Understanding defensive peripersonal space through mathematical modelling

UCL CoMPLEX

PhD Thesis

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I, Rory Bufacchi, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

The spatial location of environmental events with respect to one's body largely dictates their behavioural relevance. Given that stimuli occurring near the body have a greater potential to cause harm, even the phylogenetically-old defensive hand-blink reflex (HBR) increases in magnitude with stimulus proximity. The HBR has allowed for a preliminary characterisation of a defensive peripersonal space (DPPS). The work described here provides a full spatial characterization of DPPS using formal geometrical modelling of HBR data, and highlights the functional significance of DPPS through its dependence on various contextual factors. Modelling and empirical results indicate that (1) the shape of the body area defended by this DPPS can be approximated as a half-ellipsoid centred on the face. (2) The DPPS extending from this to-be-defended area has the shape of a bubble elongated along the vertical axis. (3) This DPPS is malleable: its shape is continuously updated based on gravitational cues. The DPPS also changes in disease: while blind individuals do also display a HBR, (4) the nervous system only develops the ability to *modulate* HBR magnitude if vision is present during early childhood. (6) In trigeminal neuralgia (TN), a condition in which innocuous trigeminal stimulation triggers paroxysmal unilateral facial pain, DPPS is larger on the side of space ipsilateral to TN. This reflects an increased estimated potential of sensory events to cause harm on that side of space. Finally, (7) DPPS expands when the HBR-eliciting stimulus is moving towards the face. These findings show that the brain purposefully modulates the defensive HBR with proximity in a context-dependent manner, in order to ensure optimal behavior and protection from estimated threats. At a more theoretical level this work also critically discusses ambiguities in the terminology used to report empirical results about peripersonal space, which have generated much confusion in the field.

Impact statement

Defensive responses are enhanced when threatening objects are near the body. However, such enhancements are currently not clearly described, and the neural mechanisms underlying them are not yet fully understood. Indeed, most theories on defensive response enhancement are vague and lack predictive power.

This thesis takes a step towards mathematically formalising a theory which explains and predicts how the strength of defensive responses are increased with proximity to the body. In this work, the postulated mathematical model is assessed using data from the hand-blink reflex, a defensive reflexes in humans.

This mathematical model has several advantages which can benefit scientists' understanding of how the brain represents space near the body. First, it allows for more rigorous testing and prediction of hypotheses about the *cause* of experimental findings. Second, it allows for understanding various different types of responses within a similar theoretical framework: that of probabilistic danger assessment. Third, it can be used as a basis to formulate more complicated models. Finally, as is argued in the final chapter of this thesis, it could lead to a more rigorous definition of peripersonal space. These benefits are particularly relevant given the scope of peripersonal space research: in the last five years, more than 400 scientific articles have been published on the topic, but a clear definition is still lacking.

The results and model put forward in this thesis might also be of use outside of basic science: the design of living and working spaces, user interfaces, dynamic environments and even robotic assistants can all benefit from a more rigorous understanding of how humans modulate their defensive responses in space. Furthermore, robotics and artificial environments could even use a more advanced version of the model postulated here to recreate human-like behaviour in artificial agents. In a world which is increasingly automated, this will allow for humans to more naturally integrate themselves with it.

Table of Contents

1 Preface

The aim of this work is to further our understanding of the Defensive Peripersonal Space (DPPS), the portion of space surrounding an individual within which defensive responses are enhanced.

This thesis is divided into several Chapters. Chapter 2 provides a general introduction to the field. Chapters 3-6 describe several studies performed during my time at the Iannetti lab. Chapter 7 discusses the findings from Chapters 3-6 in light of findings from the wider field, and provides a perspective on peripersonal space which aims to address some current confusions in the field.

I sincerely hope you enjoy reading this thesis as much as I have enjoyed performing the work behind it.

1.1 Brief note on nomenclature

Before we get into the meat of the thesis, it should be briefly clarified how terms related to peripersonal space will be used throughout the thesis. The reason is that peripersonal space terminology has gradually shifted, probably due to the shift from monkey single neuron studies to human behavioural, EEG and fMRI studies. In monkey single neuron studies, ‘peripersonal space’ strictly referred to the space near the body in a geometric sense, and ‘peripersonal neurons’ were those neurons whose firing rate increased with proximity to a body part. Since the advent of studies on humans however, ‘peripersonal space’ has come to mean anything from ‘the geometric space near the body’, through ‘the response function of a specific behavioural or neurophysiological measure’, to ‘the neural construct of nearness’. In fact, these meanings of the term peripersonal space are often used interchangeably within the same article or even sentence, which can lead to considerable confusion. The discussion of this thesis (Chapter 7) fleshes out and discusses this issue in greater depth. To circumvent this issue and prevent confusion, this thesis uses the following nomenclature: the term ‘near space’ will indicate the physical space near the body (i.e. the space within a small Euclidian distance of the body); the term ‘peripersonal space’ (PPS) will refer to the portion of space within which a certain biological measure is increased in magnitude (hence a phrase such as ‘PPS-related measure’, refers to a measure which increases in magnitude with proximity to the body); and ‘defensive peripersonal space’ (DPPS) will refer to the portion of space within which a biological measure *clearly related to the defence of a body part* is increased in magnitude. Admittedly, such definitions of PPS and DPPS do carry the issue that they simplify a continuous response gradient into an in-or-out zone. This is another issue that will be addressed in the discussion (Chapter 7).

1.2 Acknowledgements

The data presented in Chapter 3 (Experiments 1.1-1.6) was collected by myself, except for experiments 1.1 and 1.2, which were previously collected by Chiara Sambo. Results from experiments 1.1 and 1.2 had already been published before I re-analysed them (Sambo et al., 2012a; Sambo and Iannetti, 2013).

The data in Chapter 4 was mostly collected by myself, with assistance from Sharim Ponticelli. All data in Experiments 2.1 and 2.2 were entirely collected by myself, and Sharim Ponticelli helped me to collect data from several of the subjects included in Experiments 2.3 and 2.4

The data in chapter 5 was collected by Sarah Wallwork.

The data in chapter 6 was collected at UCL in London, and at Sapienza University in Rome. The data in London was collected by myself, and Giulia Di Stefano collected the data in Rome.

All the statistical and modelling analyses in this thesis were performed by myself.

2 General Introduction

2.1 Unique properties of the space near the body

When we encounter objects and events in our daily lives, the manner in which we interact with them is strongly dependent on their proximity to our body. We all know the feelings of being crowded, of having another person breathing down our necks, of a desired object being just outside of reach, or of a dangerous one being too close for comfort. In this framework, it is not surprising that organisms seem to assign a particular value to sensory events and objects close to the body.

In 1941 the Honourable Lord (and quite fittingly named) Walter Brain discovered the first evidence that specific parts of the brain were more involved in processing stimuli nearer to the body, than in processing those further away (Brain, 1941). He described three patients with extensive right-parietal lesions who only showed impairments in dealing with objects when those objects were nearby. These results led him to postulate that stimuli in grasping distance might be processed in different brain areas from those in walking distance. Around a similar time, the Swiss zoologist Heini Hediger was studying changes in animals' behaviour with proximity to humans or conspecifics. He showed that animals have a 'flight distance', a distance from their body wherein a human would very likely cause the animal to flee, and which could change in size depending on the environmental context (Hediger, 1950). Further seminal work on the properties of space near the body came from the anthropologist Hall's influential book about the importance of space to human behaviour (Hall, 1969). Although the empirical evidence that he provided was occasionally so sparse that it would not be accepted today, he did lay the first detailed framework of divisions of space near the human body; he distinguished between intimate space (up to 45 cm), personal space (up to 1.2 m), social space (up to 3.6 m), and the public space (further than 3.6 m). He linked each of these spaces to specific behaviours if objects or animals were to enter them. For example, one might allow a very close friend to approach nearer than 45 cm, but an enemy would be kept at a much larger distance if at all possible. Building upon these seminal observations, a field of research had emerged that busied itself understanding the behavioural and psychological effects of the near space (Hall et al., 1968).

2.2 Primate peripersonal neurons

However, since Brain's original observations in 1941, little progress had been made towards understanding how the brain processes near space differently from far space until the discovery of a certain type of monkey neuron more than three decades later. When recording spiking rates from single neurons in diverse brain regions, several different groups found neurons which had similar response properties: (1) they were bimodal, responding both to touch and vision, (2) their visual receptive fields were localised in the space near the body (Hyvarinen and Poranen, 1974), (3) their visual receptive fields were almost always near or directly adjacent their tactile receptive fields (Leinonen and Nyman, 1979; Rizzolatti et al., 1981a; Colby et al., 1993; Graziano and Gross, 1993), and (4) their visual receptive fields were independent of gaze direction (Gentilucci et al., 1983), but instead moved when the tactile receptive fields moved (Graziano et al., 1994, 1997; Fogassi et al., 1996). In fact, trimodal neurons, which are similar to these bimodal neurons but also show auditory receptive fields, have also been discovered. The auditory receptive fields were usually in register with the tactile receptive fields, and also responded in the near space directly behind the animal (Graziano et al., 1999).

Other factors which have been found to play a role in the response magnitude of such bimodal and trimodal cells were joint movement (both active and passive) (Leinonen and Nyman, 1979; Rizzolatti et al., 1981b; Gentilucci et al., 1988), specific directions or patterns of stimulus movement (Rizzolatti et al., 1981a; Colby et al., 1993; Graziano and Gross, 1993), and the salience and type of objects (Colby and Goldberg, 1999). Furthermore, at least in some studies, a monkey’s movements directed towards those areas wherein a neuron’s visual receptive field lay, were found to evoke increased activity (Hyvarinen and Poranen, 1974; Gentilucci et al., 1988). Fascinatingly, some of these bimodal neurons fired tonically while an object was stationary in their visual receptive field, but even kept doing so in total darkness as long as the monkey still believed the object to be present (Graziano et al., 1997).

It is not surprising that these neurons were soon named ‘peripersonal neurons’ (Rizzolatti et al., 1981a), and that their discovery led to various theories on how the space near the body might be represented in the brain by such neurons. Two of these theories found some traction, the first being a ‘visual’ theory. This theory holds that the multimodal neurons signal the location of objects. In other words, they are necessary for us to understand (consciously) where objects are through vision. The second is a ‘motor’ theory. In this theory the neuronal discharge represents a potential action, directed towards or away from a particular point in space (Rizzolatti et al., 1997; Fogassi and Gallese, 2004; Graziano and Cooke, 2006). While the motor theory seemed to gain more traction than the visual theory, most views on the matter contained at least a bit of both (e.g. Colby and Goldberg, 1999), and the theories are not necessarily in direct conflict with one another.

The motor theory was further strengthened when it was found that direct electrical stimulation of certain bimodal neurons elicited movements seemingly aimed to defend the body from a point in space which roughly matched those neurons' visual receptive fields (Graziano et al., 2002; Cooke et al., 2003). From an ethological perspective, these movements resembled defensive movements elicited by air puffs (Cooke and Graziano, 2003). Furthermore, injecting bicuculline (a compound that increases neuronal activity) or muscimol (a compound that decreases neuronal activity) into the regions from which such defensive movements were elicited, increased and decreased respectively the magnitude of defensive responses evoked by either air puffs or approaching objects (Cooke and Graziano, 2004). These observations led to the idea that the studied multisensory neurons might underlie "the construction of a margin of safety around the body and the selection and coordination of defensive behaviour" (Graziano and Cooke, 2006). These defensive responses were elicited from two specific brain areas: the ventral intraparietal area (VIP; the human equivalent of this region and its surroundings were likely damaged in most of Brain's patients (Brain, 1941)) in the depths of the intraparietal sulcus (Colby et al., 1993), and the so called 'polysensory zone', a putative region roughly matching the dorsal half of F4 (Graziano and Gandhi, 2000).

These locations are important, because the brain regions in which the bimodal 'peripersonal' neurons are located seem to partially determine (1) the distributions of tactile receptive fields on the body surface, as well as (2) the types of movements that have been linked to the neurons' firing. For example, the tactile receptive fields of bimodal putamen neurons are mainly located on the face and the arm, and their visual receptive fields do not often extend much further than 10cm from the body (Graziano and Gross, 1993). The neurons in F4 show similar locations of receptive fields, except that the trunk is also represented in those neurons, and their visual receptive fields can extend further away from the body (Fogassi et al., 1996; Graziano et al., 1997). The anterior intraparietal sulcus is mainly related to touch on, and movements of the face (Leinonen and Nyman, 1979). While VIP tactile receptive fields are similarly mainly located on the face, their firing has been linked to (defensive) movements of both the face and other body parts towards or away from regions near the face (Colby et al., 1993; Cooke et al., 2003). In contrast, bimodal neurons in area F2 mainly show tactile receptive fields covering the forelimbs and upper trunk, and they discharge during arm and hand movements (Raos, 2004). Similarly to F2, multimodal neurons in the medial intraparietal sulcus (MIP) mainly show tactile receptive fields on the upper limbs or hands, and are active during reaching and pointing movements (Colby and Duhamel, 1991).

The heterogeneity in the receptive fields and movements associated with bimodal peripersonal neurons has led some to postulate the existence of interconnected but separate parieto-premotor ‘peripersonal networks’ underlying different types of movement representation. Generally, areas such as VIP are included in what people labelled as ‘face’ networks (Colby and Goldberg, 1999), ‘defence’ networks (Cléry et al., 2015b), or ‘action and space perception’ networks (Fogassi and Gallese, 2004), while areas such as MIP and AIP are included in ‘hand’ networks (Colby and Goldberg, 1999) , or ‘reaching/grasping’ networks (Fogassi and Gallese, 2004; Cléry et al., 2015a). Whether F4 is related to defence (Graziano and Cooke, 2006) or reaching is still somewhat of an open issue, although of course it could be related to both (Fogassi et al., 1996). Regardless of this issue, and regardless of whether these labels distinguish between anatomical (e.g. face, hand) or functional differences (e.g. defence, reaching), what should be taken from this is that different groups agree on the existence of functionally distinct networks. Hence, the heterogeneity in the receptive fields and movements associated with bimodal peripersonal neurons also indicates that there are multiple representations of the space near the body in parietal and premotor areas (Rizzolatti et al., 1997; Colby and Goldberg, 1999).

2.3 Human peripersonal space

When it came to extending the monkey peripersonal neuron findings to humans in the late nineties, the omnipresent problem of human neuroscience reared its head: one cannot just perform the same experiments on humans that are performed on (other) lab animals. Consequently, a number of less invasive paradigms were devised to investigate how the human brain deals with stimuli in the space near the body.

Because of the multimodal nature of monkey peripersonal neurons, many of these paradigms rely on multimodal integration. One of the first such paradigms exploited visuo- and audio-tactile extinction in patients with right hemispheric lesions. In these patients, visual or auditory stimuli delivered in the space near the ipsilesional side of the face decreased the detection rate (i.e. extinguished the perception of) tactile stimuli on the contralesional side. In contrast, visual stimuli delivered further away from the face, but still on the ipsilesional side of space, did not (Làdavas et al., 1998; Farnè and Làdavas, 2002). Furthermore, extinction was greatest when the visual or auditory stimuli were near a homologous body part to the tactile stimulation (Farnè et al., 2005a). Interestingly, the region of space within which audiotactile extinction occurred, expanded after active tool use: there was increased audiotactile extinction when visual stimuli were presented near the tip of an actively used tool when compared to a passive use or tool-less condition (Farnè and Làdavas, 2000; Farnè et al., 2005b).

Similar effects of tool use were found on the region of space neglected by a particular patient with right brain damage: when asked to bisect a line with a laser pointer, this patient showed a larger rightward bias when the line was in near space than when it was in far space. In contrast, when this subject used a stick to perform the same tasks , the difference in bisection error between near and far space was substantially smaller (Berti and Frassinetti, 2000). Therefore, PPS mapped using line bisection could expand when using a tool. In fact, pseudo-neglect can be found in healthy participants as well: they tend to mis-bisect lines slightly to the left when lines are near, but this mis-bisection shifts gradually to the right as lines moves further away from the body (McCourt and Garlinghouse, 2000). The slope of this left-to-right bisection function depends on arm length (Longo and Lourenco, 2007), and bisecting a line with a stick instead of a laser pointer nullifies the effect of distance (Longo and Lourenco, 2006). These results demonstrated not only that PPS (as mapped out by visuotactile extinction or visual neglect) could change, but also that it could do so on the basis of the relevance of motor tasks. Furthermore, the results were evocative of what was observed in certain monkey bimodal neurons, whose visual receptive field expands in depth after active tool use (Iriki et al., 1996).

Since the first extinction and neglect studies, many other behavioural paradigms have related the magnitude of visuo-tactile and audio-tactile integration to body proximity (Occelli et al., 2011). For example, multimodal interaction indexed by a crossmodal congruency task is also stronger in the near space (Spence et al., 2004a), and this pattern seems to follow a body part centred frame of reference (Spence et al., 2004b). Furthermore, when actions are being initiated and executed, this type of multisensory integration related to the limb performing the action is enhanced (Brozzoli et al., 2009, 2010). Further examples of multimodal measures that depend on cross-modal proximity, and do so in a body part centred reference frame, are temporal order judgements (Kitagawa et al., 2005; De Paepe et al., 2014, 2017), the rubber hand illusion (Makin et al., 2008), and reaction times to tactile stimuli (Tajadura-Jiménez et al., 2009; Serino et al., 2015). Importantly, these measures are also strongly related to spatial motor tasks and reachability (Serino et al., 2007; Costantini et al., 2010; Valdés-

Conroy et al., 2014), impact prediction (Kandula et al., 2014; Cléry et al., 2015a), stimulus direction (Serino et al., 2015), body motion (Noel et al., 2014; Galli et al., 2015), stimulus valence (Ferri et al., 2015b; de Haan et al., 2016), and social factors (Teneggi et al., 2013; Maister et al., 2015). These dependencies on factors other than proximity again indicate that the multimodal measures investigated in humans are strongly related to action relevance (Makin et al., 2012), similarly to the response fields of monkey peripersonal neurons (Rizzolatti et al., 1997).

There is also similarity between the neural correlates of such multimodal ‘peripersonal’ measures and the brain areas containing peripersonal neurons in macaques: using fMRI, proximity-dependent multimodal activity has been shown in human putamen, and parietal and premotor areas (Bremmer et al., 2001; Ehrsson et al., 2004; Macaluso and Driver, 2005; Sereno and Huang, 2006; Brozzoli et al., 2011, 2013; Gentile et al., 2011), which largely correspond to the areas within which bimodal peripersonal neurons have been found in the monkey brain (Cléry et al., 2015b). Other proximity-dependent multimodal areas identified through fMRI are the lateral occipital cortex (Makin et al., 2007), the supramarginal gyrus (Brozzoli et al., 2011), and the superior parietal occipital junction (Quinlan and Culham, 2007; Gallivan et al., 2009). Disrupting the functioning of premotor and parietal areas through TMS also has been found to eliminate the improvement of reaction time to tactile stimuli on the hand when sounds are near (Serino et al., 2011). Finally, the amplitude of certain event-related potential peaks can correlate with stimulus proximity, although the cortical generators of these EEG effects are still unknown (Sambo and Forster, 2009a, 2011; Valdés-Conroy et al., 2014).

Thus, there are clear parallels between these human PPS measures and monkey peripersonal neurons (Ladavas, 2002). Nonetheless there is still a fundamental difference between them. The individual peripersonal monkey neurons seem to be linked to very specific groups of actions (Fogassi and Gallese, 1996; Colby and Goldberg, 1999; Graziano and Cooke, 2006), while multimodal integration is relevant to almost any type of action: the more information can be gleaned about an object through various senses, the better. Importantly, this is true for both reaching/grasping actions and defensive/avoidance actions (Brozzoli et al., 2014; van der Stoep et al., 2016). It is therefore not surprising that when results are discussed from multimodal interaction studies that are intuitively more related to grasping or appetitive movements, the reach-to-grasp aspect of multimodal integration is emphasised (e.g. Serino et al., 2007; Costantini et al., 2010; Valdés-Conroy et al., 2014). On the other hand, when results are discussed from studies more intuitively linked to defence and threat (e.g. Kandula et al., 2014; Cléry et al., 2015a; Ferri et al., 2015; de Haan et al., 2016), the defensive aspect of multimodal integration is emphasised. Such divergent discussions have led to a debate on whether PPS as indexed by multimodal integration is defensive, appetitive, or whether there are two or more distinct types of PPS (de Vignemont and Iannetti, 2015).

Clearly, it is difficult to model and interpret the meaning of a PPS as derived from measures that might relate to a large number of actions. Recently however, our lab has found that a simple defensive brainstem reflex is also modulated by proximity of the eliciting stimulus to the body (or in fact, the face): the hand-blink reflex (Sambo et al., 2012b).

2.3.1 The hand blink reflex as a measure of defensive peripersonal space

The hand-blink reflex (HBR) is a prototypical defensive reflex elicited by electrical stimulation of the median nerve (Valls-Solé et al., 1997; Miwa et al., 1998). The HBR consists in the stimulus-evoked contraction of the *orbicularis oculi* muscles, measured by recording their activity with surface electromyography (EMG), and is larger when stimuli are applied to the upper than to the lower limb (Miwa et al., 1995). In the past this had been interpreted as due to the shorter conduction distance and more synchronised afferent volleys generated by the electrical stimulation (Álvarez-Blanco et al., 2009). However, our lab recently showed that this is unlikely to be the reason (Sambo et al., 2012b). Instead, when eliciting the HBR from *stimulation at the wrist*, the HBR magnitude was enhanced when the stimulated hand was placed near the face, as compared to when it was far away. This finding was irrespective of whether this proximity was caused by changing the position of the arm, or by rotating the head while keeping the arm position constant. Furthermore, such HBR enhancement was similar in magnitude when the participants had their eyes closed (Sambo et al., 2012b). Taken together, those results indicated that the brain stem circuits mediating the HBR undergo tonic and selective top-down modulation from higher order cortical areas that encode the location of somatosensory stimuli in external coordinates. Such modulation has a clear behavioural value: when a threat is closer, it poses a greater danger, and a more effective blink reflex can mitigate the greater potential harm. In other words, HBR could be used to describe *defensive* peripersonal space (DPPS): the space defined by the increased magnitude of the defensive HBR response (see Chapter 1.1 and Chapter 7 for a further explanation of the way the term DPPS is used in this thesis. Unless otherwise stated, throughout the thesis the term DPPS will refer to the DPPS *as defined by HBR magnitude*).

Using the HBR as a DPPS-related measure does have a drawback: under laboratory conditions, not all participants show large enough HBR responses over baseline noise. In previous studies, the percentage of responders (i.e. subjects who showed a clear HBR in three consecutive trials with a 30s inter-stimulus interval (Valls-Solé et al., 1997; Sambo et al., 2012b)) has been found to be approximately 65% (Miwa et al., 1995, 1998; Valls-Solé et al., 1997; Sambo et al., 2012b; Sambo and Iannetti, 2013; Fossataro et al., 2016; Wallwork et al., 2016). Importantly however, this figure is consequent to the large variability in HBR thresholds among the population, and reflects the response elicited by stimulus intensities within ethically-acceptable stimulation energies: prior to testing, the stimulus intensity able to elicit a well-defined and stable blink reflex is determined for each participant. This is achieved by increasing the stimulus intensity until a clear HBR is observed in three consecutive trials, or the participant refuses a further increase of stimulus intensity (Valls-Solé et al., 1997). Any participants who refuse a further increase of stimulus intensity before reproducible blinks are observed, is considered HBR non-responsive. Therefore, it is likely that most participants labelled as non-responders simply did not receive stimulations strong enough to reliably elicit an HBR. Given that within HBR responders there is no pattern relating the results of experiments to their response threshold (Sambo et al., 2012b; Bufacchi et al., 2016), the results observed in these HBR responders are therefore likely to generalize to the entire population.

A second drawback of using the HBR as an experimental measure of DPPS is that it habituates over time. To minimise this habituation, somatosensory stimuli were delivered at a relatively long inter-stimulus interval of ~30s, and a 2-5 minute break was interposed between relatively short blocks (~10 minutes each) (Miwa et al., 1998; Sambo et al., 2012b). As a result, it is difficult to test more than 5 experimental conditions within the duration of a typical experiment, which occasionally necessitates an across-experiment design. It is also possible that the habituation affects the classification of participants as responders or non-responders: a participants who habituates particularly quickly might only show a clear HBR after the first 2 out of 3 stimulations, and thus be classified as a non-responder. However, this possibility currently remains unexplored.

In contrast to the above drawbacks, there is an important and rather unique advantage of using the HBR to investigate the manner in which defensive responses depend on proximity of a stimulus to the body (i.e. the spatial features of DPPS): a change of the position of the stimulated hand in egocentric coordinates does not alter the intensity of the sensory input eliciting the response. The use of the blink reflex elicited by, for example, auditory stimuli, would present the major drawback of different stimulus intensities when the stimulus is in different spatial locations. Coming back to the insights gleaned from the HBR, in subsequent studies, more interesting properties of the DPPS as defined by the HBR were found. For example, the somatotopic specificity of the HBR enhancement was found to be partially homosegmental, i.e., it is greater for the HBR elicited by the stimulation of the hand near the face compared with the other hand, always kept far from the face. Furthermore, the HBR was only enhanced when participants expected to receive stimuli on the hand close to the face. Therefore, the modulation of HBR magnitude is strongly dependent on cognitive expectations.

Whether these expectations affect the HBR in a uniform manner regardless of hand position, or do so differently for different hand positions (and thus also affect the shape of DPPS), is currently unknown. However, a comparison of two recent studies can shed some light on this issue; both of these studies found an effect of hand movement on HBR (Wallwork et al., 2016; Bisio et al., 2017), but seemingly in opposite directions. Wallwork et al. (2016) found that the HBR magnitude is increased when the hand moves towards the face, but not decreased when the hand moves away from the face, while Bisio et al. (2017) found that the HBR magnitude is not increased when the hand moves towards the face, but is decreased when the hand moves away from the face. The key to reconciling these results lies in the slight differences in experimental design: in Bisio et al. (2016), the expectation of receiving somatosensory stimuli was different under different experimental conditions, and it is likely that the expectation of stimuli altered the DPPS shape (Bufacchi, 2017). This comparison and its implications are discussed in more depth in the appendix (section 10).

The HBR modulation is also suppressed when a thin wooden screen is placed between the participants’ face and their hand; the screen might be said to reduce the extension of DPPS, so that the hand is never inside the peripersonal space of the face, even in the “near” condition (Sambo et al., 2012a). All the above findings strengthened the notion that the HBR magnitude is adjusted depending on context in a purposeful manner, much like the other human PPS measures and peripersonal monkey neurons described in the preceding section. In fact a further similarity between the DPPS as defined by HBR and other PPS measures is that it is affected by interpersonal interactions (Fossataro et al., 2016).

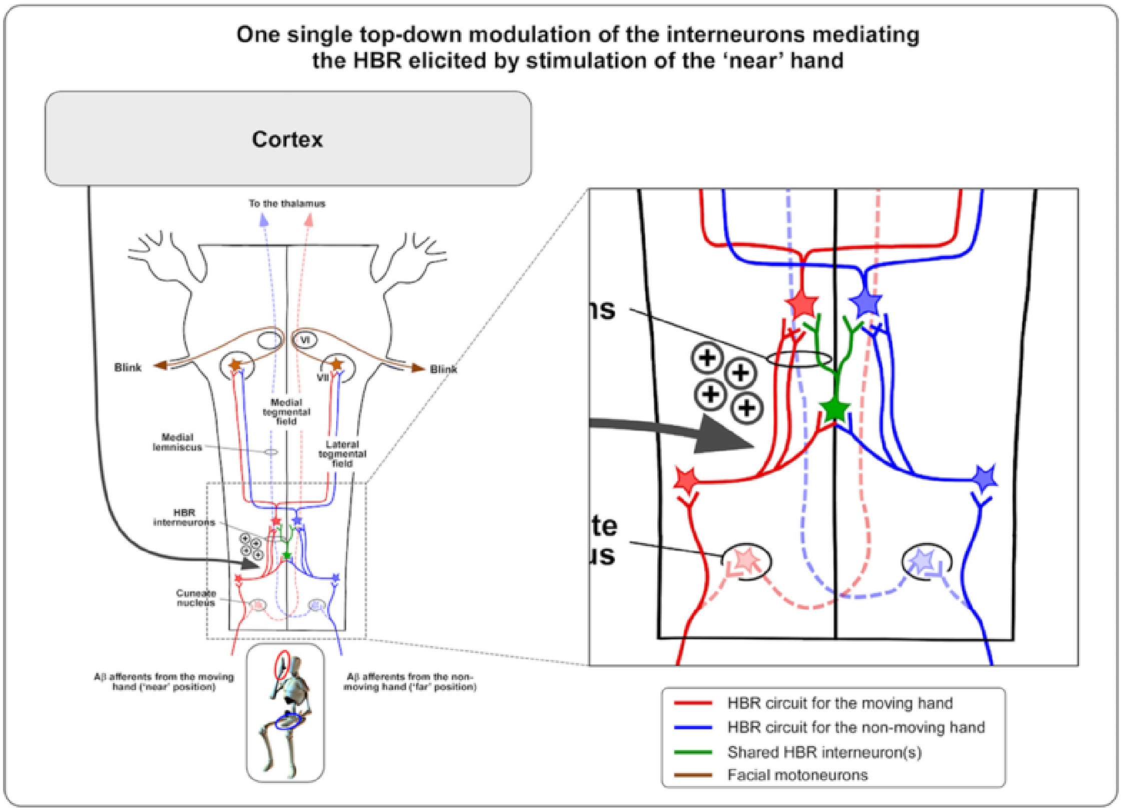

Figure 2.1, modified from Sambo et al. (2012a). ***Possible brainstem circuitry subserving the cortical modulation of the HBR.*** *The brainstem circuits mediating the HBR elicited by the stimulation of the two hands might share a subset of interneurons. This model allows for a single top-down modulation directed uniquely to the brainstem interneurons mediating the HBR elicited by the stimulation of the moving hand.*

Based on their findings, Sambo et al. (2102a) also postulated brainstem circuitry subserving the cortical modulation of the the HBR (Figure 2.1). This proposed brainstem circuitry of the HBR at medullary and pontine level also explains the fact that HBR measured from the eye contralateral to the stimulated hand is smaller in magnitude than that elicited from the ipsilateral eye. This 'ipsi-contra effect' does not depend on proximity in healthy participants (Sambo et al., 2012b), although, as we will see in Chapter 6, it can be different in disease.

A shortcoming of the HBR studies not mentioned up to this point, and in fact also of many other studies on human PPS-related measures (van der Stoep et al., 2016), is that only two stimulus positions were tested: near and far. Such designs can lead to oversimplification and various interpretational issues, such as the notion that there is a single 'in-or-out peripersonal space'. These issues will be elaborated further in the discussion of this thesis (Chapter7). A first step towards addressing such issues was made by eliciting HBR when the hand was placed at four distances from the face (Sambo and Iannetti, 2013). This study not only showed that there is a non-linear monotonic increase of HBR magnitude with proximity to the face, but also that the exact shape of this function depended on the trait anxiety of an individual: subjects with higher trait anxiety showed a HBR response function consistent with a ‘larger DPPS’ (Sambo and Iannetti, 2013). Nonetheless, it still sampled the near space very sparsely, and did not provide information about the 3D shape of the DPPS.

3 Modelling part 1: A geometric model of defensive peripersonal space

3.1 Background

Despite the amount of work performed on the HBR, the spatial features of the DPPS derived from the HBR have so far been poorly defined, and are limited to descriptive estimates of its extent along a single dimension. Here we postulated a family of geometric models of the DPPS, to address two important questions with respect to its spatial features: What is its fine-grained topography? How does the nervous system represent the body area to be defended? As a measure of the DPPS, we used the strength of the defensive blink reflex elicited by electrical stimulation of the hand (hand-blink reflex, HBR), which is reliably modulated by the position of the stimulated hand in egocentric coordinates. We tested the Goodness of Fit of the postulated models to HBR data from six experiments in which we systematically explored the HBR modulation by hand position in both head-centred and body-centred coordinates. The best fitting model indicated that (1) the nervous system's representation of the body area defended by the HBR can be approximated by a half-ellipsoid centred on the face, and (2) the DPPS extending from this area has the shape of a bubble elongated along the vertical axis. Finally, the empirical observation that the HBR is modulated by hand position in head-centred coordinates indicates that the DPPS is anchored to the face. The modelling approach described here can be generalised to describe the spatial modulation of any defensive response.

This study has been published as Bufacchi et al. (2016).

3.2 Introduction

In previous work on DPPS indexed by HBR (i.e. in Sambo & Iannetti (2013)), the position of the threatening stimulus in external space was only modulated across four positions along a single axis perpendicular to the face, at a downward angle of approximately 15 degrees from the eye (Figure 3.1). Furthermore, the estimate of the individual DPPS shape was obtained using step models, in which there is no information about HBR strength in between the four stimulation positions. Consequently, this modelling approach does not allow for making any predictions about the HBR response elicited by stimuli in spatial locations where no measurements were taken, and thus cannot be used to derive a finer shape of the DPPS surrounding the face.

Therefore, in this study we aimed to obtain a general characterization of the spatial features of the DPPS by formulating a family of models. These models simulate how the brain computes the different levels of threat represented by identical stimuli that differ in their egocentric spatial position. In these models, the strength of the defensivse response is expressed as a mathematical function of the spatial location of the threat. To formulate and test the models, we analysed data from two previously published experiments (Sambo et al. 2012a; Sambo et al. 2012b), and four new experiments (Figure 3.1). In two of the new experiments, the position of the threat was modulated along the medio-lateral and rostro-caudal axes on a coronal plane in front of the face. In the third new experiment, the threat was placed in front of, to the side of, or behind the head, while the head orientation was either forward or sideways. The fourth new experiment included a subset of the stimulation positions used in all other experiments, to control for the variability in response magnitude across datasets, and therefore allow for a combined analysis of all datasets. We simultaneously fitted the data from these six experiments to a series of geometric models in which the HBR magnitude was calculated from the geometric probability of the individual being hit by a threat, and which covered the entirety of space surrounding the body, rather than just the positions at which the HBR magnitude was measured.

Besides the position of the threat, another important factor determining the goodness of fit of the geometric model is the shape of the body district to be defended. Therefore, we also tested whether and how a range of shapes of the defended area altered the goodness of fit. Theoretically, the number of testable shapes is infinite. However, a large number of such shapes are physiologically implausible. Therefore, given that the HBR is a defensive response performed by muscles innervated by the facial nerve, we limited the testing to four different geometries representing defended areas related to the head: the entire head (full-ellipsoid), the face (half-ellipsoid), the top part of the face (quarter-ellipsoid), or the eyes (two half ellipsoids) (Figure 3.2). Thereby, we assessed how the brain geometrically represents the body part to be defended.

3.3 Materials and Methods

3.3.1 Participants

We analysed the data collected in two previous experiments (Experiments 1.1 and 1.2, performed before I joined the Iannetti lab), as well as data from four new experiments (Experiments 1.3, 1.4, 1.5 and 1.6). All experiments were conducted in groups of healthy participants, as follows. Experiment 1.1: 15 participants (7 women), age range 20-37 years, mean age (±SD) 27.4 ± 5.7 years (Sambo and Iannetti, 2013); Experiment

1.2: 7 participants (3 women), 26-37 years, 32.9 ± 5.7 years (Sambo et al., 2012b); Experiment 1.3: 10 participants (7 women), 18-40 years, 24.1 ± 6.7 years; Experiment 1.4: 10 participants (7 women), 21-30 years, 22.7 ± 3.9 years; Experiment 1.5: 10 participants (5 women), 18-31 years, 22.9 ± 3.4 years; and Experiment 1.6: 11 participants (6 women), 19-40 years, 24.0 ± 5.7 years. The 41 participants in the four new Experiments (1.3-1.6) were HBR responders (Miwa et al., 1998) identified from a group of 63 recruited subjects. Therefore, 65% of recruited subjects were HBR responders. This figure is consistent with previous reports (Sambo et al. 2012a; Sambo et al. 2012b; Sambo & Iannetti 2013; Miwa et al. 1998).

All participants were right-handed. Participants gave written informed consent before taking part in the study. All procedures were approved by the local ethics committee.

3.3.2 Stimulation and Recording

The procedures for Experiments 1.1-1.6 were identical, except for the hand positions and number of stimuli delivered to each hand, as detailed below and summarized in Figure 3.1. Transcutaneous electrical stimuli were delivered using surface bipolar electrodes placed on the median nerve at the wrist. The electrodes were covered in conductive paste, and taped to the participants' skin using hypoallergenic tape, thus ensuring constant pressure across experimental conditions. For each participant, we first determined the stimulus intensity able to elicit a well-defined and stable blink reflex (see Chapter 2.3.1). Participants were told that the stimulation should elicit a strong, unpleasant but not painful sensation. Accordingly, none of the participants reported painful sensations, even at high stimulus intensities.

The mean stimulus intensities used in the experiments were as follows: 42.3 mA (Experiment 1.1), 43.5 mA (Experiment 1.2), 53.8 mA (Experiment 1.3), 48.2 mA (Experiment 1.4), 39.0 mA (Experiment 1.5) and 55.8 mA (Experiment 1.6). The stimulus duration was 200 µs, and the interval between successive stimuli was ~30 s. Electromyographic (EMG) activity was recorded from the *orbicularis oculi* muscle, bilaterally, using surface Ag-AgCl electrodes. The active electrode was placed over the mid-lower eyelid and the reference electrode a few centimeters laterally to the outer canthus. Signals were amplified and digitized at a sampling rate of 8,192 Hz (ISA 1004, Micromed, Treviso, Italy), and stored for offline analysis.

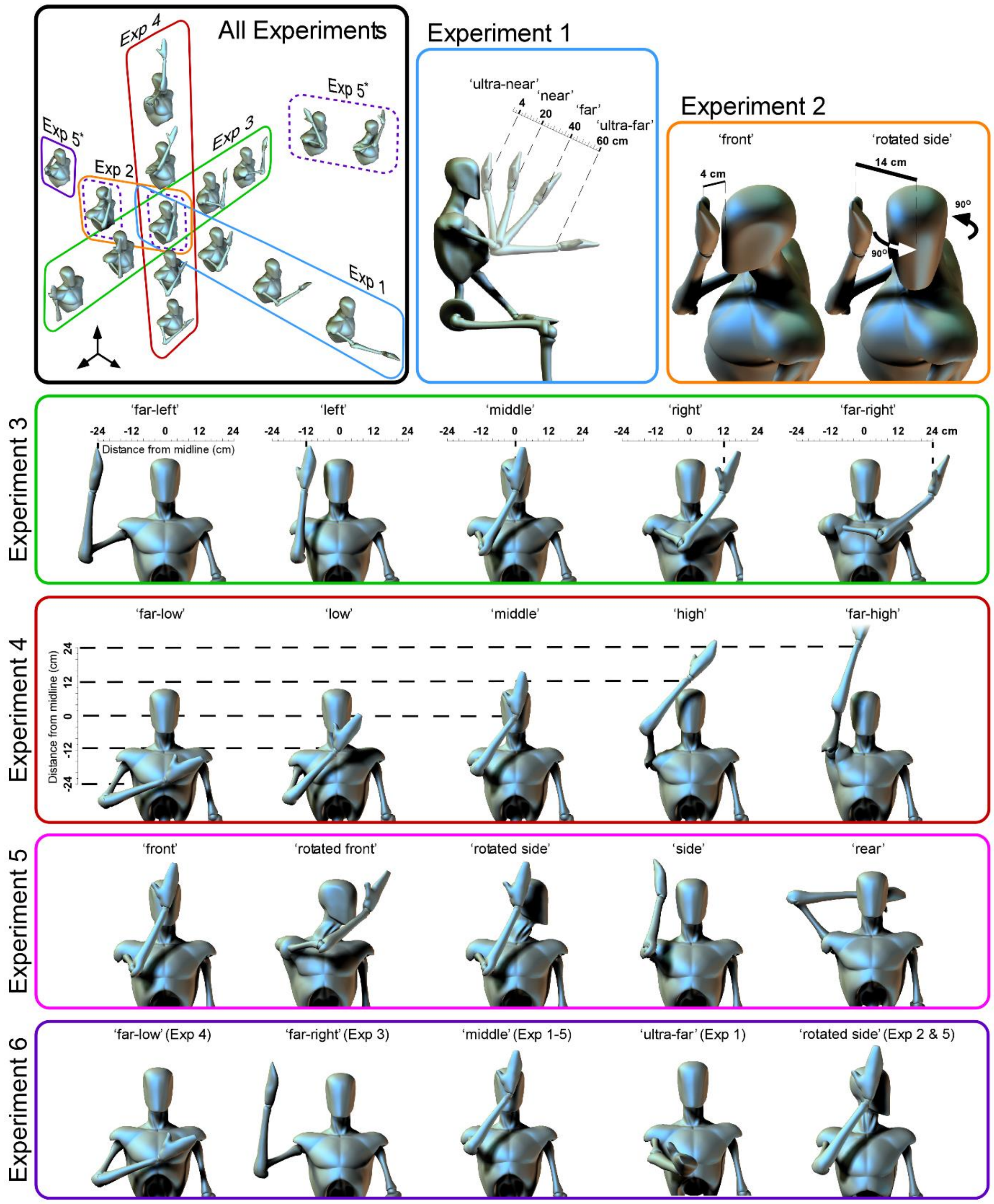

Figure 3.1. Hand positions at which the HBR was recorded in the Experiments 1.1-1.6 *(in this figure, they are referred to as Experiments 1-6). The HBR was elicited by electrical stimulation of the right median nerve at the wrist. The top left panel shows an overall view of the postures used in Experiments 1.1-1.6. The remaining panel shows the hand-positions adopted in each of those experiment separately.*

In Experiment 1.1 HBR responses were recorded while the participants' stimulated hand was placed at four distances from their eyes: 'ultra-far': 60 cm; 'far': 40 cm; 'near': 20 cm; 'ultra-near': 4 cm. The hand not undergoing the postural manipulation was never stimulated, and was kept on a table throughout the duration of the experiment. During the recording participants were instructed to keep their gaze on a fixation cross (1.5 x 1.5 cm) placed at approximately 30 cm from the eyes, and 45 degrees below eye level.

The experiment consisted of two blocks. In each block, stimuli were delivered to either the right or the left wrist (i.e. the wrist of the arm undergoing the postural manipulation). The order of blocks was balanced across participants. In each block, 32 electrical stimuli were delivered: eight for each of the four hand-face distances. The data for the two blocks were pooled, resulting in a total of 16 stimuli per condition. The stimuli were delivered in pseudo-random order, with the constraint that no more than two consecutive stimuli were delivered for the same hand-face distance.

In Experiment 1.2 the HBR was recorded while the position of both the hand and the arm was kept constant, and the proximity of the stimulated hand to the face was manipulated by rotating the head. Thus, the participants' forearm was kept flexed in the same near position all the time, and their head was either kept straight in anatomical position ('front' condition) or rotated sideways by 90° ('rotated side' condition).

This experiment also consisted of two blocks. In each block, 20 stimuli were delivered to either the right or the left wrist. Of these, 10 were delivered in the front condition, and 10 in the side condition. The order of the blocks was balanced across participants.

In *Experiment 1.3* the HBR was recorded while the participants' right hand was placed in 5 positions on a coronal plane located 4 cm from the nose, along a horizontal line at eye-level (Figure 3.1). The five positions were symmetrical with respect to the midline, as follows (negative values denote positions on the left side): 'far-left': -24 cm; 'left': -12 cm; 'middle': 0 cm; 'right': +12 cm; 'far-right': +24 cm. The positions were marked out on a board placed in front of the participant.

In *Experiment 1.4* the HBR was recorded while the participants' right hand was placed in 5 positions on a coronal plane located 4 cm from the nose, along a vertical line on the body midline (Figure 3.1). The five positions were symmetrical with respect to eye-level, as follows (negative values denote positions below eye-level): 'far-low': -24 cm; 'low': -12 cm; 'middle': 0 cm; 'high': +12 cm; 'far-high': +24 cm. The positions were marked out on a board placed in front of the participant.

In *Experiment 1.5* the HBR was recorded while both the position of the participants' right hand and the direction of the participants' face were manipulated. This yielded 5 different conditions. Two conditions were identical to Experiment 1.2 (‘front’ and ‘rotated side’ conditions). In the third condition, the head was rotated 90^o to the left, and the hand was placed directly in front of the face (‘rotated front’ condition). In the fourth condition, the head faced straight forward, and the hand was placed to the right of the head, beside the right ear (‘side’ condition). In the fifth condition, the head faced straight forward, and the hand was placed directly behind the head (‘rear’ condition).

In *Experiment 1.6* the HBR was recorded while the participants’ right hand was placed in 5 positions, each of which was present in at least one of Experiments 1.1-1.5. In the ‘middle’ position the hand was placed on the midline at eye level, 4 cm from the nose. This position was included in all other Experiments (and labeled as ‘ultra-near’ in Experiment 1.1, ‘front’ in Experiments 1.2 and 1.5, and ‘middle’ in Experiments 1.3 and 1.4). The other four positions were the ‘ultra-far’, ‘rotated side’, ‘far-right’, and ‘far-low’ positions from Experiments 1.1, 1.2, 1.3 and 1.4, respectively.

As expected from previous reports (Sambo et al., 2012a; Sambo and Iannetti, 2013), in Experiments 1.1 and 1.2 there was no difference in the HBR elicited by stimulation of the right and left hands ($p=0.09$ and $p=0.51$, respectively; paired t-test). Therefore, in Experiments 1.3, 1.4, 1.5 and 1.6 we only stimulated the right hand, thereby allowing us to explore the effect of 5 different hand positions within a single experiment. Experiments 1.3, 1.4, 1.5 and 1.6 consisted of two blocks. In each block, 25 stimuli were delivered to the right wrist, five at each hand position. Hence, across the two blocks, a total of 10 stimuli per hand position were delivered (50 stimuli across the five hand positions). This number of stimuli per hand position was chosen to obtain a reliable HBR, whilst still allowing us to explore as many hand positions as possible within one experiment. The order of hand positions was pseudo-randomized, with the constraint that no more than two consecutive stimuli were delivered for the same hand position.

3.3.3 Data preprocessing

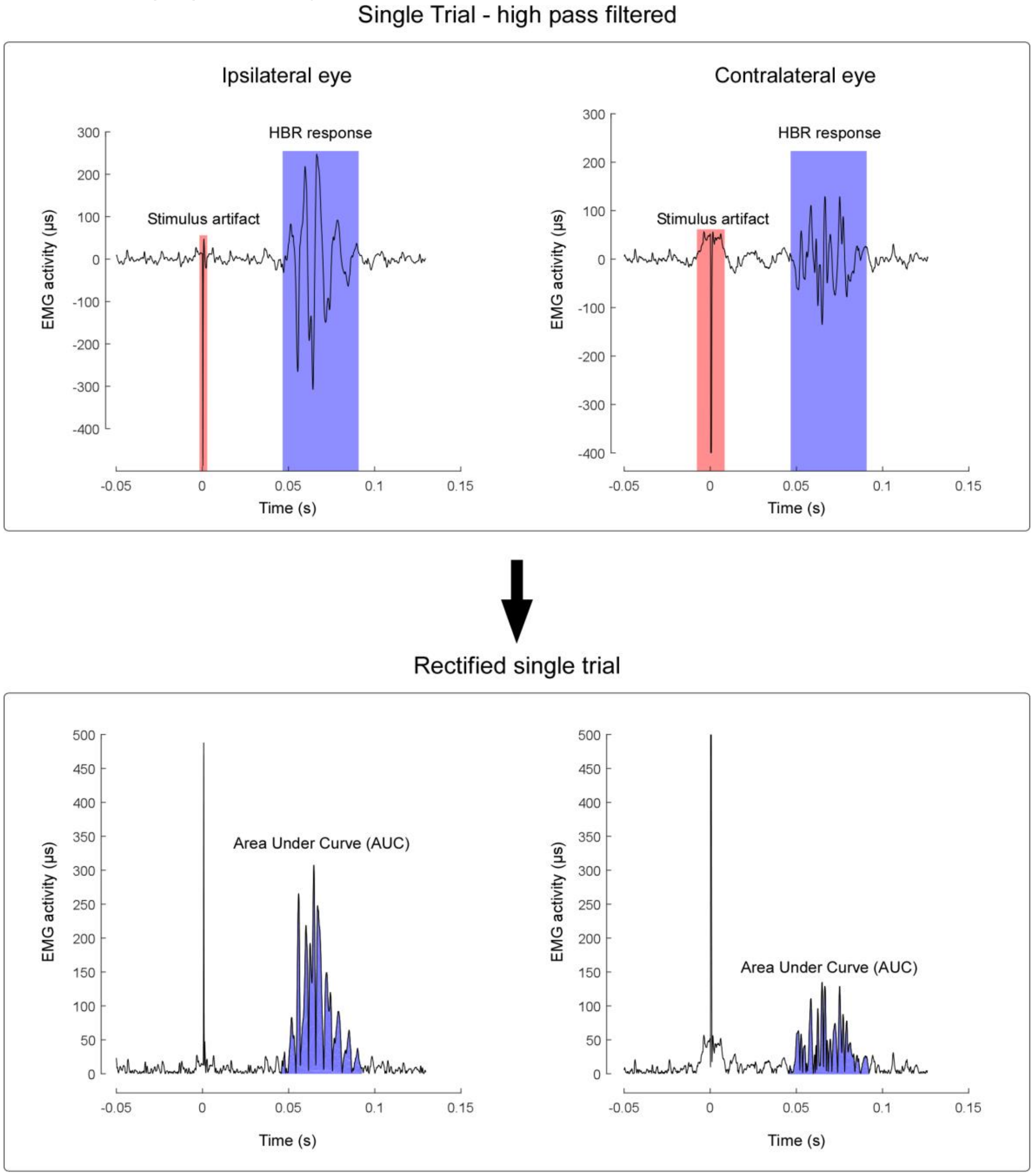

Figure 3.2. Illustrative EMG traces of a representative subject. *The HBR was recorded through superficial EMG electrodes attached to the skin near the eye – one lateral to the outer canthus, and the other underneath the lower eyelid. The top panel shows representative single-trial waveforms. The stimulus (electric shock) artefact is visible at t=0ms. The HBR response consists in high frequency oscillations of the EMG traces, reflecting the electric activity in the Orbicularis Oculi muscle. The bottom panel shows the rectified signals, which are used to extract HBR magnitudes as the integral of the EMG activity during the response time window (Area Under Curve; AUC).*

EMG signals from each participant in each experiment were high-pass filtered (55 Hz) and full-wave rectified. The magnitude of the HBR was estimated as the time-integral, or area-under-curve (AUC) of each single-trial response, separately for each eye (see figure 3.2 for illustrative single-trial waveforms). Within each trial, the AUC of the response recorded from the eye ipsilateral and contralateral to the stimulated hand were subsequently averaged together to improve the response signal to noise ratio. The rationale for such procedure was the evidence of no interaction between hand position and recording side in determining the HBR magnitude (Sambo et al., 2012a). The AUCs at each position were finally averaged across trials, to give a single average AUC value for each subject at each hand position.

3.3.4 HBR magnitude normalization

To model the datasets from all six experiments and all subjects simultaneously, the AUCs were first shifted so that at the ‘ultra-near’, ‘middle’ and ‘front’ positions (in Experiments 1.1, 1.3 & 1.4 and 1.2 & 1.5, respectively) the AUCs were set to 0 for each subject. Second, the AUCs in Experiments 1.1-1.5 were normalised using the AUCs of the response at the corresponding positions in Experiment 1.6 as anchors. As an illustrative example, if the mean AUC at the ‘far-right’ position in Experiment 1.3 was X, and the mean AUC at that same ‘far-right’ position in Experiment 1.6 was Y, given that the AUCs at the ‘middle’ position of both Experiments were set to 0, the AUCs of the responses in all positions of Experiment 1.3 were rescaled, as follows:

$$\mathrm{AUC}_{3,RESCALED} = \frac{Y}{X}\mathrm{AUC}_{3,ORIGINAL} \qquad \textbf{\textit{(1)}}$$

3.3.5 Testing for normality and equal variance

The validity of the considered models was assessed by their goodness of fit (GoF) to the mean HBR magnitudes at all positions. The GoF modelling approach compares the chi-squared (χ^2) test statistic of the fit of any given model to the data, to a χ^2 distribution of the appropriate degrees of freedom, resulting in a GoF score and a corresponding *p*-value. Therefore, if the GoF-score is *larger* than 1.850 (which corresponds to the threshold of $p=0.05$ in the χ^2 distribution considered), the probability of the model being correct is *smaller* than 0.05, and the model must be rejected. Hence, the smaller the GoF score and the larger the p-value of a model, the more strongly the model is accepted. This approach requires (1) that data are normally distributed, and (2) that the variance across hand positions is equal. Because we fit the models to the mean HBR magnitudes at each position, we used the standard error of the mean as measure of data variance. The Anderson-Darling test was used to assess normality of the distribution, and the Bartlett's test to assess differences of variance.

To meet these two requirements, data from two subjects in Experiment 1.1 had to be excluded. In these subjects the variance of the HBR response was different across hand positions (p=0.005 and P=0.0046; H_0 = equal variance). Furthermore, a variance-stabilising transformation had to be applied (Everitt and Skrondal, 2010). After the exclusion of these subjects and variance-stabilising power-transformation of the data ($AUC \rightarrow AUC^{0.25}$), HBR magnitude had equal variance (P=0.3131; H_0 = equal variance) and was normally distributed across all hand positions (Anderson-Darling test, P = 0.1319; H_0 = normal distribution).

3.3.6 Modelling the defensive peripersonal space

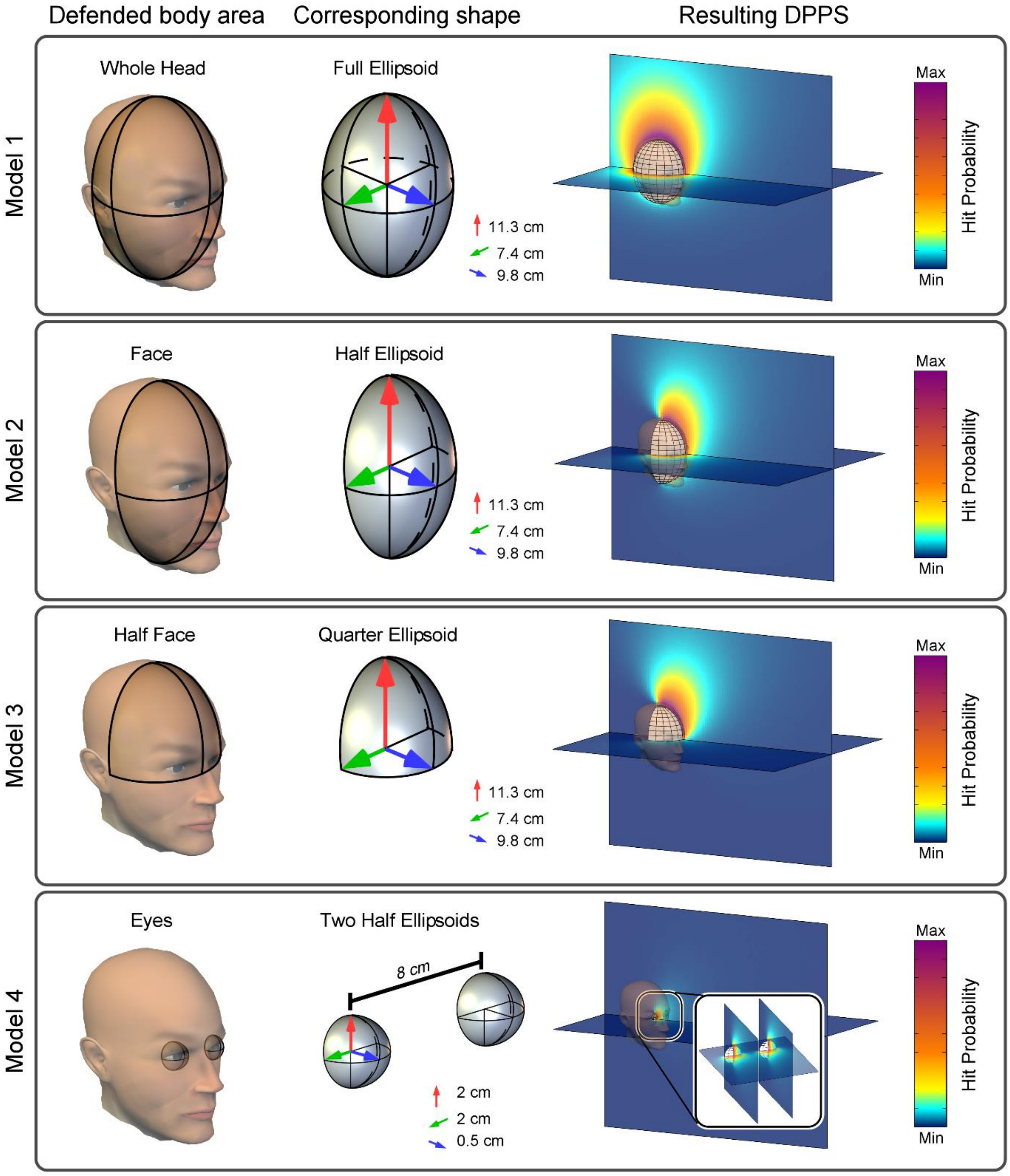

Figure 3.3. *Geometric models.* *In these models the increase in HBR magnitude reflects the probability of a defended area being hit. Here we consider four possible shapes of defended areas, corresponding (from top to bottom) to the entire head, the face, the half face, and the eyes. These areas are approximated by an entire ellipsoid, a half-ellipsoid and a quarter-ellipsoid, and two smaller half-ellipsoids, respectively. The 3D plots on the right show the predicted HBR enhancement depending on the spatial location of the stimulus.*

The defensive peripersonal space was characterised using a series of *geometric* models.

These models use geometrically-derived formulae to describe a danger function underlying the observed changes in HBR magnitude according to (1) the position of the threat in external space, and (2) the spatial features of the area being defended.

This approach results in the formalization of the intuitive idea that the closer a potentially harmful stimulus is to an individual, the greater its probability to do harm, which therefore results in a stronger defensive reaction as follows.

Consider an agent *A* and a threat *B*, which is potentially harmful to *A*. *A* can perform a defensive action called, in this context, a *blink*. We define as *hitting* the potential harm that *B* can do to *A*. We then assume the following:

- *B* is observed at a point in space connected to the centre of *A* by the vector $\vec{r}$
- As soon as *B* appears, it makes a linear hitting action
- The *hitting* action occurs in a random direction
- If the *hitting* trajectory intersects *A*, *A* is hit
- *A* aims to minimise the probability of being harmed, which is proportional to the probability of being hit by *B*:

$$\mathrm{P}(\mathrm{B\ hits\ A}, \vec{r}\,) \tag{2}$$

- The purpose of a *blink* is to reduce the damage done by *B* if *A* is hit
- A stronger *blink* will further reduce the damage caused by *B* to *A*
- Blinking has a cost: the probability of *A* being harmed in other ways (besides being hit by *B*) increases with the strength of blinking. (If blinking had no cost, then A would never stop blinking at maximal intensity)

Given these assumptions, the increase in blink strength should be related to $\mathrm{P}(\mathrm{B\ hits\ A}, \vec{\mathrm{r}})$, as long as the probability of *A* being harmed in other ways (i.e. besides being hit by *B*) while blinking is smaller than the probability of being harmed by *B*. In other words, the agent *A* reacts to the threat *B* with a blink, whose magnitude is proportional to the probability of *A* being hit by *B*: $\mathrm{P}(\mathrm{B\ hits\ A}, \vec{r}\,)$.

Therefore, the probability of being hit is reflected by the ratio between the number of trajectories of the hitting action that will result in *A* being hit, and the number of all possible trajectories:

$$\mathrm{P}(\mathrm{B\ hits\ A}, \vec{r}) = \frac{\Omega}{4\pi} \tag{3}$$

where Ω is the solid angle of the agent A from the perspective of B, i.e. that portion of space within which a trajectory will result in A being hit, and 4π is the solid angle of all space. We calculated this ratio with a Monte-Carlo method very similar to ray-tracing (Appel, 1968), in which 2 million random trajectories originating from B were generated. Each trajectory was defined by a vector whose *x*, *y* and *z* components were drawn from a standard normal distribution with unit variance. The effect of gravity on the trajectory of the threat was taken into account by a specific model parameter (C_{grav}). This value was the shift of the mean of the normal distribution from which the z-components were drawn, and it was optimised to fit the data. As the number of trajectories approaches infinity, the ratio between the number of trajectories hitting *A* and the total number of trajectories approaches the probability of the agent *A* being hit (Equation (3)).

We linearly transformed the probability of *A* being hit $P(C_{grav},\mathbf{r})$ into the magnitude of the defensive HBR response $S(\mathbf{r})$, as follows

$$S(\vec{r}) = aP\left(C_{grav},\vec{r}\right) + b \tag{4}$$

where *a* and *b* are the two fitting parameters in the linear model. Therefore, equation (4) allows the calculation of the blink-strength at any point in space around the defended object.

Given the shape of the head, we considered four possible geometries for the agent A (i.e. the representation of the body area that is to be defended). The first three geometries corresponded to (1) the full head, (2) the face and (3) the upper half of the face, and were respectively modelled by a full-ellipsoid, a half-ellipsoid, and a quarter-ellipsoid. The ellipsoid modelling these three geometries of the agent A had semi-axes of 9.8 (x), 7.4 (y), and 11.3 cm (z) (Figure 3.3). These values were derived from topometric atlases (United States Army, 2000), and reflected the average dorso-ventral, medio-lateral, and rostro-caudal dimensions of the human head, respectively. The fourth geometry corresponded to (4) the two eyes, and it was modelled by a pair of half-ellipsoids with semi-axes of 0.5 (x), 2 (y), and 2 cm (z) (Figure 3.3). These values reflected the average dorso-ventral, medio-lateral, and rostro-caudal dimensions of the human orbit. For the threat B, we consider a single geometry: a point.

For each considered shape of the agent A, we optimised *a, b* and C_{grav} in equation (4), to obtain a best-fit of blink magnitude at each position for all 6 experiments simultaneously. Hence, 3 parameters were used to fit the models. The optimisation was done by finding the minimum χ^2 test statistic through the '*fminsearch*' function in Matlab, which uses the Nelder-Mead simplex algorithm (Lagarias et al., 1998). This statistic also allowed us to calculate a GoF and its corresponding p-value by comparing it to a standard χ^2 distribution.

3.4 Results

3.4.1 Descriptive results

To assess the overall effect of hand position on the HBR magnitude we performed one-way, repeated-measures ANOVAs (Experiments 1.1, 1.3, 1.4, 1.5 and 1.6), and a paired t-test (Experiment 1.2). We found evidence for an effect of the factor 'hand position' as a source of variance in all experiments (Experiment 1.1: F=28.0, p<0.0005; Experiment 1.2: t=-6.4, p=0.001; Experiment 1.3: F=5.9, p=0.018; Experiment 1.4: F=4.7, p=0.042; Experiment 1.5: F=4.6, p=0.004; Experiment 1.6: F=18.3, p<0.0005). In experiments 1.1, 1.3, 1.4, 1.5 and 1.6 we performed post-hoc Tukey's tests to determine between which positions the HBR magnitudes differed.

In Experiment 1.1, the HBR increased monotonically with the proximity between the stimulated hand and the face. There was strong evidence for a difference in HBR magnitude between all positions (p<0.001), except between the 'ultra-far' and 'far' positions (p = 0.754).

In Experiment 1.3, there was evidence of a difference between positions 'middle' and 'far-left' (p=0.016), 'middle' and 'right' (p=0.022), and 'middle' and 'far-right' (p=0.026). There was also weak evidence of a difference between 'middle' and 'left' positions (p=0.055). There was no evidence of other differences (all other comparisons: p≥0.150).

In Experiment 1.4, there was evidence of a difference between 'far-low' and 'middle' (p=0.016), between 'far-low' and 'high' (p=0.001), between 'far-low' and 'far-high' (p<0.0005), and between 'low' and 'far-high' positions (p=0.039). There was no evidence of other differences (p≥0.087).

In Experiment 1.5, there was evidence of a difference between 'front' and 'rotated side' (p=0.037), between 'front' and 'side' (p=0.047), between 'front' and 'rear' (p=0.002), between 'rotated front' and 'rotated side' (p=0.038), between 'rotated front' and 'side' (p=0.045), and between 'rotated front' and 'rear' (p=0.032). There was no evidence of other differences (p≥0.697).

In Experiment 1.6, there was evidence of a difference between 'middle' and all other positions: 'middle' and 'far-low' (p = 0.047), 'middle' and 'rotated side' (p=0.015), 'middle' and 'far-right' (p=0.027), and between 'middle' and 'ultra-far' (p=0.027). There was no evidence of other differences (p≥0.285).

3.4.2 Model Fitting

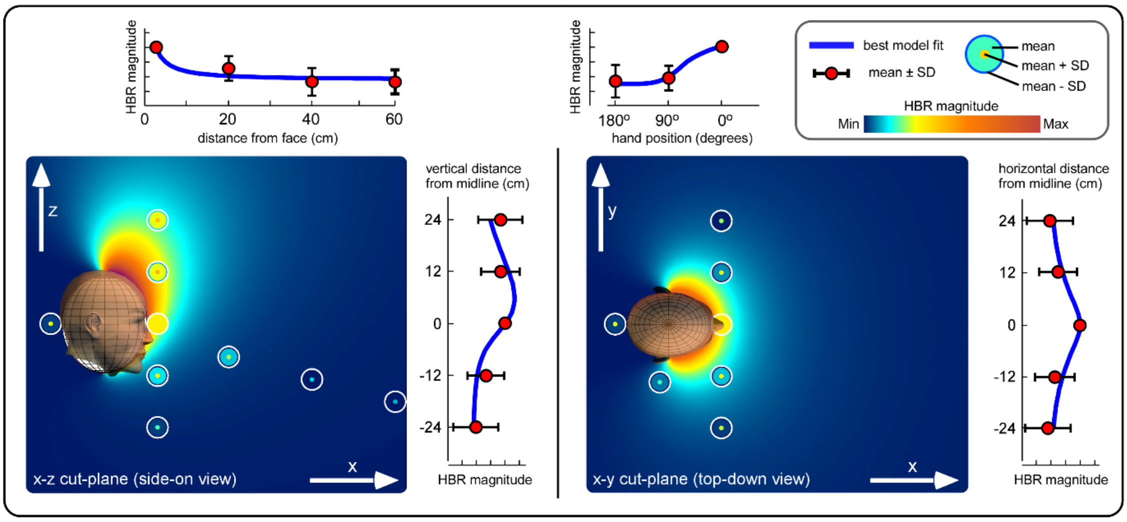

Figure 3.4. ***Effect of hand position on HBR magnitude, and geometrical modelling of DPPS.*** *Combined description of the experimental data with the best fitting geometrical model. The measured HBR data (mean±SD) are represented as concentric circles located where the measurements were taken. The background colour represents the HBR magnitude predicted by the best-fitting geometric model. The line graphs at the side of each colour plot show HBR magnitudes (mean±SD) along each axis, together with the best fitting geometric model (blue line). The best fitting model indicates that the DPPS extends from the face area, and has the shape of an elongated bubble, extending forward and upward. The upward extension of the DPPS indicates that the internal model of hitting probability might take into account gravity (expressed by parameter C_{grav} in the model).*

Figure 3.4 shows the magnitude of the HBR elicited when the hand was in different positions, from all 6 experiments. It also shows how the best fitting geometric model compares to the measured data. The geometric model that best fitted the data was the half-ellipsoid (model 2: p=0.3742, GoF=0.1832, C_{grav}=1.05). It predicted a DPPS with a pseudo-ellipsoidal shape, which extends from the face upward and outward (Figure 3.4). Therefore, the modelled DPPS was symmetrical on the horizontal plane, but asymmetrical on the vertical plane with respect to the centre of the face. Note that a

$p>0.05$ indicates that the model is accepted, and the larger the p-value, the better the model fit. Concurrently, the lower the GoF, the better the model fit.

The only other model to not be rejected was the eyes-only model (model 4: $p=0.1831$, GoF=0.850, $C_{grav}=0.85$), which predicted a DPPS qualitatively similar to that described above at the distances tested, albeit with two distinct areas of further increase in predicted HBR magnitude, one around each eye.

The models in which the defended area was represented by a full-ellipsoid (model 1: corresponding to the whole head) and a quarter-ellipsoid (model 3: corresponding to the top half of the face) were both rejected (model 1: $p<0.0001$, GoF=7.595; model 3: $p=0.044$, GoF=1.944).

Both accepted models predicted that the HBR increases monotonically and non-linearly with the proximity between the threat and the defended area. Given that the p-values of models 2 and 4 were larger than 0.05 (a threshold value that, within the χ^2 distribution considered, corresponds to a GoF of 1.850), these models were accepted by the data, thus indicating that three parameters (a, b and C_{grav}) are sufficient to fit the data from all 6 experiments.

3.5 Discussion

In this study we developed a family of theoretical models to characterize the fine-grained topography of the DPPS, as defined by the HBR increase, as a function of the spatial position of the hand in egocentric coordinates. These models are based on a set of assumptions about how the nervous system represents threatening stimuli. We mathematically expressed the strength of the defensive HBR as a function of the probability of the face being hit by a threat, which in turn is a function of the position of the stimulated hand in space. We performed a combined analysis of two previous datasets and four newly-collected datasets. We obtained four main results.

First, the HBR magnitude is affected by the position of the hand on the coronal plane along both a medio-lateral and a vertical axis (Figure 3.4) - that is, stimuli delivered in the 'middle' position elicited significantly stronger responses than stimuli delivered in more lateral (Experiment 1.3) and lower (Experiment 1.4) positions. Second, the HBR magnitude is not increased when the hand is behind the head, even if the hand is very near to the head (Experiment 1.5). Third, the HBR magnitude is modulated by the position of the hand in head-centred coordinates (Experiment 1.5). The fourth result is derived from the previous three. Geometric modelling revealed that the DPPS defined by the HBR has the shape of an elongated bubble, extending forward and upward from the face (Figures 3.3 and 3.4).

3.5.1 <u>HBR modulation by threat position on the coronal plane</u>

The modulation of HBR magnitude as a function of the egocentric position of the threat has so far only been explored along the sagittal plane (Sambo & Iannetti 2013; Sambo et al. 2012a; Sambo et al. 2012b). Along that plane, the HBR magnitude increases monotonically and non-linearly with proximity of the hand to the face. This result allowed for inferring the *1D extent* of the DPPS in front of the face, but did not provide any information on the *3D shape* of the DPPS. Here, we added two spatial dimensions to the DPPS characterisation, and measured the HBR magnitude along a medio-lateral axis (Experiment 1.3) and a vertical axis (Experiment 1.4) along the coronal plane. We found that the stimulation of the hand in the ‘middle’ position elicited a significantly stronger HBR than in the lateral and inferior positions. Therefore, the HBR magnitude increased with proximity of the hand to the face even when the position of the threat was displaced perpendicularly to the previously explored axis. This indicates that the increase in HBR magnitude with proximity of the hand to the face is consistent across different spatial dimensions. This experimental observation is in accordance with the qualitative concept of the DPPS as an area within which potentially harmful stimuli pose a greater threat, and thus elicit stronger defensive reactions.

The dependence of defense-related responses on the position of the stimuli in egocentric coordinates is also supported by the finding that proximity enhances the galvanic skin response elicited by a threatening stimulus (Combe and Fujii, 2011), although the galvanic skin response seems not to be exclusively related to threatening situations (Shi et al., 2007).

The results of Experiments 1.3, 1.4, 1.5 and 1.6 provide novel physiological data, as they describe the HBR modulation along different spatial dimensions, and therefore roughly describe the shape of the DPPS. Although the HBR increase seems overall consistent in different spatial dimensions, always increasing monotonically when the distance between the threat and the face was reduced, we observed some interesting differences in the HBR modulation along the rostro-caudal axis on the coronal plane. Indeed, out of all stimulus positions used in Experiment 1.4 (‘far-low’, ‘low’, ‘middle’, ‘high’, ‘far-high’) the HBR magnitude at the ‘middle’ position was only found to be different from that at the ‘far-low’ position. Therefore, along this axis the DPPS does not seem to expand symmetrically from the centre of the face, as it does along the medio-lateral direction (Figure 3.4).

3.5.2 *Absence of HBR modulation when the threat is behind the head*

In Experiment 1.5 we observed that placing the threat in rear space, i.e. directly behind the head, did not increase the HBR magnitude (the HBR magnitude at the 'rear' position was not different from that at either of the 'side' conditions, but was found to be smaller than the HBR magnitude at the 'front' conditions, Figure 3.4). At first glance, this result might seem at odds with the observation that audio-tactile interactions, which are commonly used as peripersonal space related measures, are stronger in rear space than in frontal space (e.g., Farnè and Làdavas, 2002). However, the different modulations of audio-tactile and HBR measures in rear space are entirely compatible, and depend on the functional significance of the physiological measure chosen. Indeed, the lack of visual representation in rear space forces individuals to rely more on auditory processing to detect threats behind the head (Occelli et al., 2011; Van der Stoep et al., 2015). Furthermore, the audio-tactile measures might reflect the detection of more general stimuli of interest (be they threatening or appetitive; Chapter 2), while the HBR is a defensive response spatially related to the eye. Consequently, the HBR is only expected to be modulated when the threat is located in a subset of the positions within which audio-tactile interactions are modulated.

3.5.3 *HBR modulation depends on hand position in a head-centred reference frame*

In Experiment 1.5, we also demonstrated that the HBR modulation depends on hand position in a head-centred reference frame: rotating the head altered the HBR magnitude when the hand was kept in the same position, but not when the hand moved along with the head. Indeed, we found no difference in HBR magnitude between the 'side' and 'rotated side', or between the 'front' and 'rotated front' conditions (Figure 3.4). This result supports the notion that DPPS is coded in body-part centred frames of reference (Fogassi et al., 1996; Graziano et al., 1997; Farnè et al., 2005a; Serino et al., 2015).

3.5.4 *A geometric model underlying the increase in HBR*

The major objective of this study was to develop a family of geometric models which describe the DPPS defined by the HBR, by modelling the dependency of the HBR magnitude on the respective position of the threat and the body district to be defended. These geometric models describe the spatial dependence between the magnitude of defensive responses and the position of the threat in peripersonal space. Notably, in these models, a predicted HBR magnitude is defined for all points in space. Therefore, to determine the *shape* of the DPPS, one must define a cut-off value, and consider all positions at which the predicted HBR magnitude is larger than the cut-off to be inside the DPPS. Importantly, regardless of the chosen cut-off value, the shape of the volume described by the best fitting model was an elongated bubble, extending mainly from the top half of the face (Figures 3.3 and 3.4). This bubble-like shape was symmetrical on the horizontal plane (i.e. it extends equally on the right and left sides), but asymmetrical on the vertical plane (i.e. it extends more above than below the centre of the face). Within this bubble (and in fact because it was defined using a cutoff value, outside this bubble as well), the defensive response increases monotonically and non-linearly with proximity to the defended area.

The geometries tested here were not exhaustive of all possible geometries of defended body areas. We could, in fact, have tested an infinite range of geometries, representing every body part. However, because the blink reflex consists in the contraction of eye-closing muscles, we expect the modulation of HBR magnitude to reflect the activity of a neural circuit which protects the face, eyes and/or head (rather than, for example, the back or the foot). In fact, from the results of Experiments 1.3-1.5 it can be intuitively seen that geometries not reflecting areas on or around the head would not fit the data. Therefore, we limited our analysis to a range of shapes representing parts of the head, which were most likely to give strong fitting results.

The choice of using a set of geometric models to study the spatial features of the DPPS was driven by three lines of reasoning.

First, such models can *predict* the magnitude of defensive responses to sensory events at all locations in near space (i.e. at locations that have not been experimentally measured). Notably, although other mathematical functions (e.g., a fitted polynomial) could achieve a similar prediction, they are not explicative of the underlying physiological principle explaining the observed HBR modulation.

This is the second reason why we chose to use geometric models: they arise from a set of *physiological* assumptions about the rules the nervous system obeys to regulate the magnitude of a defensive response. In other words, these models allow for the testing of the physiological assumptions of *why* the HBR magnitude changes as a function of hand position. The assumptions we defined imply that the nervous system calculates the probability that a body part is harmed by a potentially dangerous stimulus. This calculation takes into account (i) stimulus position, (ii) the shape of the defended area, and (iii) the effects of gravity. Based on the calculated harm probability, the nervous system consequently adjusts the strength of the defensive action. Therefore, the observed best fit of the geometric model 2 (Figure 3.4) provides physiological information about how the body area to be defended and the surrounding DPPS are represented: specifically, it supports the idea that the nervous system regulates the excitability of the circuitry underlying the HBR to defend the face in particular. However, the solid fit of model 4 (Figure 3.4) does not allow us to exclude the possibility that the HBR is modulated to defend the eyes. Given that the area with the largest difference between the HBR magnitudes predicted by the two models is a small region at the nasion (Figure 3.3), it is practically extremely difficult to measure the HBR at that position. Therefore, the small differences in HBR magnitude at the tested positions were not sufficient to reject either model. Importantly, the DPPS shapes resulting from the two models are very similar (Figure 3.4).

Further physiological information comes from the non-zero value of the optimised variable C_{grav}. This observation suggests that the nervous system takes into account gravity when estimating the probability of being hit by a threat. This is consistent with existing evidence that humans and non-human primates have internal models to estimate the effects of gravity, both in relation to one's own posture (Angelaki et al. 2004; Merfeld et al. 1999) and to external objects (Schwartz, 1999).

The third reason for choosing a geometric model is that they can be *generalised* to describe a range of potentially defensive responses, as long as the assumptions on which the models are based hold true. Indeed, the framework of the geometric models described in this study can be applied to any shape of defended area, any type of defensive response or any type of eliciting stimulus. For example, the geometric properties of the shortening of response times to tactile stimuli as function of the relative position of auditory or visual stimuli and the hand (e.g. Serino et al. 2007; Occelli et al. 2011; Sambo & Forster 2009; Macaluso & Maravita 2010) would be amenable to be formally investigated with the approach described here, as would the modulation of the activity of bimodal visuotactile neurons as a function of the location of a visual stimulus (e.g. Rizzolatti et al., 1981; Colby et al., 1993; Fogassi et al., 1996; Graziano et al., 1997).

It is interesting to note that the tactile receptive field of such bimodal visuotactile neurons could be seen as a counterpart of the concept of a defended area presented in this article. Similarly, the visual receptive field of such neurons (which surrounds and is anchored to their tactile receptive field, Fogassi et al. 1996), could be seen as a counterpart of the concept of a DPPS anchored to the area to defend. In this way, the geometric model can be seen as a formalised bridge between low-level physiological data (i.e. firing rates of bimodal parietal neurons; Graziano & Cooke 2006) and higher level defensive behaviours (i.e. blinking; Sambo et al. 2012b).

4 Modelling part 2: Gravitational cues modulate the DPPS shape

4.1 Introduction

To recap the characterization of the geometry of the DPPS surrounding the face so far: it has the shape of a bubble, elongated asymetrically along the rostro-caudal axis, extending more above than below eye level (Chapter 3).

We hypothesized that this vertical asymmetry could be an effect of gravitational cues: the probability that a threat will hit the body is higher when it comes from above. Here we altered the body's posture relative to the direction of gravity, and used the geometrical modeling approach to test this hypothesis. We expected two alternative outcomes: (1) the DPPS shape remains asymmetrical along the vertical axis of the body regardless of the orientation of the head with respect to gravity (i.e. the DPPS moves along with the head as if it were a helmet). Alternatively, (2) the DPPS asymmetry changes when the orientation of the head changes with respect to gravity (i.e. the DPPS always extends upward as if it were a helium-filled balloon).

In reality, we found a mixture of both outcomes: the nervous system uses a malleable DPPS representation, and continuously updates the threat value of stimuli based on gravitational cues. However, the resulting DPPS shape is not completely malleable: even when participants lie on their back, it still extends slightly further along the vertical axis of the body than would be expected if its asymmetry were only affected by gravitational cues.

Note that when we originally submitted this study for publication, we used different datasets: part of the data we used was the data from Experiments 1.3 and 1.4 in Chapter 3, and part of the data was newly collected. This original data showed that the model supporting hypothesis 2 (i.e. wherein the brain uses a malleable DPPS representation) far outperformed the model supporting hypothesis 1 (i.e. where the DPPS shape remains asymmetrical along the vertical axis of the body regardless of the orientation of the head with respect to gravity). However, we received an insightful comment from a reviewer. The reviewer asked whether the asymmetry in HBR magnitude along the vertical axis, observed in the results of Experiment 1.4, might be due to the additional effort of holding the hand above the head. Hence I collected a control experiment, in which we tested for the effect of effort on HBR magnitude. To our surprise, we did find a fairly strong effect. In brief, exerting effort in order to keep the hand in a specific position affected the HBR magnitude, albeit less strongly than displacing the hand from ~60cm to ~4cm from the face, as shown in Chapter 3.

Therefore, I completely recollected the data necessary for this study, with a minor change in methodology; this time, I supported the participants' arms, in order that no effort was exerted to hold the arm in a particular position. However in retrospect, there is a possibility that the muscular activation necessary to hold the arm in a position above the head might actually provide the body with the gravitational cues it needs to update the DPPS shape effectively. Thus, this chapter includes (1) the analysis of the original data for this study where we did not control for effort, (2) the results from the experiment on the effect of effort, and (3) the analysis of the novel data collected while controlling for the effect of effort. Nonetheless, regardless of whether the muscular activation - and hence effort - is used as a gravitational cue, the take away message of these experiments is that the nervous system uses a malleable DPPS representation, continuously updating it based on gravitational cues.

This study has been published as Bufacchi and Iannetti (2016).

4.2 Materials and Method

This chapter contains data from nine separate experiments. As explained in the introduction to this chapter, in four experiments (labelled 2.1a-2.4a) we controlled for the effect of effort on HBR magnitude, and in four other experiments (labelled 2.1b-2.4b) we did not. The single experiment in which we assessed the effect of effort directly was labelled 2.5. Other than controlling for effort, the procedures in experiments 2.1a, 2.2a, 2.3a and 2.4a were identical to those in experiments 2.1b, 2.2b, 2.3b and 2.4b, respectively.

4.2.1 Stimulation and Recording

Experiments 2.1a and 2.2a correspond to experiments 1.3 and 1.4 in chapter 3, but have been relabeled to maintain symmetry with experiments 2.1b and 2.2b. Therefore, details of stimulation and recording procedures of Experiments 2.1b and 2.2b are the same as those of Experiments 1.3 and 1.4 in chapter 3. Procedures of Experiments 2.3a,b and 2.4a,b were identical to 2.1a,b and 2.2a,b respectively, except for the posture of the subjects. Procedures of Experiment 2.5 were identical to those of the other experiments in this chapter, except that postures were different and certain conditions entailed holding a 1kg weight. Briefly, transcutaneous electrical stimuli were delivered to the right median nerve at the wrist. Stimulus intensity was adjusted, in each participant, to elicit a reproducible blink reflex. Stimulus duration was 200 μs, and the interval between two successive stimuli was 30 s. Electromyographic (EMG) activity was recorded from the *orbicularis oculi* muscle, bilaterally, using pairs of surface electrodes, with the active electrode over the mid-lower eyelid and the reference electrode lateral to the outer canthus. Signals were amplified and digitized at a sampling rate of 8,192 Hz (ISA 1004, Micromed, Treviso, Italy), and stored for offline analysis.

4.2.2 Participants

4.2.2.1 Experiments 2.1a-2.4a

We collected data from 42 healthy participants (28 women, 18-42 years, 24.6 ±5.9 years), who were all HBR responders. All participants, except one who participated in Experiment 2.4a, were right-handed.

Each experiment was conducted on 14 participants. Ten Participants took part in more than one experiment: two participants took part in all four experiments, and eight participants took part in two experiments. Datasets for Experiments 2.1a and 2.2a were collected previously (Experiments 1.3 and 1.4, Chapter 3). To obtain the 22 new HBR responders used in Experiments 2.3a and 2.4a, we screened 30 subjects. Hence, 73% of subjects were HBR responders. This percentage is consistent with previous reports (Sambo et al., 2012a, 2012b; Sambo and Iannetti, 2013).

4.2.2.2 Experiments 2.1b-2.4b

We collected data from 29 right-handed healthy participants (19 women, 19-42 years, 24.2 ±5.0 years), who were all HBR responders. To obtain these HBR responders, we screened 55 subjects. Hence, 53% of subjects were HBR responders. This percentage is slightly lower than previous reports (Sambo et al., 2012a, 2012b; Sambo and Iannetti, 2013).

We conducted the four experiments comprising this study on 21 participants each. All participants who took part in Experiment 2.1b also took part in Experiment 2.3b. Similarly, all participants who took part in Experiment 2.2b also took part in Experiment 2.4b. This allowed us to perform a within-subject analysis. Participants gave written informed consent before taking part in the study. All procedures were approved by the local ethics committee.

4.2.2.3 Experiment 2.5

We collected data from 14 participants to test whether the effort required to keep the hand in certain stimulation positions contributes to the HBR magnitude. All participants were HBR responders, and were recruited from the group of participants that took part in Experiments 1.3-1.6.

4.2.3 *Experimental Procedures*

Participants were seated in a comfortable chair. In each participant, we first determined the stimulus intensity able to elicit a well-defined and stable blink reflex in response to electrical stimulation of the median nerve at the wrist (HBR). As described in Chapter 2.3.1, this was achieved by increasing the stimulus intensity until a clear HBR was observed in three consecutive trials, or the participant refused a further increase of stimulus intensity (Sambo et al., 2012b). Only participants showing a reproducible HBR underwent further testing.

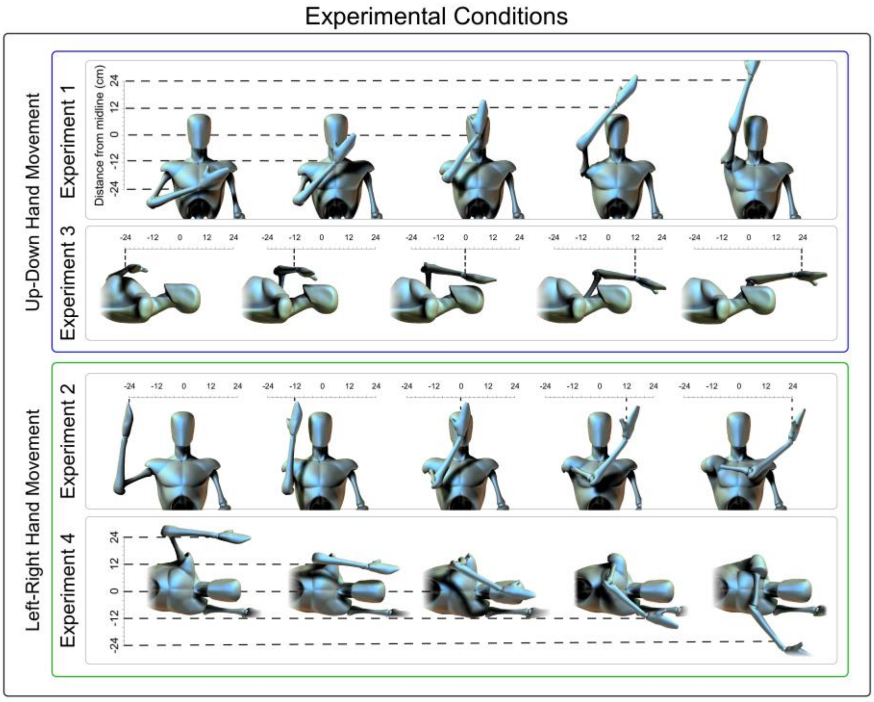

Figure 4.1. ***Experimental setup for Experiments 2.1a,b-2.4a,b.*** *Hand positions in Experiments 2.1a-2.4a were identical to those in 2.1b-2.4b respectively (and are referred to as Experiments 1-4 in this figure). In Experiments 2.1a,b-2.4a,b stimuli were delivered on a coronal plane located 4 cm from the nose. In Experiments 2.1a,b and 2.2a,b, participants were upright. In Experiments 2.1a,b, the stimulated hand was placed in 5 positions, along the body midline, symmetrically with respect to eye-level. In Experiments 2.2a,b, these positions were along a horizontal line at eye-level, symmetrically with respect to the midline. In Experiments 2.3a,b, participants were lying supine, and the stimulated hand was placed in the same positions as in Experiments 2.1a,b, in head-centred coordinates. In Experiments 2.4a,b, participants were lying on their side, and the stimulated hand was placed in the same positions as in Experiments 2.2a,b, in head-centred coordinates. In Experiments 2.1b-2.4b only, once the*

participants had placed their hand in the correct position, the experimenter held the participants' forearm in place, so that the arm was relaxed completely.

In Experiments 2.1a,b and 2.*2a,b* participants were upright (Figure 4.1 and 3.2). We electrically stimulated the right wrist, while the right hand was placed in 5 positions per experiment, on a coronal plane located 4 cm from the nose. In Experiments 2.1a,b and 2.3a,b these positions were along the body midline, symmetrical with respect to eye-level, as follows (negative values denote positions below eye-level): 'far-low': -24 cm; 'low': -12 cm; 'middle': 0 cm; 'high': +12 cm; 'far-high': +24 cm. In Experiments 2.2a,b and 2.4a,b, these positions were along a horizontal line at eye-level, symmetrical with respect to the vertical body midline, as follows (negative values denote positions on the participant's right side): 'far-right': -24 cm; 'right': -12 cm; 'middle': 0 cm; 'left': +12 cm; 'far-left': +24 cm. These positions were marked on a board placed in front of the participant.

If the hypothesis that the DPPS vertical asymmetry is determined by gravitational cues is correct, the shape of the DPPS should remain asymmetric along the *gravity* axis, regardless of head orientation. Alternatively, the DPPS could remain asymmetric along the *head* vertical axis, regardless of head orientation with respect to gravity. To distinguish between these two possibilities, we altered body posture relative to the direction of gravity. In Experiments 2.3a,b, participants lay supine. In Experiments 2.4a,b, participants lay on their left side on a bench, with their head at the edge of the bench, their face pointing perpendicular to the ground (Figure 4.1 and 4.2).

In Experiments 2.1b-2.4b, the participant's arm was held in place by the experimenter, while the participant was instructed to relax their arm muscles. The order of hand positions was pseudo-randomized, with the constraint that no more than two consecutive stimuli were delivered for the same hand position. All experiments consisted of two blocks. In each block we delivered 5 stimuli at each of 5 hand position, for a total of 25 stimuli.

In Experiment 2.5, somatosensory stimuli were delivered in four different conditions (as in Figure 4.2, below). In Condition 1, the hand was resting on a desk in front of the participant with the palm facing upwards, in position 'Far' (approximately 60 cm from the face). In Condition 2, the hand was in the exact same 'Far' position, but a 1 kg weight was placed on the palm. Condition 3 was identical to condition 2 (hand in position 'Far', with a weight on it), but participants were instructed to raise their entire forearm approximately 1cm off the desk whilst holding the weight – thus requiring considerable effort to keep the hand in position. In Condition 4 the hand was in the same position 'Near' used in the other experiments, i.e. at eye-height, approximately 4 cm in front of the face.

4.2.4 Data analyses and statistics

EMG signals from each participant were high-pass filtered (55 Hz) and full-wave rectified. The HBR magnitude was calculated as the area-under-curve (AUC) of each single-trial response, separately for each recording site. The AUCs were first averaged across ipsilateral and contralateral recording sites and then across the all trials at each hand position. Finally, for Experiments 2.1ab,-2.4a,b the AUCs were normalized for each subject as Z-scores and for each experiment between 0 and 1.

4.2.4.1 Experiments 2.1a-2.4a

To investigate the effects of hand position and body position we performed two different two-way ANOVAs, one using the data pooled from Experiments 2.1a and 2.3a, and the other using the data pooled from Experiments 2.2a and 2.4a. In Experiments 2.1a and 2.3a, the two experimental factors were 'hand-position' (five levels: 'far-down', 'down', 'mid', 'up' and 'far-up'), and 'body-position' (two levels: 'upright' and 'supine'). In Experiments 2.2a and 2.4a, the two experimental factors were 'hand-position' (five levels: 'far-left', 'left', 'mid', 'right', and 'far-right'), and 'body-position' (two levels: 'upright' and 'sideways').

4.2.4.2 Experiments 2.1b-2.4b

In the same manner as for Experiments 2.1a-2.4a, we performed two repeated measures ANOVAs. One was performed on the data pooled from Experiments 2.1b and 2.3b, the other on the data from experiments 2.2b and 2.4b. The experimental factors were identical to those used for experiments 2.1a-2.4a.

4.2.4.3 Experiment 2.5

Because this experiment was a control Experiment, and to minimise the probability of finding false negatives, we performed uncorrected paired t-tests between all conditions.

4.2.5 Model fitting

In the geometric model of DPPS derived and tested in Chapter 3, the HBR magnitude is calculated from the geometric probability of the face being hit by a threat. The hitting probability in turn depends on the probability distribution of the directions in which the threat might be acting. Importantly for the objective of the current study, the previously observed rostro-caudal asymmetry of the DPPS (with larger extension above than below eye level) was modeled with a 'gravity parameter' (C_{grav}), consisting in a vector whose direction was fixed and matched the direction of gravity. Given that C_{grav} magnitude alters the probability distribution of hitting actions along the direction of the vector, a high C_{grav} value indicated a DPPS more extended above eye level.

In the three alternative versions of the model tested here, the direction of the C_{grav} vector was altered. In the 'helmet' model version, C_{grav} acted downward in *head-centred* coordinates, and it therefore did not reflect the influence of gravitational cues on the DPPS shape. In the 'balloon' model version, C_{grav} acted downward in *earth-centred* coordinates, and it therefore reflected the influence of gravitational cues on DPPS shape. Finally, in the 'no gravity' model, C_{grav} was set to zero and therefore the DPPS was symmetrical around the face, both horizontally and vertically.

The validity of each model version was assessed by its goodness of fit (GoF) to the mean HBR magnitudes at all hand positions, once for Experiments 2.1a-2.4a, and once for Experiments 2.1b-2.4b. The GoF modelling approach is described in more detail in Chapter 3.3.6. Briefly, it compares the Chi-squared (χ^2) test statistic of the fit of any model version to the data, to a χ^2 distribution of the appropriate degrees of freedom, resulting in a GoF score and a corresponding *p* value[1]. Given that this approach requires that (1) the data are normally distributed, and (2) the variance across hand positions is equal, HBR magnitudes were first normalised to the 'mid' hand position in each subject for this analysis only, and then tested for normal distribution (using the Anderson-Darling test) and equality of variance (using the Bartlett's test), as in Chapter 3. The results of these analyses showed that HBR magnitudes were normally distributed (Experiments 2.1a-2.4a: p=0.70; Experiments 2.1a-2.4a: p=0.37.H_0=normal distribution) and had equal variance (Experiments 2.1a-2.4a: p=0.78; Experiments 2.1a-2.4a: p=0.98; H_0=equal variance).

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[1] Note again that if the GoF-score is *larger* than 1.850 (which corresponds to the threshold of p=0.05 in the χ^2 distribution considered), the probability of the model being correct is *smaller* than 0.05, and the model must be rejected. Hence, the smaller the GoF score and the larger the p value of a model, the more strongly it is accepted.

4.3 Results

4.3.1 Descriptive results

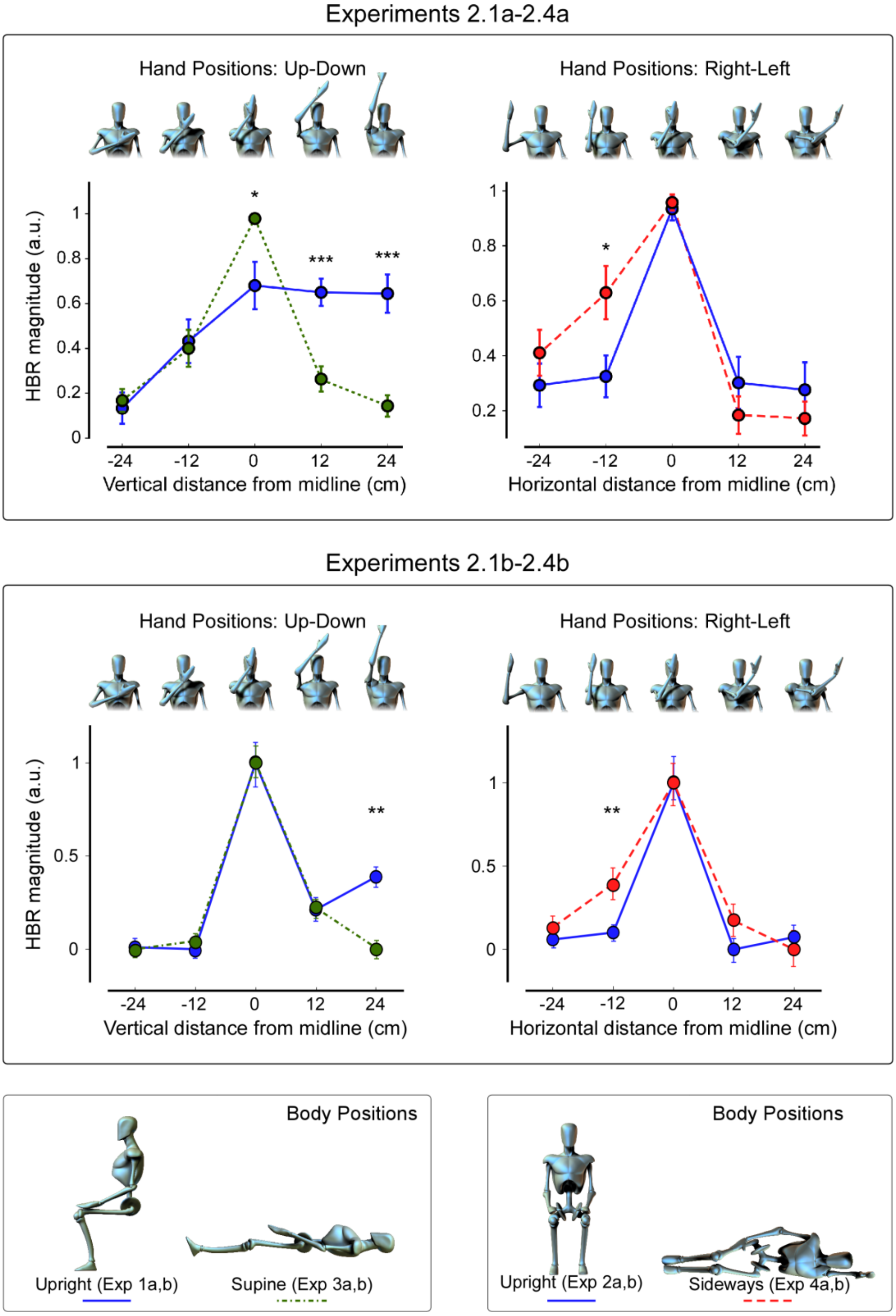


Figure 4.2. ***Effect of gravitational cues on DPPS shape****HBR magnitude following stimulation of the hand in different positions (top row of figurines; see also Figure 4.1). The top panel shows results from Experiments 2.1a-2.4a, while the second panel*

*shows results from Experiments 2.1b-2.4b. HBR magnitude is expressed as Z-scores within-subject, and normalised between 0 and 1 within-experiment. HBR magnitude was overall larger when the stimulated hand was above the head in earth-centred coordinates, regardless of body position. Error bars indicate the standard error of the mean (SEM). Asterisks indicate: *p<0.05, **p<0.01, ***p<0.001. All post-hoc statistical comparisons of Experiments 2.1b-2.4b are reported in Figure 2.1 and Table2.1. While the largest HBR magnitude was on average always observed when the hand was in position ‘0cm’, body posture clearly modulates the HBR magnitude, and therefore alters the shape of the DPPS on the basis of gravitational cues.*

4.3.1.1 Experiments 2.1b-2.4a

A two-way 5x2 ANOVA on the data pooled from Experiments 2.1a and 2.3a showed significant effects of ‘hand-position’ (F=23.10, p<0.0005) and ‘body-position’ (F=6.64, p=0.011). There was a significant ‘hand-position’ x ‘body-position’ interaction (F=10.26, p<0.0005). This interaction arose from (1) larger HBR magnitudes in hand positions ‘high’ (t=4.66, p=0.0001) and ‘far-high’ (t=5.14, p<0.00005), and (2) smaller HBR magnitudes in hand position ‘mid’ (t=-2.77, p=0.0102) when participants were upright. Therefore, in the set of experiments where the effect of effort was *not* controlled, when an individual lay supine, the DPPS shape was no longer elongated above eye level, but became symmetrical along the head vertical axis (Figure 4.2).

A two-way 5x2 ANOVA on the data pooled from Experiments 2.2a and 2.4a showed a significant main effect of ‘hand-position’ (F=30.02, p<0.0005), and a significant ‘hand-position’ x ‘body-position’ interaction (F=2.62, p=0.038). This interaction arose from larger HBR magnitudes in hand position ‘right’ (t=-2.47, p=0.0202) when participants were lying on their side. Therefore, in the set of experiments where the effect of effort was *not* controlled, when individuals lay on their left side, the DPPS shape became asymmetrical: it had a larger extent on the right side, i.e. *opposite* to the direction of gravity (Figure 4.2).

4.3.1.2 Experiments 2.1b-2.4b

A 5x2 repeated-measures ANOVA on the data pooled from Experiments 2.1b and 2.3b showed strong evidence for an effect of ‘hand-position’ (F=46.293, p<0.0001) and evidence for a ‘hand-position’ x ‘body-position’ interaction (F=2.7512, p=0.034). This interaction arose from a larger HBR magnitude in hand position ‘far-high’ when participants were upright as compared to when they were supine (t=3.7617, p=0.0013).

Therefore, in the set of experiments where the effect of effort *was* controlled, when an individual was supine, the DPPS shape was no longer elongated equally far above eye level, but became less asymmetrical along the head vertical axis (Figure 4.2).

A 5x2 repeated-measures ANOVA on the data pooled from Experiments 2.2b and 2.4b showed strong evidence for main effects of ‘hand-position’ (F=32.776, p<0.0001) and ‘body-position’ (F=11.996, p=0.0025). This latter main effect arose from a larger HBR magnitude in hand position ‘right’ (t=-2.929, p=0.0083) when participants were lying on their side. Therefore, in the set of experiments where the effect of effort *was* controlled, when individuals lay on their left side, although the HBR magnitude remained largest in position ‘middle’, the HBR increase in position ‘right’ indicates that the DPPS shape became asymmetrical: it had a larger extent on the right side, i.e. *opposite* to the direction of gravity (Figure 4.2).

Experiments 2.1b & 2.3b		Upright (Exp 2.1b)					Supine (Exp 2.3b) h				
		-24cm	*-12cm*	*0cm*	*12cm*	*24cm*	*-24cm*	*-12cm*	*0cm*	*12cm*	*24cm*
Upright (Exp 2.1)	*-24cm*		0.844	**<0.001**	**0.005**	**<0.001**	0.893	0.349	**<0.001**	**0.001**	0.575
	-12cm	0.087		**<0.001**	**0.012**	**<0.001**	0.973	0.405	**<0.001**	**<0.001**	0.610
	0cm	>1.827	>1.827		**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.893	**<0.001**	**<0.001**
	12cm	1.385	1.212	>1.827		0.240	**0.001**	**0.023**	**<0.001**	0.803	**0.003**
	24cm	>1.827	>1.827	>1.827	0.529		**<0.001**	**0.001**	**<0.001**	0.322	**0.001**
Supine (Exp 2.3)	*-24cm*	0.060	0.015	>1.827	1.695	>1.827		0.344	**<0.001**	**0.001**	0.550
	-12cm	0.419	0.371	>1.827	1.080	1.695	0.424		**<0.001**	**0.015**	0.679
	0cm	>1.827	>1.827	0.060	>1.827	>1.827	>1.827	>1.827		**<0.001**	**<0.001**
	12cm	1.695	>1.827	>1.827	0.110	0.444	1.695	1.167	>1.827		**0.001**
	24cm	0.249	0.226	>1.827	1.484	1.695	0.266	0.183	>1.827	1.695	
Experiments 2.2b & 2.4b		Upright (Exp 2.2b)					On Side (Exp 2.4b)				
		-24cm	*-12cm*	*0cm*	*12cm*	*24cm*	*-24cm*	*-12cm*	*0cm*	*12cm*	*24cm*
Upright (Exp 2.2)	*-24cm*		0.584	**<0.001**	0.893	0.654	0.083	**0.005**	**<0.001**	**0.025**	0.786
	-12cm	0.243		**<0.001**	0.823	0.430	0.352	**0.008**	**<0.001**	0.112	0.579
	0cm	>1.827	>1.827		**<0.001**	**<0.001**	**<0.001**	**0.001**	0.899	**<0.001**	**<0.001**
	12cm	0.060	0.099	>1.827		0.601	0.468	**0.025**	**<0.001**	0.071	0.585
	24cm	0.199	0.352	>1.827	0.232		0.056	**0.006**	**<0.001**	**0.011**	0.994
On Side (Exp 2.4)	*-24cm*	0.799	0.416	>1.827	0.323	0.888		0.061	**<0.001**	0.256	0.194
	-12cm	1.389	1.293	1.695	1.062	1.350	0.870		**0.005**	0.321	**0.029**
	0cm	>1.827	>1.827	0.056	>1.827	>1.827	>1.827	0.139		**0.001**	**<0.001**
	12cm	1.062	0.727	>1.827	0.835	1.223	0.511	0.445	1.695		**0.046**
	24cm	0.120	0.246	>1.827	0.243	0.003	0.588	1.031	>1.827	0.932	

Table 2.1. ***ANOVA post-hoc t-tests between all hand positions of Experiments 2.1b-2.4b****. P-values are shown in top right half of table, and p <0.05 are in bold. Effect sizes are given as Cohen’s d, in the bottom right half of the table.*

4.3.1.3 Experiment 2.5

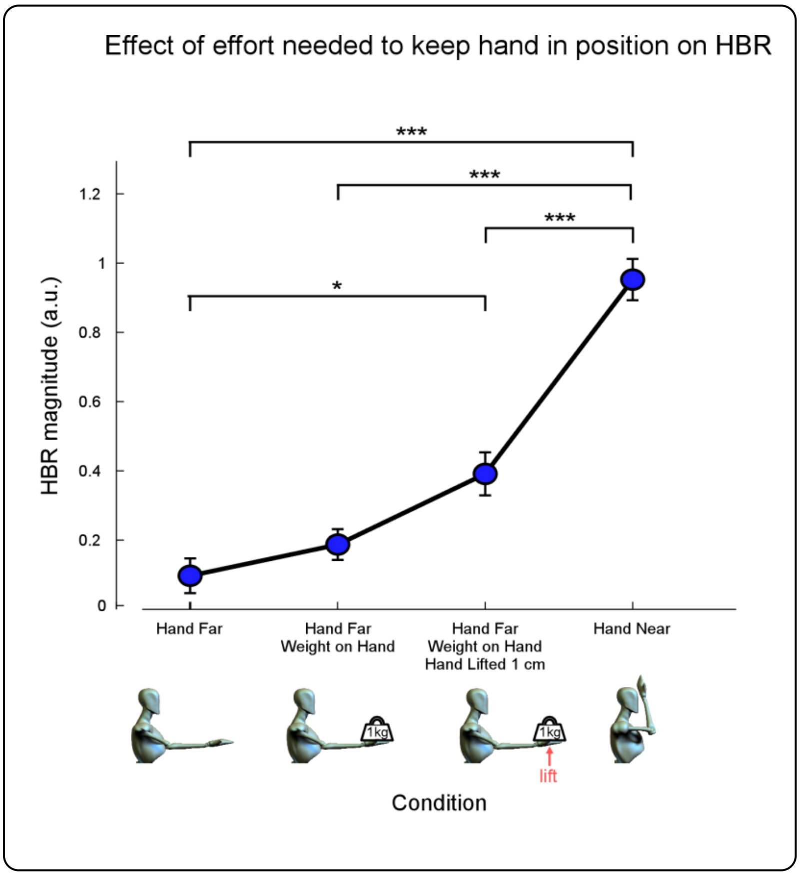


Figure 4.3. *Contidions and results of Control Experiment 2.5.* *This experiment investigated how the effect of effort in keeping the hand in stimulation position contributes to the HBR magnitude.*

Four out of six of the t-tests performed on the data from Experiment 2.5 gave a p-value <0.05 (figure 4.3). These t-tests showed strong evidence that the HBR magnitude was larger in Condition 4 (i.e. when the hand was near the face) than in all other three Conditions (i.e. when the hand was far from the face) (p<0.0001 for all 3 comparisons). Furthermore, there was evidence that HBR magnitude was larger in Condition 3 (i.e. hand far from face during effort) than in Condition 1 (i.e. hand far from face without effort) (p=0.0155). Other comparisons were not statistically significant.

These results indicate that the difference in effort required to hold the hand in different positions contributes, to a certain degree, to the HBR magnitude. Indeed, on the basis of these results, Experiments 2.1b-2.4b were collected. Note however, that the size of the effect of effort is smaller than the near-far effect, even though the effort exerted in this control experiment is larger than that required to place the hand near the face, or in any other position. This indicates that the brain might actually use muscular activation as gravitational cue when it updates the DPPS. The results of Experiment 2.5 also raise the issue of whether effort effects are present within Experiments of earlier and later chapters. However, this issue is unlikely to pose a problem for two reasons. First, the effect of effort is much smaller than the effect of hand position, as evidenced by the substantial difference in HBR magnitude between conditions 3 and 4 of Experiment 2.5. Second, when the effects of other factors are tested, (such as Trigeminal Neuralgia in Chapter 7), the comparison is drawn between conditions in which the hand is in the same position, and thus the effect of effort is the same. Therefore, while effort certainly is a factor to bear in mind when designing HBR experiments, the results and conclusions of the other Chapters of this work are not likely affected by it.

4.3.2 Model fitting

To formally test the effect of gravity on DPPS shape, we used three versions of the geometric model of DPPS (Chapter 3.3.6), in which the HBR magnitude is dictated by the probability of the face being hit by a threat. In the ‘balloon’ version, gravitational cues influence DPPS shape: the DPPS always extends upwards like a helium-filled balloon. In the ‘helmet’ version, there is no influence of gravitational cues on DPPS shape: the DPPS moves along with the head like a helmet. When fitting the data from Experiments 2.1a-2.4a, the ‘helmet’ version was clearly rejected ($p=0.0025$, GoF=2.80), whereas the ‘gravity’ version was solidly accepted ($p=0.68$, GoF=-0.457). When fitting the data from Experiments 2.1b-2.4b however, both versions were accepted (‘balloon’: $p=0.094$, GoF=1.30; ‘helmet’: $p=0.079$, GoF=1.42). A third, alternative version postulating no DPPS asymmetry in any body posture was rejected when fitting the data from experiments 2.1-2.4 a and b ($p=0.037$; GoF=2.07). In other words, when the effect of effort is not controlled for, the DPPS behaves as a balloon, while when the effort is controlled for, the DPPS behaves partially as a balloon, and partially as a helmet.

4.4 **Discussion**

Taken together, these results clearly support that the brain uses a malleable DPPS representation, and continuously updates the threat value of stimuli based on gravitational cues, automatically inferring the effects of physical laws.

The ability of the nervous system to adjust the DPPS shape based on gravitational cues has a clear survival advantage. Gravity causes all objects to fall. Therefore, in natural environments a threatening object is more likely to cause damage when it is above the body than when it is below – a fact obviously independent of body posture. Hence heightened defensive responses to above-body threats, which have greater hit probability, would maximally mitigate harm. Indeed, there are a few hints of a vertical asymmetry in the threat value assigned to environmental events. Vertical asymmetries in visual perception are well documented (Rezaul Karim and Kojima, 2010) and, as an example more directly related to threatening stimuli, larger sympathetic skin responses are elicited by a visual threat approaching vertically rather than horizontally (Rossetti et al., 2015).

Information of body orientation is mainly consequent to the central integration of vestibular, visual, and somatosensory inputs (Carpenter, 1990), which are constantly being fed to an internal model of gravity (Merfeld et al., 1999; Lacquaniti et al., 2014). Therefore, the cortical areas which are thought to underlie the HBR modulation, namely a network including the human homologues of the ventral intraparietal sulcus (VIP) and the F4 region (Duhamel et al., 1998; Graziano and Cooke, 2006; Cléry et al., 2015b), must continuously adjust the DPPS representation in response to these inputs. The aforementioned set of parietal regions, especially the VIP and its human homologue (Bremmer et al., 2001; Makin et al., 2007; Holt et al., 2014), do indeed receive dense vestibular and visual connections (Suzuki et al., 2001; Grefkes and Fink, 2005; Chen et al., 2011a, 2011b).

The concept that a change in harm probability (determined, in the current experiments, by different body postures relative to gravity) causes a change in DPPS shape is in line with previous findings, and provides an overarching narrative. For example, when the hit probability of objects in front of the body increases because of locomotion (Noel et al., 2014), because of stimuli approaching a body part (Graziano and Cooke, 2006; Canzoneri et al., 2012), or because of a greater speed of stimulus approach (Fogassi et al., 1996), peripersonal space as indexed by various measures expands outward. Altogether, these observations support the idea that the brain continuously calculates the probability of environmental threats hitting different body territories by integrating multimodal information into internal models of the physical laws of nature. This allows for successful estimation of the potential for harm of environmental events, and an appropriate adjustment of defensive responses.

5 DPPS in disease part 1: no cognitive modulation of HBR in early onset blindness

5.1 Background

In Chapter 3 we established that the modulation of HBR is likely linked to protection of the face and eyes. An unanswered question is whether the circuits underlying the modulation develop normally if subjects are not able to see. In this study we explored that question, and found that (1) blind individuals do also display a HBR. However, (2) the nervous system only seems to develop the ability to purposefully *modulate* HBR magnitude if vision is present during early childhood.

This study has been published as Wallwork et al. (2017).

5.2 Introduction

The neurological consequences of blindness have been widely studied. One area that has escaped attention however, is the effect of blindness on defensive reflexes that subserve the protection of the face. The HBR provides an excellent method to address this topic, because the modulation of its brainstem circuitry has been clearly characterised, and it can be easily interrogated with non-invasive methods. Recording the HBR in blind individuals allowed us to address two important issues: (1) whether blind individuals also protect their face and eyes through the HBR response, and (2) whether, if present, their HBR displays the typical ‘far-near’ increase observed in sighted individuals.

5.3 Materials and methods

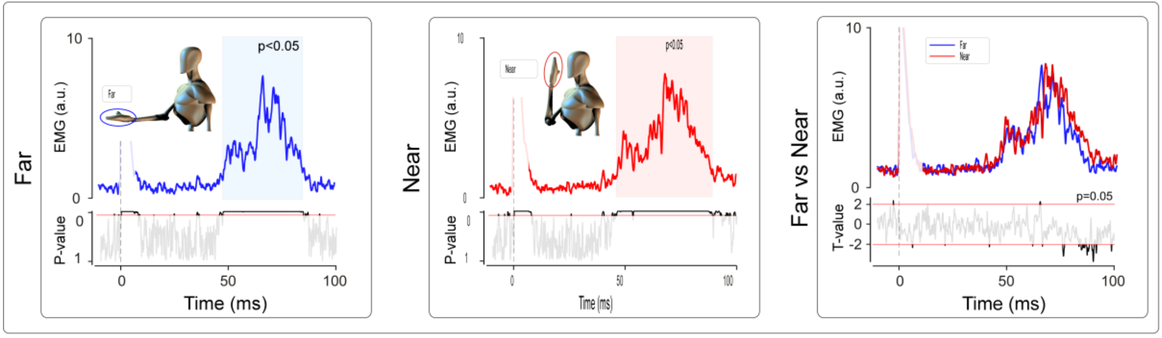
Eight totally blind people (4 female, 26-57 years) volunteered. Two had early-onset blindness that developed prior to the age of 3 years, with no recollection of being able to see. The others had late-onset blindness, acquired after 3 years of age, and were able to recall visual experiences. Ten sighted people (9 female, 18-46 years) were used as controls. The controls had their eyes open throughout the experiment.

Stimulation and recording procedures are the same as for Chapters 3 and 4, and are briefly recapped here. Intense electrical stimuli were delivered transcutaneously to the median nerve at the wrist. Stimulus intensity was adjusted to elicit a clear HBR in three consecutive trials (blind group [mean±SD]: 13.1±6.9 mA; controls: 17.5±13.3 mA). Electromyographic activity (EMG) was recorded from the orbicularis oculi muscle bilaterally, using surface electrodes. Participants, seated with their forearms resting on a pillow in front of them, received 40 stimuli (inter-stimulus-interval ~30s), delivered alternatingly with the hand either ~40-60cm (‘far’; Figure 5.1A) or ~4cm from the eye (‘near’). EMG was filtered (55-400Hz), rectified, and averaged across eyes and trials, and HBR magnitude was expressed as area-under-the-curve (AUC) (Sambo et al., 2012a). Far-near differences were reported as percentage of HBR magnitude in the ‘far’ position.

5.4 Results

A clear HBR was present in five of the eight blind patients. This ratio is consistent with previous reports in healthy controls (Chapter 2.3.1). Of these five, four had late-onset blindness, and one had early-onset blindness. The early-onset blind participant showed a clear HBR, with normal onset (45ms) and duration (48ms). In this patient, HBR responses were larger than pre-stimulus activity both in ‘far’ and ‘near’ hand positions (intervals that showed an effect with $p<0.05$: 47-85 and 46-89 ms, respectively; bootstrapping with respect to the pre-stimulus interval, Figure 5.1A). Importantly, the HBR magnitude was virtually identical in ‘near’ and ‘far’ hand positions (AUC analysis: p=0.21, paired t-test; point-by-point analysis: no difference; Figure 5.1A). In contrast, in both late-onset blind participants and controls the HBR magnitude was larger in ‘near’ than in ‘far’ positions (blind group: +49±9.3%; p=0.015; controls: +53%±11.7%; p=0.00024, one-sample t-test; Figure 5.1B). These percent increases were not different (p=0.45, independent-sample t-test).

Panel A: Early-onset blind participant



Panel B: Group comparisons

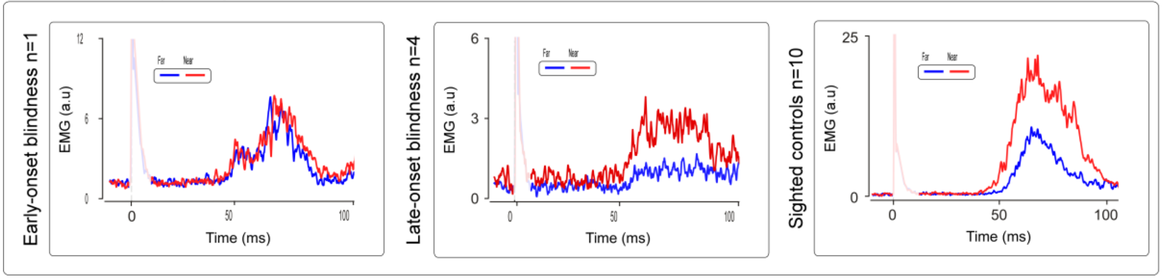


Figure 5.1. *HBR waveforms.* *Panel A. In the early-onset blind participant there was a clear HBR when the hand was in both ‘far’ (blue) and ‘near’ (red) positions (left and middle plots). However, their magnitude was not different (right plot). The top waveform*

of each plot expresses the EMG activity. The consistency of the HBR response is highlighted by the p-value waveforms at the bottom of the left and middle plots. The t-value waveform in the right plot shows the lack of difference between HBR magnitude in the two positions. Panel B. HBR responses recorded from the three groups of participants, while the hand was in 'far' (blue) and 'near' (red) positions. Contrary to the early-onset blind participant (left plot), both late-onset blind individuals (middle plot) and sighted controls (right plot) show a similar and clear enhancement of HBR magnitude when the hand was in the 'near' position (late-onset blindness participants: +49±9.3%, p=0.015; sighted controls: +53%±11.7%, p=0.00024; one-sample t-tests).

5.5 Discussion

We obtained two main results. First, blind individuals could display a similar HBR to sighted individuals, regardless of the age at which their blindness developed. This finding indicates that the medullary HBR circuit is functional regardless of the age of blindness onset. Therefore, this circuit is likely to develop either during prenatal neurogenesis or in early infancy, and it remains functional throughout life. Second, individuals with late-onset blindness showed the robust 'far-near' effect commonly observed in sighted controls, whereas the individual with early-onset blindness did not (Figure 5.1A). These results suggest that an effective cortical modulation of the HBR circuitry depends on having a functional visual system within a key and relatively small time interval during childhood, i.e. between 3 and 7 years of age. This modulation remains stable even when vision is subsequently totally lost.

A possible explanation is that early and late blind individuals use different reference frames when localizing stimuli in external space. That is, early blinds do not automatically remap tactile information in external space, but instead use an anatomically anchored reference system (Röder et al., 2004; Crollen and Collignon, 2012). It follows that the HBR modulation relies on a brain function that integrates visuo-tactile spatial information and that this function does not fully develop until 3–7 years. As mentioned in preceding chapters, the ventral intraparietal area (VIP) is a good candidate to subserve this function, given that VIP multimodal neurons represent the most likely substrate for integrating the spatial location of sensory stimuli belonging to different modalities, particularly in a face-centred reference frame(Graziano and Cooke, 2006). Furthermore, disruption of right intra-parietal sulcus (i.e. an area including VIP) function by TMS impairs the localization of stimuli in external space only in late blind and sighted people (Collignon et al., 2009).

A second, not mutually exclusive explanation is that in this key developmental period the importance of vision is learned, and the nervous system therefore deploys more resources to optimise the defence of the eyes. Consequently, the association between the stimulus being close to the eyes and the danger posed to the eye is made during this period, and the upregulation of the defensive reflex is developed.

Although these explanations require further interrogation, the observations reported here indicate that the nervous system develops the ability to modulate purposefully the magnitude of the defensive HBR if and only if vision is present during early childhood.

6 DPPS in disease part 2: Defensive space deformation in trigeminal neuralgia

6.1 Background

Perception of space has been guiding effective therapeutic interventions in a number of unilateral chronic pain conditions. However little is known about how trigeminal neuralgia (TN), a condition in which trigeminal stimulation triggers paroxysmal facial pain, affects DPPS. Given that TN is unilateral, in TN patients the DPPS surrounding the face might not be horizontally symmetric as in pain-free individuals, but instead larger around the affected side. Here we tested this a priori hypothesis by measuring the proximity-dependent modulation of the HBR. Stimuli delivered to the hand ipsilateral to TN elicited a stronger blink, particularly when it was measured from the eye ipsilateral to TN and closer to the face. Geometric modelling revealed (1) that DPPS was larger on the side of space ipsilateral to TN, and (2) this asymmetry was consequent to an increased estimated potential of sensory events to cause harm when they occur ipsilaterally to TN. These observations demonstrate that neural mechanisms underlying body protection in TN are adjusted to reduce the likelihood that external events evoke the painful paroxysm typical of this condition.

This study has been published as Bufacchi et al. (2017)

6.2 Background

An important factor in determining the estimated potential of a threat to do harm, and thereby alter the spatial properties of DPPS, might be the state of the somatosensory system; environmental stimuli occurring in spatial proximity of the area of hyperalgesia surrounding an injury are likely to be considered as a stronger threat. Chronic pain patients with hyperalgesia or allodynia may therefore be particularly sensitive to environmental stimuli close to the affected area, because of their potential to evoke a painful sensation.

Trigeminal neuralgia is a unique condition characterized by paroxysmal pain attacks of abrupt onset and very short duration, typically lasting few seconds and recurring with highly variable frequency: from 1 to over 50 a day(Cruccu et al., 2008, 2016; Antonini et al., 2014; Maarbjerg et al., 2014, 2017). The pain is most often described as stabbing or electric shock-like sensations, which are characteristically evoked (*trigger manoeuvre*) by innocuous somatosensory stimuli, such as a gentle touch, a breeze or shaving, in specific areas (*trigger zones*) within the affected division of the trigeminal territory.

Recent classifications distinguish two TN phenotypes, typical and atypical (the latter presenting with concomitant continuous pain in addition to the typical paroxysmal pain) with three possible aetiological forms: *classical* TN (the cause is compression of the trigeminal root by an arterial anomalous course - most often the superior cerebellar artery), *secondary* TN (the cause is multiple sclerosis or a benign tumour at the cerebellopontine angle), and *idiopathic* TN (no cause can be found) (Cruccu et al., 2008, 2016; Antonini et al., 2014; Maarbjerg et al., 2014, 2017). TN being a strictly unilateral condition, it is possible to hypothesize that in these patients the DPPS surrounding the face is not horizontally symmetrically distributed as in pain-free individuals (see Chapters 3 and 4), but is instead larger around the affected side.

Here we tested this hypothesis by exploiting the geometrical model (Chapter 3.3.6) to map the DPPS in 20 patients affected by TN. This allowed us to explore the functioning of neural systems underlying danger assessment and defensive behaviours in health and disease.

6.3 Materials and methods

6.3.1 Patients

Twenty patients (11 women) with classical or idiopathic trigeminal neuralgia (TN), aged 41-75 (*M*=56.2, *SD*=9.4), voluntarily participated in the study. These patients were identified as HBR-responders (Valls-Solé et al., 1997; Miwa et al., 1998; Sambo et al., 2012b; Sambo and Iannetti, 2013), out of a group of patients recruited from the pain clinic of the Department of Neurology and Psychiatry, Sapienza University of Rome (29 patients), and the Trigeminal Neuralgia Association, UK (TNA UK) (two patients). The proportion of HBR-responders as part of the initial sample (63%) was consistent with that found by us in healthy participants(Sambo et al., 2012a, 2012b; Sambo and Iannetti, 2013). We selected patients with the most typical presentation and aetiology of TN to minimize the possibility that different pathophysiological mechanisms gave rise to even slightly different perceptions of pain. Therefore, inclusion criteria were: (a) age of 30-80 years; (b) paroxysmal pain distributed to one or more trigeminal division unilaterally, (c) presence of one or more trigger zones, i.e. areas of the face which, when touched, cause an attack of pain, (d) typical TN presentation (i.e. purely paroxysmal TN), as defined by the new classification of the International Association for the Study of Pain (IASP) and the European Academy of Neurology (EAN)(Cruccu et al., 2016); and (e) duration of disease over 3 months. All participants gave written informed consent to take part in the study. The study was approved by the ethics committees of Sapienza, University of Rome and University College London. All experiments were performed in accordance with the Declaration of Helsinki, as well as local guidelines and regulations.

Patients were excluded if they had secondary TN (as demonstrated by MRI or trigeminal reflex testing(Cruccu et al., 2008)), or they had a history of any other neurological or psychiatric disorder. All patients were on an active phase of TN, based both on the patient’s report and the presence of trigger zones. Patients under pharmacological therapy (with oxcarbazepine or carbamazepine) were asked to suspend medication for at least 12 hours prior to their participation in the study.

6.3.2 Stimulation and recording

The duration of each stimulus was 200 μs, and the inter-stimulus interval (ISI) was ~30s(Sambo et al., 2012b). Electromyographic (EMG) signals were recorded bilaterally from the *orbicularis oculi* muscle using two pairs of surface electrodes; the active electrode was placed over the mid lower eyelid and the reference electrode a few cm laterally to the outer canthus. Signals were amplified and digitized using a sampling rate of 50 kHz, downsampled to 3.3 kHz, and stored for off-line analysis.

6.3.3 Experimental design

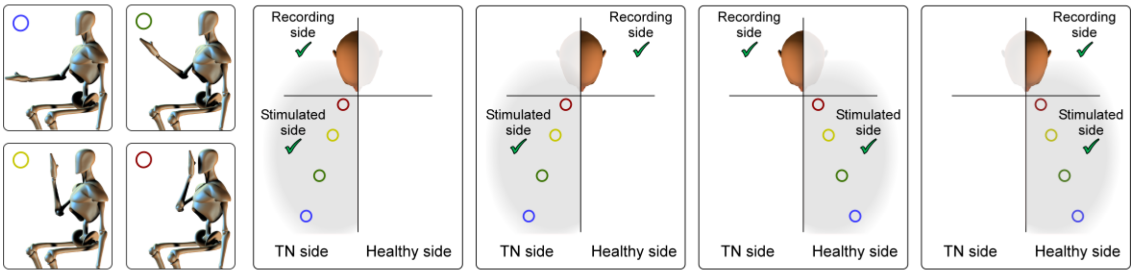


Figure 6.1. *Stimulation and recording conditions.* *Somatosensory stimuli were delivered to the median nerve at the wrist, while the hand was in four different positions: ‘ultra-near’, ‘near’, ‘far’, and ‘ultra-far’ (insets on the left). Stimuli were delivered to the hand ipsilateral to the TN side (first and second columns), and to the hand contralateral to the TN side (third and fourth column). The hand-blink reflex (HBR) was recorded using surface EMG from the eye ipsilateral to the stimulated hand (first and fourth column) and from the eye contralateral to the stimulated hand (second and third column). This 4 (positions) x 2 (stimulation sides) x 2 (recording sides) design resulted in 16 HBR average responses for each patient.*

Electrical stimuli were delivered transcutaneously to the median nerve at the wrist using a bipolar electrode, and EMG was recorded from the *orbicularis oculi* muscles bilaterally. HBR responses were recorded while the patient held their stimulated hand in four positions, corresponding to the following distances from their face: ultra-far (60 cm; forearm ~120 degrees relative to arm), far (40 cm), near (20 cm), and ultra-near (4 cm; forearm ~ 75 degrees relative to arm, hand in front of their ipsilateral eye) (Figure 6.1). The far and near positions were determined for each patient by measuring the distance between their stimulated hand and the face, and were clearly marked on a panel placed on the side of the patient's stimulated hand. The experiment consisted of four blocks. In each block, electrical stimuli were delivered to either the right or the left wrist (i.e. the wrist of the arm undergoing the postural manipulation). The order of the blocks was balanced across patients. In each block, four electrical stimuli were delivered for each of the four hand positions, for a total of 16 stimuli per block. The order of hand positions called by the experimenter in each block was pseudo-random, with no more than two consecutive stimuli being delivered in the same position. White noise was played throughout the experiment to mask any subtle sound made by the electrical stimulator.

6.3.4 *Preliminary recordings.*

The intensity of electrical stimuli was adjusted in each patient by gradually increasing the stimulus intensity until either a clear HBR was observed in three consecutive trials, or the patient declined a further increase(Valls-Solé et al., 1997; Sambo et al., 2012b). Only patients with a clear and stable HBR (i.e. *responders*) underwent further testing (Chapter 2.3.1).

In the patients with a stable HBR, stimulus intensity ranged between 14 and 80 mA (M = 43.7, SD = 18.2). Mean ratings for the intensity and unpleasantness of the painful sensation elicited by the electrical stimuli were 3.6/10 (SD = 2.0) and 4.7/10 (SD = 1.5), respectively.

6.3.5 *Data preprocessing*

EMG signals were analyzed using Letswave (http://nocions.org)(Mouraux and Iannetti, 2008). EMG signals from each patient were high-pass filtered (55 Hz) and full-wave rectified.

HBR magnitude was calculated as the response area-under-the-curve (AUC) of the rectified EMG, and transformed to z-scores within subject. AUCs were averaged separately for each experimental condition, resulting in 16 HBR average magnitudes for each patient.

6.3.6 HBR magnitude analysis.

To investigate the combined effects of hand position, stimulated hand, and side of face on the z-scored HBR magnitude (AUC), we performed a three-way, repeated-measures analysis of variance (rm-ANOVA ; n=20) with ‘hand position’ (four levels: ultra-far, far, near, ultra-near), ‘stimulated hand’ (two levels: ipsilateral *to TN side*, contralateral *to TN side*), and ‘recorded eye’ (two levels: ipsilateral *to stimulated hand*, contralateral *to stimulated hand*) as within-subjects factors. Greenhouse-Geisser corrections were applied whenever the assumption of sphericity was violated.

6.3.7 Geometric modelling.

Briefly, we for consistency with the previous modelling, we applied the geometrical modelling approach to the HBR data obtained by averaging the response between the two eyes (as in Chapters 3 and 4) (Figure 6.2). In addition, we tested whether our results were consistent even when considering the data from each eye separately (i.e. the data was not averaged between eyes). For the purpose of these analyses, the data must be normally distributed and have equal variance. To satisfy these conditions, we calculated the Z-scores of the power-transformed AUCs, as described in more detail in Chapter 3.

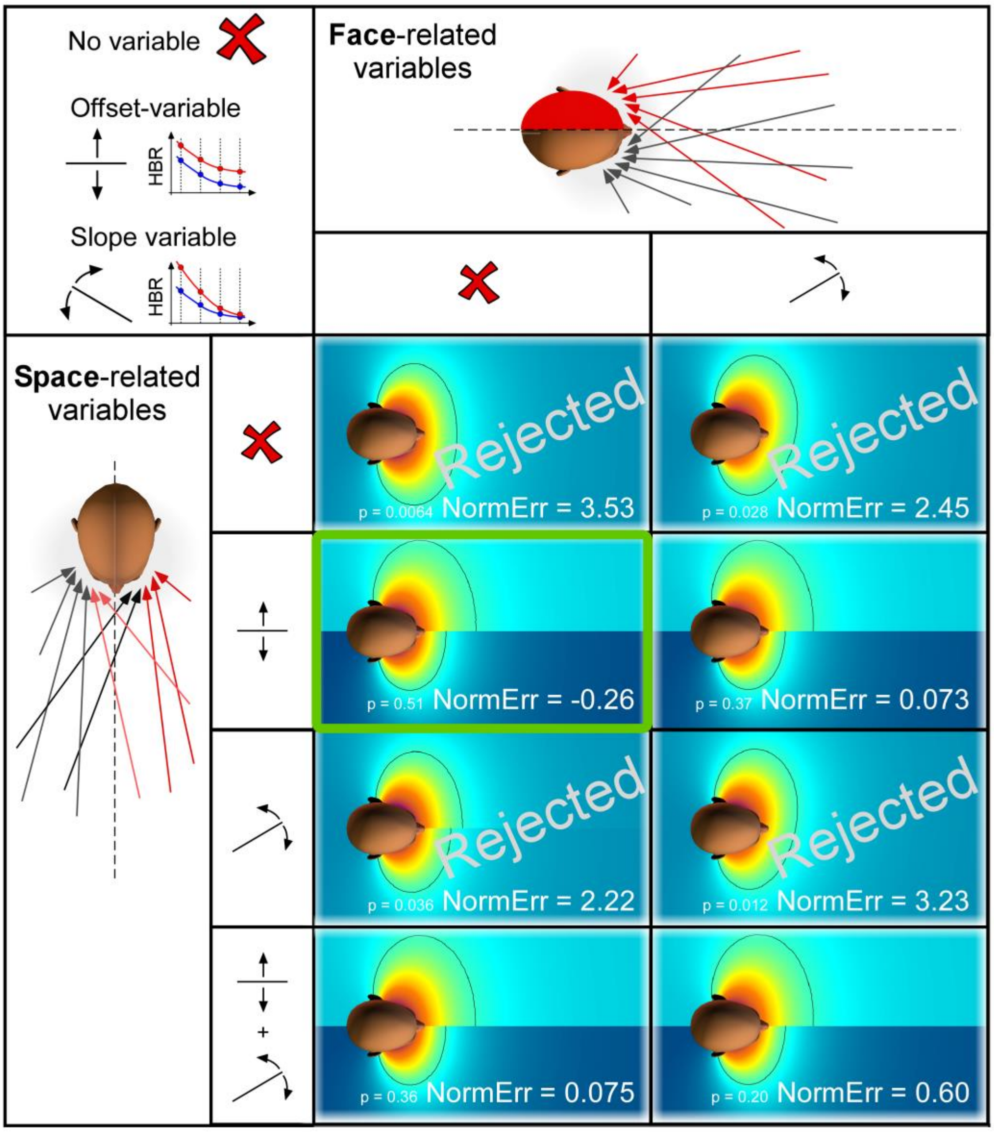


Figure 6.2. ***Geometric properties of the DPPS of the face predicted by each of the 16 tested models.*** *Two classes of variables were considered, representing underlying neurophysiological explanations for all possible TN-induced changes in DPPS shape and size. The first class of variables reflects that an event (represented by the origin of an arrow) hitting the side of the face affected by TN is estimated to do more harm (columns). The second class of variables reflects that an event occurring in the side of space ipsilateral to the TN is estimated to do more harm (rows). Since the geometrical modelling calculates the probability of an environmental stimulus to hit the face, and assumes a linear relationship between that hit probability and the HBR magnitude, the first (face) explanation could be modelled with one parameter: a change in slope (i.e. a multiplicative factor). In contrast, the second (space) explanation could be modelled using up to two variables: either a change in offset (i.e. an additive factor), or a change in slope (i.e. a multiplicative factor), or both. The resulting matrix shows the best model*

fit resulting from each of all possible combinations of the variables. Note that in some cases, adding a variable has only a very small effect on the resulting fit, which explains why some model fits look very similar. The 'NormErr' is what has been referred to in previous chapters as the goodness of fit: it is a normalised measure of how much more error each model gives in its fit to the data than expected. Therefore, the smaller (or more negative) the NormErr, the better the model fit. The p-values indicate whether a model is rejected (P < 0.05) or not (P > 0.05). DPPS models which did not pass goodness-of-fit testing are rejected, whereas the model that fitted the data best is highlighted in green.

We considered two possible underlying causes for the changes in DPPS shape and size, which are depicted by the arrows in Figure 6.2. The first (*face prioritisation mechanism*) is that the neural system underlying the modulation of the HBR circuitry takes into consideration the increased negative consequence that an external event would cause when hitting the side of the *face* affected by TN. The second (*space prioritisation mechanism*) is that the same system simply assumes that sensory events occurring in the side of *space* ipsilateral to the side of the TN represent a higher threat. Because the geometrical model assumes a linear relationship between hit probability and HBR magnitude(Bufacchi et al., 2016), the *space prioritisation mechanism* could be modelled using up to two parameters (represented by the space-related variables in the left part of Figure 6.2): either a change in slope (i.e. a multiplicative factor), or a change in offset (i.e. an additive factor), or both. This mechanism is exemplified by the red arrows that always originate in the side of *space* ipsilateral to TN regardless of the side of the face they hit. The arrows that hit the TN-affected side of the face are drawn in a lighter colour (note that the exact number of arrows is irrelevant for the analysis). Note also that because we are not modelling how the brain represents the parts of space ipsilateral or contralateral to each arm, we have assumed a step-boundary between the halves of space: the area to the one side of the face's midline is one side of space, and the area to the other side of the midline is the other side of space. While the sharp boundary depicted in Figures 6.2-6.4 is unlikely to be physiologically plausible, the aim of this model was not to characterise the boundary between right and left sides of space, but to distinguish whether the two sides of space have different properties with respect to the DPPS. In contrast to the space prioritisation mechanism, the *face prioritisation mechanism* (represented by the face-related variables in the top part of Figure 6.2) could only be modelled using a change in slope (i.e. a multiplicative factor), because the increase in threat in this mechanism is inherently linked to the probability of a threat hitting the side of the face affected by trigeminal neuralgia; thus a multiplicative factor can be applied to that probability, but a summative factor would by definition be independent of that probability. This mechanism is exemplified in the top panel of Figure 6.2, by the red arrows always hitting the side of the *face* ipsilateral to TN regardless of the side of space they originate in.

We tested all possible combinations of parameters and underlying causes discussed above, resulting in 8 different model variants, each corresponding to another cause of the differences in HBR magnitude observed between the sides of space ipsilateral and contralateral to TN. We used Chi-squared goodness of fit testing to assess which of these models (and corresponding underlying assumptions) did not explain enough variance of the data in order to be accepted (see Chapter 3). Here, we relied on a useful feature of this goodness of fit testing. Namely that this method also takes into account an important factor – the *parsimoniousness* of the models – by providing a better goodness of fit only if the fit is improved more than expected by adding just any additional variable. Therefore, this method allows us to compare the accepted nested models to see which one explains most of the variance of the data most effectively.

In the separate group of models for which we did not average the data from both eyes, we used an additional variable to model the “ipsi-contra effect” observed in healthy participants: the HBR measured from the eye contralateral to the stimulated hand is smaller in magnitude than that elicited from the ipsilateral eye (Sambo et al., 2012b). As for the face-related variables, we allowed this “ipsi-contra” variable to be either multiplicative, additive or both.

6.4 Results

6.4.1 Clinical features of Trigeminal Neuralgia

In 13 patients the TN was on the right side of the face, and in the remaining 7 it was on the left side. The trigeminal divisions affected by TN were as follows: V1 (2 patients), V2 (2 patients), V3 (5 patients), V2-V3 (3 patients), and V1-V2-V3 (8 patients). The duration of pain ranged between 3 months and 30 years (mean = 9.3, SD = 7.3 years).

Interestingly, the type of trigger had some predictive value with respect to the likelihood that an individual was a HBR responder: out of the 7 patients with only intraoral triggers, two were HBR responders (29%). In contrast, out of the 22 patients with extraoral triggers, 18 were HBR responders (82%). These percentages of HBR figures are in stark contrast with the average ~65% of HBR responders that we repeatedly observed in the normal population (Chapter 2.3.1). This qualitative observation suggests that when the TN pain is only triggered by sensory events occurring within the mouth, external events are given less behavioural relevance.

6.4.2 <u>HBR magnitude analysis</u>

The three-way repeated-measures ANOVA showed main effects of ‘hand position’ ($F=43.76$, $p=1.15*10^{-10}$), ‘stimulated hand’ ($F=5.533$, $p=0.029$), and ‘recorded eye’ ($F=160.35$, $p=1.04*10^{-10}$), as well as a two-way interaction between ‘hand position’ and ‘recorded eye’ ($F=40.87$, $p=2.12*10^{-10}$), and a three-way interaction between ‘hand position’, ‘recorded eye’ and ‘stimulated hand’ ($F=3.40$, $p=0.044$). The main effect of ‘hand position’ indicates that when the hand is close to the face the blink magnitude is increased, as already observed repeatedly in healthy participants (Sambo et al., 2012a, 2012b; Sambo and Iannetti, 2013; Chapters 3-5). The main effect of ‘recorded eye’ confirms the previously-described “ipsi-contra effect”: the HBR is stronger for the eye ipsilateral to the stimulated hand. This effect has also been repeatedly observed in healthy participants (Sambo et al., 2012b). Importantly, the main effect of ‘stimulated hand’ indicates that stimuli delivered on the side of space ipsilateral to the TN elicited an overall stronger HBR (Figures 6.3 and 6.4). The ‘recorded eye’ x ‘hand position’ interaction indicates that the ipsi-contra effect is stronger when the stimulated hand is nearer to the face. Finally, the ‘hand position’ x ‘recorded eye’ x ‘stimulated hand’ interaction indicates that this difference in ipsi-contra effect is larger when the hand ipsilateral to the TN is stimulated, than when the contralateral hand is stimulated.

Geometric modelling

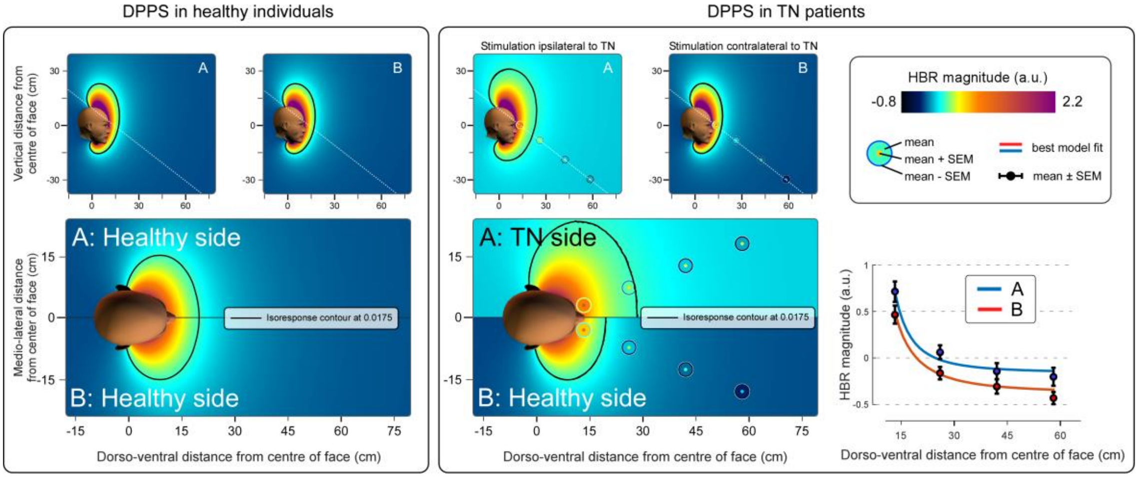


Figure 6.3. ***DPPS asymmetry in patients with TN.*** *Colour plots show the geometric properties of DPPS in healthy individuals (left panel, modelling based on the data reported in Experiments 2.1 and 2.2 from Chapter 4), and TN patients (right panel) using an axial section passing through both eyes (bottom) and two sagittal sections*

passing through each eye (top). The dotted line in the sagittal sections indicates the cutting plane used for the axial section. The background colour represents the estimated threat of environmental events predicted by the best-fitting model. The isoresponse contour line indicates the positions at which the predicted HBR magnitude is equal to the average HBR magnitude across all hand positions on the side of space contralateral to the TN (0.0175). The measured, normalised and averaged HBR data are represented as concentric circles located where the measurements were taken. The line graphs at the bottom show the mean HBR magnitude (±SEM) measured at each hand position, together with the HBR magnitude predicted by the best fitting geometric model (coloured lines). The best fitting model indicates that environmental events located in the side of space ipsilateral to the TN are considered to have a higher probability to do harm than events located in the side of space contralateral to the TN. This is reflected in a DPPS asymmetric along the mediolateral axis: the defensive bubble is extended further away from the face on the side of space ipsilateral to the TN.

6.4.3 *Modelling analysis*

Geometric modelling performed on the data averaged between eyes showed that, in contrast to what was observed in healthy participants (Chapters 3 and 4), the DPPS of TN patients is clearly asymmetric along the medio-lateral axis: TN patients showed larger HBR magnitudes on the side of space ipsilateral to the TN, when compared to the same position but on the side of space contralateral to TN. In other words, the DPPS was further extended on the side of space ipsilateral to TN (Figure 6.3). The Goodness of Fit and p-values for each tested model are shown in Figure 6.2. The only difference between the models best fitting the HBR modulation in healthy participants and in TN patients consisted of a parameter that modelled the increased threat of stimuli occurring in the side of space ipsilateral to the TN as a change in offset. In other words this model included an additive increase of HBR magnitude when stimuli were delivered on the hand ipsilateral to the TN, regardless of where that hand was positioned. All models that did not include any factor representing an increase of threat on the side of space ipsilateral to TN (either as a multiplicative or as an additive factor) were rejected (Figure 6.2).

We also tested a group of models on data in which HBR magnitude was not averaged between the eyes. The results from this modelling were consistent with the modelling of the eye-averaged data; the most parsimonious model (i.e. the model which used the fewest fitted parameters and was not rejected) included only (1) a change in offset describing the increased threat of stimuli occurring in the side of space ipsilateral to the TN, and (2) a separate change in offset describing the “ipsi-contra effect” (NormErr=1.167, p=0.125). All models which did not include both an additive variable (i.e. a change in offset) explaining the “ipsi-contra” effect as well as an additive variable describing an increase of threat on the side of space ipsilateral to TN were rejected (NormErr>3.55, p<0.0037). The best fitting model was identical to the most parsimonious model, but with an additional multiplicative variable describing the “ipsi-contra effect” (NormErr=-0.961; p=0.839), which reflects the ‘recorded eye’ x ‘hand position’ interaction in the above ANOVA. Hence this variable improves the fit of the model to the data, although it is not statistically necessary to explain the data. The further addition of a multiplicative variable to describe the increase of threat on the side of space ipsilateral to TN did not further improve the fit of the model (NormErr=-0.820; p=0.787). The addition of this variable reflects the ‘hand position’ x ‘recorded eye’ x ‘stimulated hand’ interaction, and thus does not result in the model being rejected. However, given that (1) the number of parameters used is so large relative to the number of data-points, and (2) the amount of additional variance explained so small, this extra factor is not necessary to explain the data, and does not statistically improve the fit of the model either.

Therefore, modelling of the HBR data separately for each eye (Figure 6.4) followed exactly the same rules and indicated that even when the eyes are considered individually, it is necessary to assume that the brain considers stimuli occurring within the space ipsilateral to TN more dangerous than those occurring on the other side of space. In Figure 6.4 the response displayed on side B of the left panel (i.e. the HBR recorded from the eye ipsilateral to TN, when the hand contralateral to TN is stimulated) is much weaker than the HBR shown anywhere else in that figure, or in Figure 6.3. This is consequent to the aforementioned “ipsi-contra effect”, wherein the HBR is stronger for the eye ipsilateral to the stimulated hand (Sambo et al., 2012b). This effect is still present in TN patients, as can be seen by separately comparing sides A and B *between* the left and right panels. However when this effect is combined with the overall stronger response to stimuli delivered to the hand located in the TN side of space, the result is that the HBR response is weakest when (1) recorded from the eye contralateral to the stimulated hand, and (2) elicited contralaterally to TN, which is the case for side B of the left panel of figure 6.4.

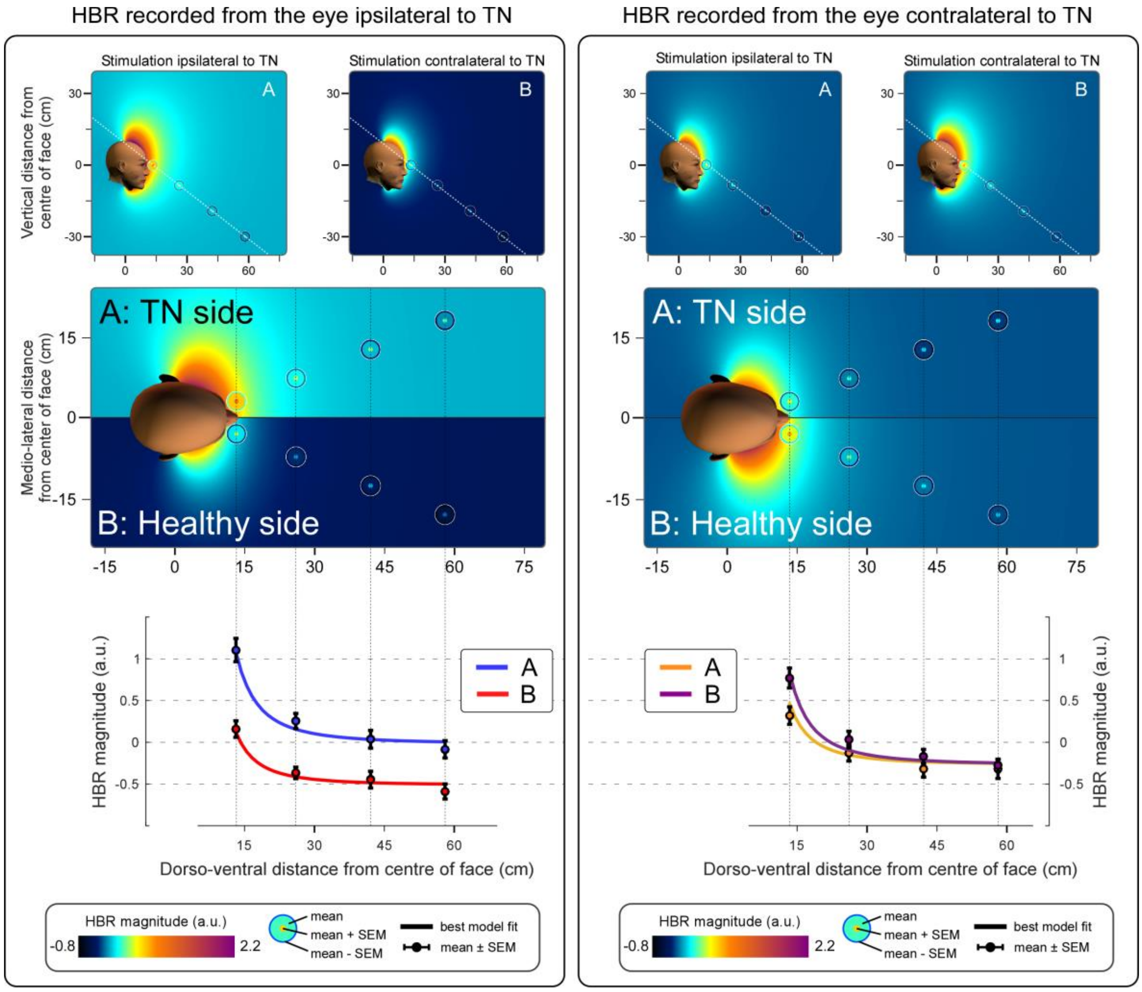


Figure 6.4. ***DPPS asymmetry for each separate eye in patients with TN.*** *Colour plots represent the estimated threat to a given eye of environmental events predicted by the best-fitting model. The layout is as described for Figure 6.3. Note that in the left panel, the HBR magnitude recorded from the eye contralateral to the TN side is overall lower than the HBR for either side on the right panel. The reason is the so-called 'ipsi-contra effect': in healthy participants, the HBR is stronger when recorded from the eye ipsilateral to the stimulated hand (Sambo et al., 2012b). In this figure the individual responses from each eye are shown, and therefore in the left panel the response for side B (showing the HBR from the eye contralateral to the stimulated hand) is expected to be smaller than for side A (showing the HBR from the same eye, which in this condition is ipsilateral to the stimulated hand). The fact that there is no inverted pattern (i.e. a response weaker on side A – contralateral to the stimulated hand, than on side B – ipsilateral to the stimulated hand) in the right panel, follows directly from the fact that we are dealing with TN patients: in contrast to healthy subjects, patients have a baseline increase of HBR magnitude when stimuli are delivered on the side of space ipsilateral to the TN (side A), resulting in an increase of HBR magnitude on that side.*

Therefore, taking into account the results from all models, it seems that to successfully explain the data it is necessary to assume that the brain considers stimuli occurring within the side of space ipsilateral to TN more dangerous than those occurring on the other side of space. Furthermore, this increase in danger on the affected side of space is likely to be a simple baseline-increase of the threat value of stimuli, rather than a multiplicative effect. Finally, *multiplicative* effects modelling (1) the increased damage done to the affected side of the face and (2) the “ipsi-contra effect”, do not invalidate the model, but are not necessary to explain the data.

6.5 Discussion

In this study we characterized the possible asymmetries in shape and size of DPPS surrounding the face in patients affected by trigeminal neuralgia (TN). In contrast to most other chronic pain conditions, in typical TN pain is rarely spontaneous. Instead in TN, electric-shock-like pain paroxysms are triggered by innocuous stimuli (e.g. a gentle touch or a puff of air) in the affected orofacial territory, which patients soon learn to avoid (Di Stefano et al., 2017). Clinically, TN patients become more alert and take a defensive posture when the examining physician approaches their face. Hence we expected that these patients had developed a DPPS with characteristics peculiar to this unique condition. We obtained two main findings. First, stimuli delivered on the side of space ipsilateral to the TN elicit a stronger HBR. Second, the normal ‘ipsi-contra effect’, wherein the HBR is larger for the eye ipsilateral to the stimulated hand (Sambo et al., 2012b), is altered in TN patients. These results indicate that the estimated potential for harm of sensory events is enhanced when they occur in the side of space ipsilateral to the TN – therefore defensive responses are upregulated to reduce the likelihood that external events evoke the painful paroxysms typical of TN.

Geometrical modeling of the HBR enhancement extended these findings, by allowing us to derive the fine-grained spatial properties of the DPPS. In healthy participants the DPPS is anchored to the face and has the shape of a bubble elongated along the vertical axis, and within (and outside) this bubble HBR responses are enhanced with proximity of the threat to the face (Chapters 3 and 4).

In TN patients the HBR magnitude increased monotonically and non-linearly with hand-face proximity (Figure 6.3) – a finding repeatedly described in healthy individuals (Sambo and Iannetti, 2013; Chapters 3 and 4). Given that (1) we delivered stimuli to both the hand ipsilateral and contralateral to the TN side, and (2) we recorded the HBR from both eyes, we were able to assess possible side asymmetries in DDPS shape. We observed that (1) stimuli delivered on the side of space ipsilateral to the TN elicit an *overall* stronger HBR (Figure 6.3), and (2) that that the ipsi-contra effect is stronger when stimulated hand is nearer to the face, and particularly so when it is ipsilateral to the TN (Figure 6.4). This is different from what was observed in healthy participants, in whom the strength of the ipsi-contra effect does not depend on hand position (Sambo et al., 2012b). Intuitively, these observations suggest that the nervous system estimates sensory events occurring in the near space ipsilateral to the TN side to be more threatening.

There are at least two possible neural mechanisms underlying this concept. One possibility (*space prioritisation mechanism*) is that the nervous system simply deems environmental stimuli to be more threatening when they occur on the side of *space* ipsilateral to the TN, regardless of the probability that the affected or unaffected side of the face will be hit. This mechanism is exemplified in the left panel of Figure 6.2, by the red arrows that always originate in the side of *space* ipsilateral to TN regardless of the side of the face they hit. The other possibility (*face prioritisation mechanism*) is that the nervous system continuously estimates the probability that environmental stimuli will hit either side of the *face*, and assigns a higher potential for harm to hitting events on the affected side of the face, regardless of where these sensory events are located within the peripersonal space. This mechanism is exemplified in the top panel of Figure 6.2, by the red arrows always hitting the side of the *face* ipsilateral to TN regardless of the side of space they originate in. Geometric modelling of DPPS allows for mathematical assessment of these options (Chapters 3 and 4), and we used this tool to statistically identify the mechanism that best underlies the experimental observations. A model corresponding to the space prioritisation mechanism clearly outperformed the other models (Figure 6.2). This winning model entailed an *additive* baseline increase in HBR magnitude only in the side of space ipsilateral to the TN, without any *multiplicative* change in the hand-face proximity effect compared to the unaffected side (Figure 6.3). Thus, the defensive ‘bubble’ of TN patients is asymmetric: on the side of space ipsilateral to the TN, defensive responses show an overall increase in magnitude. In other words, the position of the threat at which the defensive response has a given magnitude is always located further away from the face on the side of the TN (Figure 6.3). This has a clear advantage to minimise harm: indeed, threatening stimuli occurring on the side of space ipsilateral to the TN pose a particularly great risk of evoking a pain attack, and thus require more effective defensive motor responses. It is interesting to note that despite the overall differences in HBR magnitude between equal hand positions in the healthy and the affected side, the increase of HBR magnitude between the nearest and furthest position was not different. This suggests that TN changes defensive mechanisms following an additive mechanism, likely mediated by the addition of post-synaptic potentials (whether excitatory or inhibitory) directly on brainstem HBR circuitry, and not by a multiplicative pre-synaptic effect on some other modulatory mechanisms (Carstens et al., 1980).

A number of chronic pain conditions entail a disrupted cortical representation of the body and the surrounding space (Haggard et al., 2013). For example, our observation that TN patients assign a particular threat value to one hemispace is reminiscent of the findings in patients affected by unilateral CRPS of the hand (Moseley et al., 2012). In these patients, the affected hand became less painful when located in the side of space contralateral to its usual location. A possible speculation that can relate these previous observations with what we report here is that in TN patients the brain soon learns to be wary of specific external events and may come to attribute the source of the pain to these external events rather than attributing it to the body.

6.6 Conclusion

These observations demonstrate that the neural mechanisms underlying body protection are altered in patients affected by TN. In these patients, the nervous system purposefully adjusts the estimated potential for harm of sensory events occurring in the side of space ipsilateral to the TN. This adjustment enhances defensive behavior and thereby reduces the likelihood that external events evoke the painful paroxysms typical of this condition.

7 Opinions on DPPS: general discussion, and PPS as a set of continuous fields describing action relevance

7.1 Summary of results

In this thesis, I have described a number of empirical findings. In Chapter 3, I showed that the nervous system's representation of the body area defended by the HBR can be approximated by a half-ellipsoid centred on the face, and that the DPPS extending from this area has the shape of a bubble elongated along the vertical axis. In Chapter 4, I showed that the nervous system uses a malleable DPPS representation, and continuously updates the threat value of stimuli based on gravitational cues. However, when controlling for the effect of effort on HBR magnitude, the resulting DPPS shape might not be completely malleable: even when participants lie on their back, it still extends slightly further along the vertical axis of the body than would be expected if its asymmetry were only affected by gravitational cues. In Chapter 5, I showed that while blind individuals do also display a HBR, the nervous system only seems to develop the ability to purposefully *modulate* HBR magnitude if vision is present during early childhood. In Chapter 6, I showed that in trigeminal neuralgia, DPPS was larger on the side of space ipsilateral to the affected side of the face, and that this asymmetry was consequent to an increased estimated potential of sensory events to cause harm when they occur ipsilaterally to the affected side. In the appendix (section 10), I discussed how DPPS as indexed by HBR might expand when threatening stimuli approach, and used that notion to reconcile two papers from separate groups.

Taken together, these results indicate that DPPS as indexed by HBR is highly context dependent, and is adapted to ensure appropriate defensive responses, given the environmental circumstances. This strong contextual dependence fits well with the conceptual proposal which follows in the remainder of this Chapter. Below, I present some theoretical work (currently in preparation as an opinion paper) on ambiguities in the terminology used to report empirical results about peripersonal space, which have generated a great deal of confusion in the field.

7.2 Current issues and ambiguities in peripersonal space research

As mentioned throughout this work, there are many empirical observations that a number of behavioural and neural responses are altered when stimuli occur within the portion of space surrounding the body. This makes intuitive sense: observing either a predator or a prey within striking distance is far more immediately relevant than one further away, and the exact position of the stimulus relative to each body part dictates what types of movement are required to interact with it.

But what is precisely meant when referring to PPS in current literature? A great deal of confusion reigns. Is PPS the portion of physical space closest to the body, in a Euclidian sense? Is it the area within which *certain responses* are increased in magnitude? Or is it the brain representation of the space close to the body? A related issue is, that in much of the research on this topic, ‘the PPS’ is conceptualised as an “in-or-out” space; environmental events occur either inside or outside of it, and the strength of the behavioural or neural response is therefore dictated as either affected by PPS or not affected, in a binary fashion. This Chapter attempts to critically assess these issues, and concludes by proposing an ontology of PPS. I believe that under this theoretical framework the current concept of PPS can be understood and constructively explored through further experimentation.

7.3 Why is PPS often seen and discussed as an in-or-out zone?

There are several possible reasons that this might have been the case in the past, and some of those are the manner in which seminal work in the field (discussed in Chapter 2.1) was presented.

For example, Brain’s work on patients with parietal lesions (Brain, 1941), while very informative of brain function, was more of a list of symptoms than a precise scientific study. As such, subtle gradients of effects were not reported directly, in order to emphasise the memorable idea that different brain areas could represent the space near and far from the body. Albeit appealing, this dichotomic simplification might have set the tone of discussions for years to come. Similarly, Hediger’s observation of flight zones (Hediger, 1950) was assessed in a binary manner: an animal either fled, or it didn’t; a person was either *inside* the animal’s flight zone or *outside* of it. That is not to say that Hediger was not aware of a more subtle gradient. This simplification was likely chosen because it allowed for an easier communication of these observations, but nonetheless might have biased readers towards believing that animals had a strict deterministic flight distance, rather than some kind of probabilistic field or gradient of response probability. Another early example of such simplified explanation is how Hall very clearly and precisely demarcated the sizes of different types of near space (Hall, 1969). However, he never provided any evidence that such boundaries are rigid, binary, or as precise as he claimed. Instead, he seems to have used such precise measurements to ease the reader’s understanding.

A similar issue has arisen in the manner in which seminal work recordings from the peripersonal monkey neurons has been discussed (e.g. (Hyvarinen and Poranen, 1974; Leinonen and Nyman, 1979; Rizzolatti et al., 1981a; Gentilucci et al., 1983; Colby et al., 1993; Graziano and Gross, 1993). In these studies, introduced in Chapter 2.2, the large amount of empirical data clearly illustrate that the functions describing the increase of response magnitude with proximity are *gradual* (e.g. Rizzolatti et al., 1981a; Gentilucci et al., 1988; Colby et al., 1993; Graziano et al., 1994; Fogassi et al., 1996; Duhamel et al., 1998), but sometimes also fascinatingly complex, as detailed further below[2]. Besides the gradual falloff, another equally underemphasised aspect of these single-neuron recordings is that there is a sizeable portion of multimodal neurons (e.g. ~7% of recorded neurons in F4; Graziano et al. 1997) which has receptive fields that extend far further than 'reaching or working' distance, and *sometimes even to the end of the room*[3] (Colby et al., 1993; Graziano et al., 1997). Therefore some of these response functions encompass a far larger area than commonly reported. Nonetheless, the manner in which these results have been summarised, as well as referred to by other authors (and in fact by myself in Chapter 2.2), has often subtly emphasised the notion of a specific near space representation: the idea that there are neurons responding preferentially to stimuli occurring near a given body part was the most novel and memorable aspect of these studies. It is therefore not surprising that these single-neuron papers are nowadays often cited as evidence for a step-function-like explanation of an in-or-out 'peripersonal space'.

Possibly influenced by this narrative, when psychophysical experiments started being performed on humans to investigate near-space effects, these experiments would often test only the conditions near vs far (e.g. Làdavas et al., 1998; McCourt and Garlinghouse, 2000; Farnè and Làdavas, 2002; Sambo and Forster, 2009a; Sambo et al., 2012b; De Paepe et al., 2014). Such 'near vs far' experiments were performed, as

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[2] Much like the in-or-out description of PPS-related measures, the idea that these measures increase in magnitude monotonically with proximity is a vast oversimplification. For example, some bimodal neurons in both premotor and parietal regions *respond less strongly* to visual stimuli in an area very near their somatosensory receptive field, than to visual stimuli slightly further away in space (Rizzolatti et al., 1981a; Gentilucci et al., 1988; Colby et al., 1993).

[3] To make things more complicated, there seems to be a distinction in how different authors report their findings. For example, Graziano et al. and Colby et al., who discuss cortical areas seemingly more related to defensive aspects of PPS (i.e. VIP and dorsal F4), report that some bimodal neurons fire even when visual stimuli are clearly outside reaching space. In contrast, Rizzolatti et al. (e.g. Rizzolatti et al., 1981a), who mainly discuss cortical areas seemingly related to both grasping and defence (i.e. dorsal F4 and F5), report no responses to visual stimuli beyond reaching distance. It must be noted, however, that Rizzolatti and colleagues made an initial distinction between neurons which do and do not respond to stimuli in near space, and only classified neurons which responded to stimuli within reaching distance as peripersonal neurons. Nonetheless, this group did find bimodal visuo-tactile neurons with visual response properties outside of reaching distance in F4 (3.5% of tested bimodal neurons; Fogassi and Gallese, 1996).

described in Chapter 2.3, using various behavioural measures. It is important to emphasise that the understandable desire to keep experiments as simple as possible largely dictated such experimental designs, which are by no means mistaken. Indeed, researchers were most likely very aware that the observed responses changed more continuously between the tested near and far positions, and that sampling 2 points along a continuum does not negate the continuum. However, the simple fact of reporting the results obtained from only these two conditions could nonetheless, to the reader, imply a binary response pattern.

Furthermore, in the fewer experiments where more stimulus location were indeed tested, and the corresponding response clearly showed a graded falloff, often a single summary measures of PPS size was chosen in order to discuss the results under the framework of an “in-or-out” zone. For example, the point of first increase over baseline activity has been used in HBR work (Sambo and Iannetti, 2013), and the mid-point of a fitted sinusoidal function is used commonly when assessing PPS through reaction times to multimodal stimuli (e.g. Canzoneri et al., 2012; Ferri et al., 2015a; Serino et al., 2015). Again, this often does not come from a position of ignorance on the part of the researchers. However, even when it is explicitly made clear that changes in response magnitude from near space to far space are gradual, for example in line-bisection work (e.g. Longo and Lourenco, 2006; Longo *et al.*, 2015), and some of our own work on the hand-blink reflex (Sambo and Iannetti, 2013; Bufacchi and Iannetti, 2016; Bufacchi et al., 2016), the discussion is still often framed as ‘near space vs far space’. This approach is understandable - it makes analysis, interpretation and intuition easier - but it entails the loss of a crucial aspect: the profile of the function. Indeed, when an adequate number of stimulus positions are tested, it is possible to describe the entire profile of the modulation: usually the response of multimodal PPS-related measures along one dimension decreases with distance following a function resembling a sigmoid (Van der Stoep et al., 2015). Bearing this in mind, characterising the shape of a function used to assess PPS can be important. For example, when using reaction time to an approaching multimodal stimulus as a measure of PPS, a linear relationship with time indicates that the effect of expectation is dominating, while a sigmoidal relationships indicates the effect of PPS is dominating (Kandula et al., 2017). Also, the manner in which reaction times vary with proximity of an auditory stimulus depends on whether the stimulus is looming or receding (Canzoneri et al., 2012; Serino et al., 2015). Furthermore, as exemplified throughout this thesis, measuring HBR magnitude elicited by stimulating the hand when located in multiple spatial locations (i.e. more than 2) has shown that the HBR response function depends on the face's orientation, while also being influenced by gravitational cues, the sensitivity of the face and movement of the stimulated limb (Chapters 3-10).

The understanding that can be gleaned from all the above evidence is that the choice to highlight findings in a binary fashion is often made because it improves the ease of writing and understanding. While it is not invalid to conceptualise gradients as boundaries, there is nonetheless a danger of an oversimplified understanding if almost all papers in the field adopt this approach. In other words, describing the *underlying cause* of such findings as an in-or-out space can lead to confusion, and can even support radical interpretations, such as the conclusions that under certain manipulations "far becomes near" (e.g. Berti and Frassinetti, 2000). Importantly, the work conducted in my lab is not exempt from this criticism, as we have also repeatedly used similar iso-contour lines and in-or-out rhetoric in our own publications (Sambo et al., 2012a, 2012b; Sambo and Iannetti, 2013; Bufacchi et al., 2016; Wallwork et al., 2016; Bufacchi, 2017; Chapters 4-7).

Therefore, to avoid implications of a strict in-or-out zone, this chapter proposes a reconceptualization of how PPS should be discussed. Borrowing the notion of *field* from physics, the proposal is that PPS should be discussed as a *continuous set of fields*, whose magnitudes reflect the behavioural relevance of *certain sets of actions* in response to environmental stimuli. Specifically, these actions and stimuli are related to either creating contact between the stimulus and a body part, or to avoiding it. In this framework, the behavioural relevance of a stimulus to a given action still depends on proximity, but does not suddenly vanish once the stimulus is beyond a specific distance. Instead, as the stimulus moves away from the body, its relevance to a particular movement gradually diminishes. Chapter 7.4 elaborates on this idea and shows that a large amount of experimental evidence supports it. Chapter 7.5 proposes that such a field expressing the behavioural relevance of a stimulus to a given action by its own nature does not only depend on where the stimulus is located, but also on a number of other factors, including its size, possible direction of motion, speed, and semantic.

7.4 PPS as a continuous set of fields, spanning the entire space

The suggestion is then, that PPS might be better conceptualised as a *continuous set of fields* constructed by the brain, and encompassing the entire space around the organism. Hence, the term *field* is used in the same sense it is used in modern Physics, to express a quantity that has a magnitude for each point in space and time (Mcmullin, 2002). It should also be understood that field values can be approximately zero in most of space and time. Take as an example the magnetic field strength around a magnet. It falls off as the inverse cube of distance from the magnet. It is because of this large rate of change that when holding a magnetic object and approaching a magnet, we perceive a ‘boundary’ defining the area where we start feeling the attractive force exerted by the magnet. Nonetheless, the magnet creates a magnetic field that extends substantially further into space, but the strength of its field is so infinitesimally small that we cannot feel it. Similarly, a PPS field value very far from the body might be infinitesimally small most of the time, but this does not mean that it is non-existent.

A key point of this reconceptualization is that *PPS fields reflect the behavioural relevance of a stimulus to a given action or set of actions*. In order to support this statement it is necessary to take a short detour and carefully consider two issues.

The first issue is what is really meant when using the term PPS. In current literature, it is possible to identify three different meanings that are used when writing about PPS. These meaning have been often conflated, which I believe has generated a lot of confusion. The first meaning of the term PPS is, simply and literally, ‘the portion of space within a given Euclidian distance of the body’ (or, in a slightly different version which has its own pitfalls, ‘the portion of space that can be directly acted on’). The second meaning of PPS is ‘the space within which certain physiological or perceptual responses (for example, the blink reflex, or the reaction time in a multisensory detection task) are larger when the stimuli eliciting them occur near the body’. The third meaning of PPS refers to ‘the mechanisms through which the brain represents the space near the body’.

The issue is that meanings #2 and #3 are often considered equivalent: typically, the empirical observation that a physiological response function dependent on proximity (i.e. PPS in meaning #2) changes, is presented as evidence that the neural representation of near space (i.e. PPS in meaning #3) ‘expands’, ‘contracts’, or ‘changes shape’. But this equivalence between ‘the space within which certain physiological or perceptual responses are larger when the stimuli eliciting them occur near the body’ and ‘the mechanisms through which the brain represents the space near the body’ is a typical false equivalence. The problem is that the two things are related, but their relation is not exclusive. While it is certainly true that a measure dependent on spatial proximity (#2) tells us something about how the brain represents near space (#3), it is not true that a modulation of the measure dependent on spatial proximity (#2) necessarily means that the brain has changed it way of representing near space, and considers an object to be more or less near (and that “PPS has expanded/contracted” – in meaning #3). The point is that there are other reasons *not related to how the brain represents near space* that could have caused the modulation of a response that is typically larger when the stimuli eliciting them occur near the body’. This confusion occurs very often: for example, when the response field of the reaction time to multimodal stimuli changes (i.e. meaning #2) due stimulus valence, authors have concluded that the manner in which the brain represents (i.e. meaning #3) space surrounding the body (i.e.meaning#1) changes as well (Ferri et al., 2015b).

If we instead shift perspective, and start relating the responses from peripersonal neurons or PPS-related behavioural measures to the relevance of specific actions, the issue of conflation is avoided. Also, it becomes clear that the equivalence between meanings 2 and 3 is false: if a monkey neuron responds more to a stimulus when that stimulus is moving towards the monkey, as compared to when it is moving away, this is because that stimulus is more relevant to the actions that that monkey neuron is involved with encoding, but not because the way the brain represents space near the body has, in general, changed. The monkey itself however might still be well aware that the location of the stimulus hasn’t changed between the two directions of movement. Note that even though there have been occasional observations of proximity judgements being affected by factors that also affect PPS, these differences in estimations are extremely small compared to the actual proximities (e.g. Vagnoni et al., 2012).

For all these reasons, we can only talk with confidence about the fields which describe the magnitude of these *measures* in space, rather than the fundamental *neural* representation of what the brain might or might not consider to be near space. Therefore, to refer to PPS in a rigorous manner one should use the second meaning of the word: the set of fields which describe how certain responses are increased when stimuli are closer to a body part.

This leads us to the second issue that we need to consider: there are substantial differences in the response functions of the many biological and behavioural PPS-related measures.

Again, a parsimonious explanation for the fact that some of these measures have a vastly different sensitivity to stimuli presented in the same regions of space, is that they are related to actions whose biological function are relevant for different body parts. For example, the HBR results in defence of the face (Sambo et al., 2012a; Chapter 3), and the stimulation of multimodal VIP neurons elicits particular defensive postures (Cooke and Graziano, 2004). Therefore, it is not surprising that the spatial fields derived from HBR and certain VIP neurons can be vastly different: HBR responses are increased when stimuli are delivered near the face, whereas a specific VIP response might be stronger when the stimulus is near, just to give an example, to the upper arm (Graziano et al., 1997). Thus, while it is clear that each of these measures can be intuitively related to PPS (meaning #1, the physical space near the body), it is equally clear that these measures can define PPS fields of different shapes and sizes (meaning #2 – response functions of measures). In other words, the PPS field derived from a particular response is going to be shaped by whatever function that response subserves. An additional perspective which emphasises the differences in PPS fields derived by different measures is their correlation with specific psychological traits. For example, claustrophobic fear correlates with extension of the PPS field indexed by line bisection tasks (Lourenco et al., 2011), but not with the extension of the PPS field indexed by the HBR (Sambo and Iannetti, 2013). Instead, trait anxiety does not correlate with extension of PPS field indexed by line bisection tasks (Lourenco et al., 2011), but does correlate with the extension of the PPS field indexed by HBR (Sambo and Iannetti, 2013). While both correlations intuitively make sense, their discrepancy highlights the nuances involved in attempting to define and understand PPS as a unitary concept. Such discrepancies hint towards PPS as an overarching class of response fields, rather than a single entity.

Elaborating on this concept of many different action-related PPS fields, different events occurring in the environment (sensory stimuli identifying potential threats, but also affordances, etc) require different actions. The proposal here is that the brain estimates the value of external events, differently for the type of behaviour that these events might trigger. This estimation is, understandably, heavily dependent on spatial location in egocentric coordinates (although not only – see later), but in a spatially different way for each type of action needed to react to the sensory event. Therefore, depending on the event, the various measures of PPS will also respond differently. The multiple PPS fields can be vastly different because each PPS fields codes how relevant a specific set of actions might be to the current and near-future situation of an animal.

Importantly, each measure used to derive a PPS field probably refers to a partly different subset of actions. Thus, there is not a single PPS. These PPS action fields might be related in the same way that different sports might have common features, even if there is not a single ‘ultimate sport’; while there is the concept of what sport is, there is no such thing as *the* sport.

This definition of PPS as a set of relevance-estimation fields by no means implies that there is no difference in how the nervous system processes stimuli in near and far space – but it does imply that there is no single strict boundary between the neural representations of events in the far and near regions. For example, the fact that at a certain point in space an animal flees from a potential predator does not mean that the field underlying that action is non-continuous. Using the concept of a field of *potential action relevance*, we can see that an animal might be continuously sampling the repertoire of its potential actions, and once the probability of a specific action dominates over the rest, the animal will most likely, at some point, perform that action.

7.5 Not just proximity: A unified perspective on a valence-assessing system.

So far I have suggested that if the PPS is to be understood as a unitary concept, it should only be as a class of fields that describe the relevance of actions and stimuli. The common denominator of these actions is that they either create contact between the stimulus and a body part, or they avoid it. It should be clear by now that such fields relate to stimulus proximity to the body. But is it that enough? This last section adds another block, and suggests that the continuous PPS fields strongly depend on multiple variables, not just on stimulus proximity. Unlike previous conceptualizations of PPS, which often viewed these other variables as interesting exceptions to the rule, this perspective argues that one should not be surprised at the number of other variables, given that the ultimate effect of having such action fields is to enable optimally efficient, context dependent behavioural responses. Note that the examples below are drawn from defensive behaviour, but the principles discussed here do not change much for appetitive behaviour.

A first additional factor that can affects a PPS field is the movement of the stimulus. This can be highlighted by a quick thought experiment: as an intuitive example we can consider the threat posed to an imaginary animal when we vary the context that the animal finds itself in. Let us imagine that the animal observes a rock rolling or another animal moving towards it. If that movement occurs with high speed, the animal would need to deploy a motor repertoire vastly different in comparison to if an object has almost come to a standstill, even if either object is first observed in the same position.

Similarly, observing a rock or other animal moving on a direct collision course necessitates a different movement repertoire to ensure/avoid contact than if the object were moving tangentially to our hypothetical animal. This notion that PPS fields are defined also by object movement is in fact in line with *another* under-highlighted aspect of the original monkey single-neuron recordings: their enormous variability in response properties as a function of the stimulus movement.

Although it is often mentioned that the multimodal neuron responses are generally larger for stimuli moving towards a body part, most neurons also show some response to stimuli moving away, and a large portion of neurons are even tuned to movements in different directions than looming. Here, this is exemplified using the VIP as a stereotypical brain structure containing peripersonal bimodal neurons. In fact, 80% of all neurons (note that this figure includes both unimodal and multimodal cells) in VIP respond at least twice as much to stimuli moving in some preferred direction, and the borders of VIP were originally functionally identified as the points at which direction-selective visual responses could be found (Colby et al., 1993; Graziano et al., 1997; Duhamel et al., 1998). Even the neurons selectively responding to looming stimuli are not necessarily monotonic: while the majority of these neurons do respond most strongly to stimuli in the nearest stimulus position tested (e.g. 5cm from the body part with the relevant tactile receptive field), some respond better to stimuli located at further distances (e.g. 20cm from the somatosensory receptive field), and a few even further than that (Colby et al., 1993). Furthermore, some bimodal neurons in VIP respond preferentially to stimuli *moving away* from the body (Duhamel et al., 1998). Interestingly, in these bimodal cells, the tactile response is triggered when the tactile stimulus is *removed* from the receptive field. Further examples of the large response variability with respect to stimulus movement, are that some other bimodal neurons respond preferentially to the simple appearance of a stimulus than to its movement, and others even show a preferred orientation of the static stimulus (Duhamel et al., 1998). In fact, VIP neurons include so much directional information that recordings from VIP can be used to reliably decode self-motion and heading direction relative to the environment (Bremmer et al., 2002; Chen et al., 2011c) although, crucially, they are not causally involved in heading perception (Chen et al., 2016). This evidence further strengthens the case for VIP as a centre underlying the functioning of actions and for processing stimuli that are related to avoiding contact between a stimulus and a body part. Note that many other cortical regions besides VIP equally reveal the complexity of PPS response fields, as they also contain neurons sensitive to a large number of features other than proximity, such as stimulus size, stimulus direction, stimulus speed, clockwise vs anticlockwise rotation, as well as both active and passive joint movement to name a few (Rizzolatti et al., 1981a; Fogassi et al., 1996; Graziano et al., 1997). All in all, this demonstrates that PPS fields are not just determined by proximity: PPS fields derived from, for example, VIP neurons with the same tactile RF but differentially sensitive to movement, would be very different even if the stimulus used to derive those fields were the exact same.

Another important factor determining the PPS field besides body proximity can be the environmental landscape. We could imagine that, faced with a charging lion, a zoo guest might behave very differently if there were a protective glass pane between them than if there weren't. Thus, the PPS field derived by the same response might be different depending on the contextual change represented by the presence of glass. While this can appear intuitive and hand-waving, there is evidence that PPS measures do actually take such environmental features into account. For example, the area of space in which the hand-blink reflex magnitude is modulated changes in the presence of a protective screen (Sambo et al., 2012a).

In addition, as mentioned in Chapter 2.2, a steady stream of recent findings have been showing that various other behavioural and neurophysiological PPS-related measures are also affected by more than just proximity to a body part. These factors include simple cues relating to the dynamics and spatial properties of a given situation such as walking (Noel et al., 2014; Amemiya et al., 2017), posture relative to the direction of gravity (Bufacchi and Iannetti, 2016), current motion of the hand (Brozzoli et al., 2009, 2010), direction of stimulus movement (Serino et al., 2015), and precise stimulus trajectory (Cléry et al., 2015a). Even the valance and meaning of stimuli and environment have recently been shown to affect PPS-related measures (Heed et al., 2010; Taffou and Viaud-Delmon, 2014; Ferri et al., 2015b; de Haan et al., 2016). The above type of effects on PPS-related measures have been labelled *dynamic effects*, that is, effects caused by abrupt changes in the individual or environment. Another class of effects on PPS measures, are plastic ones; effects that occur only following training or learning (Cléry et al., 2015b). These changes, such as changes of multimodal neurons' response fields after tool use (Iriki et al., 1996; Chapter 2), have been discovered longer ago and are more extensively described. They additionally provide strong support to the idea that PPS measures are affected by many factors other than stimulus proximity.

Given the clear importance of context to PPS measures, it is still surprising that there is not more work investigating their various context dependencies. One reason for this is that many general PPS studies are performed under lab conditions and restrictions. This means that experiments are kept as simple as possible, often by presenting stimuli only in a small region in frontal space, at eye-or-hand height, and while the subject is stationary and only possibly performing very minor tasks (van der Stoep et al., 2016).

Nonetheless, it should now be clear that despite the seeming surprise expressed every time a new context-dependence of a PPS field is found, there are many factors which influence PPS responses. In fact, so many factors that modulate PPS-related measures are appearing, that a shift in perspective might be necessary – perhaps we should move from seeing these factors as interesting anomalies, to seeing them as part of a bigger whole. In other words, PPS fields are so dependent on other factors than stimulus proximity, that they should not be considered separately from these other factors any longer, but rather as a function which takes into account many separate variables at all times, only one of which is proximity. This perspective change is in fact encapsulated in the proposal of *PPS fields describing the relevance of actions and stimuli that are related to either creating contact between the stimulus and a body part, or to avoiding it*. Under such reasoning, the dependencies of the PPS fields on all variables arise naturally, due to the necessities of the actions they underlie.

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10 Appendix - Extra opinions on DPPS: Approaching threatening stimuli cause a DPPS expansion

10.1 Background

A question I am often asked – and have often asked myself – is whether the DPPS as indexed by HBR is affected by motion of the threat (i.e. whether the DPPS changes if somatosensory stimuli eliciting the blink reflex are delivered while the hand is moving). While I have not performed such experiments or analysed such data myself, two studies by others have recently been published, showing the effect of limb movement on HBR magnitude. However, at first glance the results from those two studies seemed incompatible. In this Appendix, I postulate a possible way of reconciling them, which boils down to the idea that DPPS expands when threatening stimuli approach.

This commentary has been published as Bufacchi (2017).

10.2 Discussion

In a recent paper, Bisio et al. (Bisio et al., 2017) delivered HBR-eliciting stimuli while participants moved their hand. They instructed participants to make a single hand movement towards and then away from their face (or vice-versa) roughly every 30 seconds, and stimulated the hand at one of six time-points during this motion. They reported that HBR magnitude was affected by this hand movement when the hand was *near* the face: in that position, when the hand was moving *away* from the face, the HBR magnitude was *decreased* compared to when the hand was moving towards the face (Figure A1, panel A, left). In contrast, HBR magnitude was not dependent on movement direction when the hand was in the other two positions farther from the face. Remarkably, they showed a similar effect when participants imagined moving their hand, but did not actually perform the movement. They provided a convincing directional interpretation: the HBR magnitude in the near positions can be reduced by a movement of the threat away from the body part that needs to be defended. The dependence of HBR magnitude on movement was also suggested by the results of Wallwork et al. (2106), which, however, consisted in a seemingly opposite pattern: where Bisio et al. reported an HBR decrease at the near position when the hand was moving away from the face, Wallwork at al reported no difference between movement directions at the near position. Furthermore, Wallwork et al reported an HBR increase at the far position when the hand was moving towards the face, while Bisio et al. reported no difference between movement conditions at that position (Figure A1, panel A, left). Both articles suggest that the cause for the observed effects might be the ability of the nervous system to predict the future location of the hand. However, their two explanations are opposite: in Bisio et al. the prediction of where the hand is going to be is assumed to cause a down-regulation of HBR magnitude but not an up-regulation, while in Wallwork et al. it is assumed to cause an up-regulation of HBR magnitude, but not a down-regulation.

A simple but different explanation could reconcile these two seemingly opposite observations, which could in fact be instances of the same physiological phenomenon. This explanation, demonstrated in Chapter 4 and 6, is that the DPPS size is not stationary, but changes depending on the context. In the case where the hand moves, DPPS size might therefore increase when threatening stimuli move toward an endangered body area. Interestingly, this notion is present in the title of the article by Bisio et al., but not elaborated on. Considering the wider body of work on peripersonal space (not only in relation to defence) provides further support for this explanation. It has been shown that the size of peripersonal space is malleable within subject (van der Stoep et al., 2016). For example, tool use reshapes action space around the tool (Longo and Lourenco, 2007), and walking expands peripersonal space forward (Noel et al., 2014). Even more interestingly, the firing rate of the cells thought to underlie defensive responses to stimuli in the near space (i.e. the DPPS specifically) is not only dependent on the stimulus position, but also on its movement direction and its speed: many these cells generally fire more when (1) the stimulus moves towards the body, and (2) it moves faster (Graziano and Cooke, 2006).

Unfortunately, Bisio et al. did not discuss this possibility, and instead assumed the opposite, namely that the DPPS is of fixed size (Figure A1, panel A, right). This reasoning led to the conclusion that *'… these findings might be explained as a down-regulation of the HBR response when planning to move far from the face, albeit the hand was inside the defensive peripersonal space'*. In other words, they claimed that when the hand is moving away from the face, the HBR is down-regulated to baseline levels, *even though it is inside the DPPS of the face*. This reasoning seems inconsistent when using the definition of the DPPS as the zone within which the HBR magnitude exceeds a specific threshold, as Bisio et al. do.

The notion that the DPPS is malleable is consistent with its survival advantage: the probability that a threat will hit the face is higher when the source of that threat (the stimulation on the wrist) is moving towards the face. This increased probability of hitting in turn increases the threat's potential for harm, and therefore necessitates a stronger HBR, to proportionally match the increased danger of the threat (Chapters 3 and 4).

Under this framework, the HBR increase that Bisio et al observed at the nearest position when the hand is moving towards the face can be interpreted as an *expansion* of DPPS. In other words, the DPPS (if it is defined as the area within which the HBR magnitude exceeds a specific value) expands from a size where it does not reach the nearest hand position from the face, to a size where it encompasses that nearest position (Figure A1, panel B, right). Similarly, the increase in HBR magnitude at the far position when the hand is moving toward the face observed by Wallwork et al (2016) would then be an *expansion* of DPPS to encompass that furthest position, from a size where the DPPS only encompassed the nearest position. Note that this line of reasoning makes the assumption that in Wallwork et al (2016) there is a ceiling effect: the HBR magnitude has a maximum value, and this value is reached at the near position. When the DDPS expands to encompass the furthest position, the HBR elicited when the hand is at that position also reaches the ceiling magnitude.

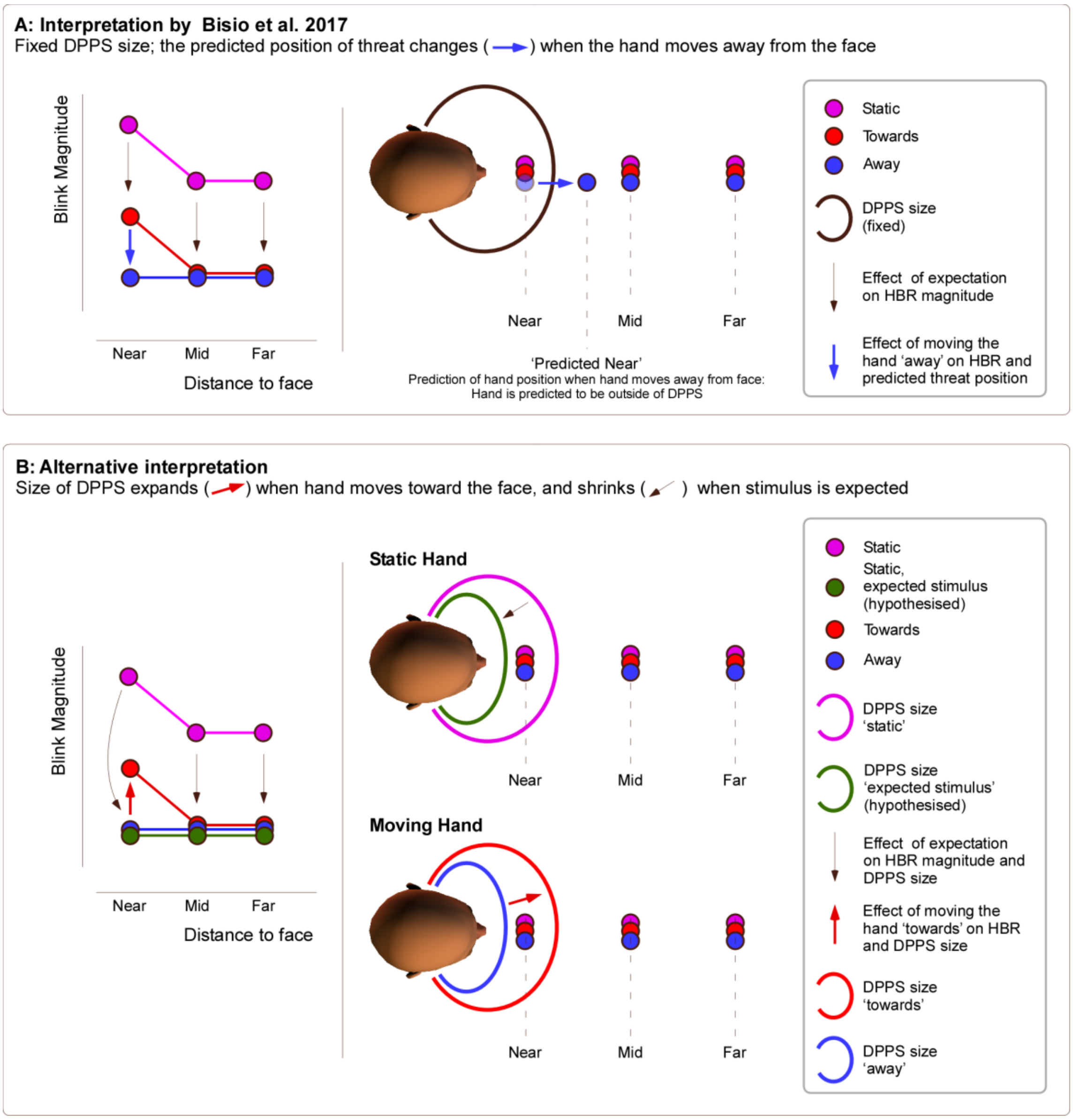
Even if this reasoning is correct, an important issue that remains to be solved is which DPPS measure Bisio et al considered as a baseline; Figure A1 shows that they tested the HBR magnitude under 3 conditions: while the hand was moving toward the face, away from it, and not moving at all. They took the *pattern* of HBR increase in the static condition as a baseline measure: in that condition, the HBR magnitude at the near position is larger than the HBR magnitude in the other two positions. They then reasoned that, because this pattern was present in the towards condition but not in the away condition, in this latter condition the hand's predicted (or expected) position must have been outside the DPPS. Importantly, however, in the static condition, Bisio et al. measured an HBR *overall* much larger than in the two movement conditions. Therefore, using the static condition as a baseline measure of DPPS size is unlikely to be correct. In fact, the difference between static and moving conditions is most likely caused by expectation; in the moving conditions, subjects spent most of their time with the hand resting on a table, then moved it toward and away from their face once per trial when prompted by the experimenter. During this movement the shock was delivered when the forearm was at a specific angle. Therefore, as Bisio et al. also point out, participants knew that they could only possibly get a shock once they started moving. This expectation effect most likely resulted in participants linking the movement of their arm to the delivery of a shock, thereby decreasing the surprise and hence the threatening value of the shock.

Therefore, in *any* conditions where the subject's hand is moved, the baseline *size* of the DPPS might be decreased due to higher stimulus predictability (again, this is if the

DPPS is defined as the area within which the HBR magnitude exceeds a specific value). This would result in a smaller HBR magnitude difference between the near and far conditions, or even no difference at all if the baseline DPPS size were small enough. Therefore, a better baseline would have been a condition in which the participants trigger the shock, and wherein the shock occurs within ~4 seconds from the trigger (i.e., a similar temporal delay between when the participants began the movement, and when the shock occurred in Bisio et al 2017). If in this condition the HBR is equal in the nearest and the furthest hand positions (or at least is more similar in magnitude than when the hand is moving towards the face), this would demonstrate that, when the stimulus is expected, the DPPS is smaller than the distance between the nearest hand position and the face. In this way, when the hand is moving toward the face, the DPPS size would increase from baseline, resulting in an increase in HBR magnitude at the nearest hand position. This explanation is also supported by the case where the movement of the hand is not temporally linked to the stimulus onset (Wallwork et al., 2016): in that situation, the baseline DPPS size (i.e. when the hand does not move) is not substantially different from the condition in which the hand moves away from the face.

Interpreting the results of the discussed studies within the framework of an expansion of DPPS emphasizes the proposed link between the activity of cortical areas underlying the spatial modulation of defensive responses in the near space (such as VIP and parts of F4; Cooke and Graziano, 2004) and the brainstem circuits mediating the HBR (Sambo et al., 2012a). Indeed, VIP neurons are highly selective to the direction and velocity of stimuli (Colby et al., 1993) and receive dense proprioceptive inputs (Lewis and Van Essen, 2000), while the receptive field of many F4 neurons expands in depth when the stimulus speed increases (Fogassi et al., 1996). Such response features would be necessary to cause an expansion of DPPS in response to the movement of the forearm relative to the face. Accordingly, VIP has been proposed to subserve impact prediction (Cléry et al., 2015a). These areas receive input from the superior collicus and pulvinar (Makin et al., 2012), both of which respond to looming stimuli and are involved in time-to-collision judgements (Billington et al., 2011). The superior colliculus is also strongly involved in enacting defensive responses across species (Pereira and Moita, 2016) and has multimodal response properties (Triplett et al., 2012). Interestingly therefore, it is possible that the brainstem circuits mediating the HBR might also be influenced by midbrain areas.

In conclusion, a parsimonious explanation of the results of Bisio et al. is that the DPPS size increases when the hand carrying the threatening stimulus is moving toward the face, following the estimated increase in probability that the moving threat will harm the face.



A: Interpretation by Bisio et al. 2017
Fixed DPPS size; the predicted position of threat changes (→) when the hand moves away from the face

B: Alternative interpretation
Size of DPPS expands (↗) when hand moves toward the face, and shrinks (↙) when stimulus is expected

Figure A1. ***Schematic of hand movement effects on Hand-Blink Reflex (HBR) magnitude.*** *Panel A: in the interpretation put forward by Bisio et al. (2017) the size of the DPPS (if that size is defined as the area within which the HBR magnitude exceeds a specific value) is fixed. Left sub-panel: sketch of HBR magnitude across different conditions. Right sub-panel: assumed DPPS (black line) and predicted positions of the threat (coloured circles). In this interpretation, when (1) the threat is near the face and (2) it moves away from the face, the position of the threat is predicted to shift outside the DPPS (blue arrows in right sub-panel), with a consequent decrease in HBR* *magnitude at the near position (blue arrow in left sub-panel). In both conditions where the hand moves, the movement of the hand is linked to the stimulus onset, therefore causing an overall HBR magnitude decrease. Importantly, Bisio et al assume this 'expectation effect' to be equal at all hand positions (black arrows in left sub-panel).* Panel B: *an alternative interpretation is that the DPPS size is malleable. Left sub-panel: sketch of HBR magnitudes across different conditions, also including hypothetical real baseline magnitude when the eliciting shock is expected. Right sub-panel: implied size of DPPS (coloured lines) and predicted positions of the threat (coloured circles). In this alternative interpretation, when the threat moves towards the face, the DPPS expands (red arrow in right sub-panel), causing an increase in HBR magnitude at the near position (red arrow in left sub-panel). In this interpretation, the expectation effect results in both an overall HBR magnitude decrease and in a DPPS shrinkage (black arrows in both sub-panels). While both interpretations are plausible, only the alternative interpretation fits with prior empirical observations (i.e. Wallwork et al. 2016).*