline session, but the non-target fingers received warm stimulation (red circles). The combination of warm and cold stimuli evokes the paradoxical, sometimes-painful, burning heat sensation reported in the Thermal Grill Illusion. (c) The thermal grill effect was measured as overestimation of the target temperature in thermal grill conditions, relative to baseline. Note that crossing the fingers reduced the thermal grill effect when the middle finger was the target, but increased it when the index finger was the target. Bars indicate standard deviation across participants.

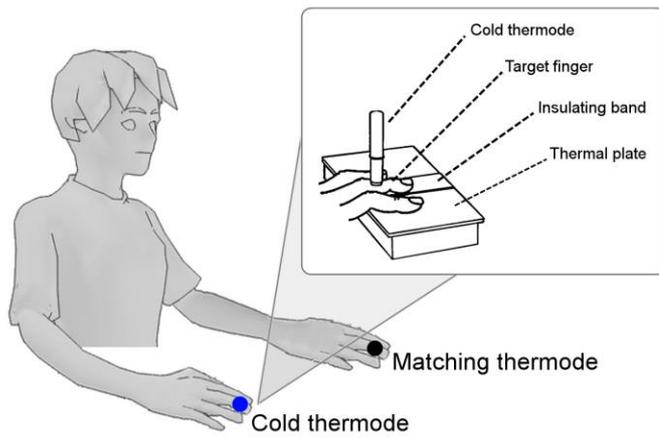
Figure 2. Spatial influences on thermal perception

(a) The classic unmasking model of TGI (redrawn from [18]). Colours and letters indicate stimulus and skin temperatures, and the neural pathways corresponding to the temperature: “blue/C” = cold, “red/W” = warm. (b) A modified model involving additional thalamo-cortical summation of multiple warm stimuli, and interaction with cold pathway from the middle finger. The gray levels indicate levels of activation (firing rates) in the warm and cold pathways (darker grey colour = strong activation). Warm activation is assumed to spread gradually across a neural representation of external space, leading to inhibition of cold on the middle finger (light grey C indicating weak activation). The putative inhibitory synaptic interaction between warm and cold pathways is omitted for clarity. (c) Summation of warm inputs occurs *after* remapping of somatotopic inputs into external spatial coordinates. Crossing the fingers therefore reduces the inhibition of cold on the now-peripheral middle finger, because it is less affected by spreading warm activation. The stronger cold activation results in stronger inhibition of nociceptive afferents, and a reduced

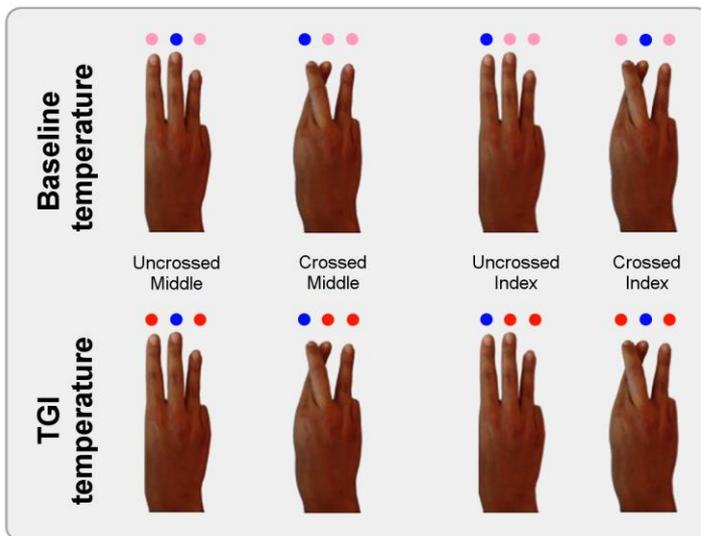
nociceptively-mediated TGI sensation. (d, e) The thermal grill sensation depends on the central spatiotopic position of the cold finger relative to the warm fingers, and not on finger crossing per se. When cold stimulation is given to the index finger, the TGI sensation is reduced in the uncrossed posture (d), relative to the crossed posture (e).

Figure 1

A



B



C

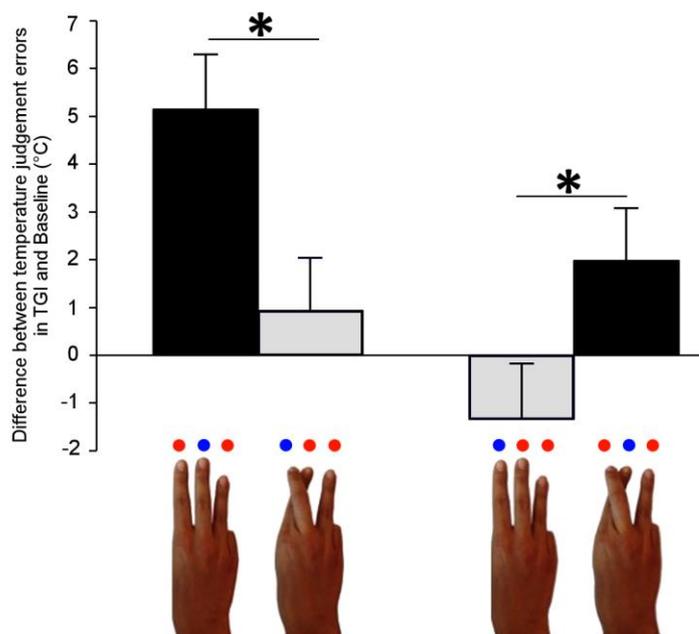
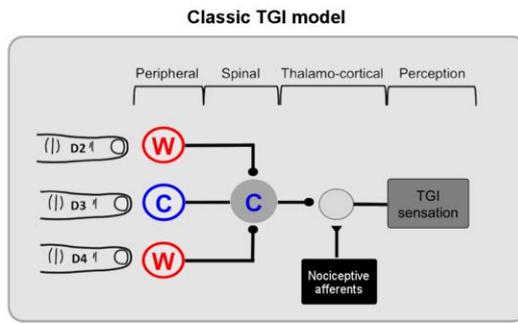
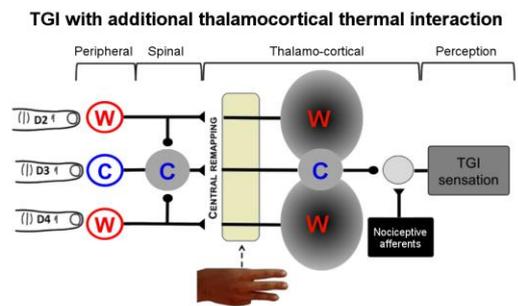


Figure 2

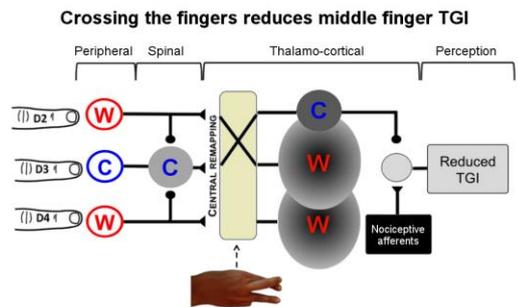
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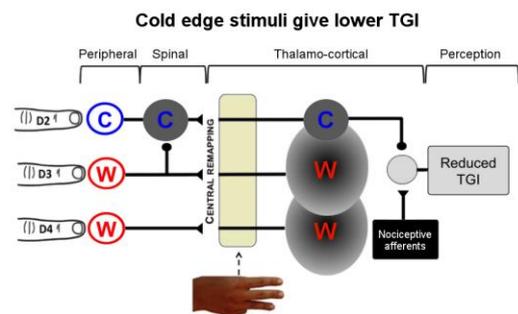
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D



E

