Peripersonal Space : hand-centred coding in perceptual and learning processes

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N°d'ordre NNT : **2021LYSE1247**

THESE de DOCTORAT DE L'UNIVERSITE DE LYON
opérée au sein de
l'Université Claude Bernard Lyon 1

Ecole Doctorale N° 476
Ecole Doctorale Neuroscience et Cognition

Spécialité de doctorat :
Neuroscience

Soutenue publiquement le 12/11/2021, par :
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Remerciements - Acknowledgement

It was a great, long and awesome journey. Searching for it led me to two different countries, with different languages and different people, but with one factor in common: "Where does this accent come from?". Putting one's life in a suitcase and seeing that every time something does not fit is not easy, but the people who accompanied me on the journey, directly or indirectly, for a short period or for its entire duration, made me love it. For this I would like to thank you all, in no particular order.

Most people won't have to put up with about 300 pages of manuscript, reading only this aknowledgement part. For this reason I would like to thank first of all all the members of the thesis jury who, unfortunately for them, had to deal with my absolute lack of synthesis (as well as with my somewhat questionable graphic / chromatic choices). Thank you very much (and sorry).

Mi ricordo come é cominciato il viaggio: "Siediti pure qui, e quando Claudio esce lo blocchi e gli dici chi sei". E da quando ti ho bloccato, di cose ne sono cambiate. Sempre pronto a incoraggiare, sempre presente quando ho avuto bisogno, sia in laboratorio che al di fuori (starei ancora cercando una casa se non fosse per una tua firma). Mi hai sempre dato fiducia, a parte quando si trattava dei miei slanci artistici (e guardando alcuni dei primi PowerPoint, forse comprendo la ragione). Senza contare la prima conferenza a Roma, le serate insieme, il Martini bianco e le canzoni a fine serata. É stato un lungo viaggio, e lo abbiamo percorso insieme. Grazie di esserci stato.
E un grosso grazie anche ad AleF., che ha messo un semplice tirocinante ad aspettare e bloccare qualcuno che non aveva mai visto prima, dando il via all'avventura. Se sono partito da "Ok, proviamo la tesi, ma il peripersonal space non é molto nelle mie corde" per arrivare a "Vi piace il mio modello teorico totalmente speculativo sul PPS?" buona parte del merito va a te. Grazie.

Merci aussi à tous les chercheurs, les post-doctorants (soprattutto al mio guru di R, Dr. Elvio), les doctorants (o aspiranti tali, o non più tali ma sempre e comunque tali, Dr. Silvia) et les stagiaires (tous, mais en particulier en ce qui concerne ces trois cas irrécupérables de Mattia, Leonardo et Valeria : avoir appris le français vous coûte une référence non italienne) qui d'une manière ou d'une autre ont fait partie de mon voyage. Tout cela n'aurait pas été pareil sans vous.

Ma se tutto questo si é realizzato, un grosso grazie lo devo alla mia famiglia. A mamma, che quando ho pensato di smettere col brutto vizio dell'università mi ha spinto a continuare, e che non mi ha ancora diseredato nonostante io non mi faccia mai sentire. A papà, che mi ha insegnato a insistere, perché quando si vuole qualcosa la si puo' ottenere. Alle mie sorelle, perché se sono riuscite a sopravvivere all'infanzia é sicuramente grazie a me, ma mi hanno poi insegnato più di quanto loro pensino. Ai miei nonni, che probabilmente non saranno presenti il giorno della discussione, ma so che avrebbero molto voluto esserci, come sempre. Grazie.

Et enfin, un grand, immense merci à la personne qui se demande si je l'ai oubliée. A celle qui dit que je ne l'écoute jamais, que je suis têtu et que j'ai un sale caractère. Mais qui me soutien et me supporte chaque jour. A celle qui m'a fait faire partie de sa famille, me

sentant chez moi même loin de chez moi (merci Jérôme, Catherine, Thom et Cyp !). Au début de ce voyage nous ne nous connaissions pas encore, mais la partie que nous avons parcourue ensemble était la meilleure. Et bien que ce voyage soit terminé, un nouveau est sur le point de commencer, toujours ensemble, et j'espère que ce sera un voyage plus long et encore meilleur que celui qui vient de se terminer. Si aujourd'hui je parle, pense et écris dans une autre langue que la mienne, c'est à toi que revien l'essentiel du mérite. Si à chaque fois je n'avais pas la motivation de continuer je continuais, le mérite t'en revien. Tu me pousses chaque jour à être meilleur que la veille, et je crois que c'est ta plus grande qualité. En plus d'avoir un caractère aussi mauvais que le mien et de supporter mon ironie déplacée. Où que nous allions, si t'y est, ce sera toujours "chez nous". Merci Audrey, merci d'être là.

Contents

Résumé

Quarante ans exacts se sont écoulés depuis l'apparition du terme « espace péripersonnel » (EPP, Rizzolatti et al., 1981a, 1981b), cette région de l'espace dans laquelle notre vie quotidienne prend place, dans laquelle nous pouvons interagir avec les objets et les personnes qui nous entourent. Les premières études de la littérature électrophysiologique de cette représentation spatiale ont observé dans des régions spécifiques du cerveau des macaques l'existence de neurones multisensoriels capables de coder des stimuli tactiles, visuels et/ou auditifs en fonction de leur distance des parties spécifiques du corps. Ces neurones bi- ou tri-modaux présentent en effet des champs récepteurs tactiles centrés sur une partie précise du corps, comme le visage ou la main, et des champs récepteurs visuels et/ou auditifs se superposant spatialement aux premiers. De cette façon, les mêmes neurones sont capables de répondre à des stimulations tactiles, visuelles et auditives délivrées sur ou à proximité d'une partie spécifique du corps. De plus, ces champs récepteurs multisensoriels sont « ancrés » les uns aux autres : le mouvement de la main du singe impliquait une mise à jour non seulement des champs récepteurs tactiles, mais aussi des champs visuels. Ce référentiel centré sur les parties du corps du codage des stimuli multisensoriels au sein de l'EPP nous permet de garder les informations relatives à la position des différentes parties du corps et des objets environnants toujours à jour, dans le but de planifier et de mettre en œuvre des actions efficaces.

Des études neurophysiologiques et comportementales sur des patients souffrant d'extinction et sur des patients héminégligeant suite à des lésions cérébrales de l'hémisphère droit ont permis de mettre en évidence, même chez l'homme, l'existence et la modularité du PPS. Des études ultérieures en neuro-imagerie ont apporté un soutien à cette preuve, mettant en évidence un réseau de régions fronto-pariétales et sous-corticales capables de coder des stimulations multimodales en fonction de leur distance du corps.

Les fonctions supposées de cette représentation spatiale sont multiples : servir de médiateur dans la relation entre la perception de stimuli externes et l'exécution d'actions ciblées, la surveillance de l'espace autour du corps afin d'identifier les menaces potentielles et mettre en œuvre des réactions défensives, organiser et gérer l'espace entre nous et les autres dans

le cas de différents types d'interactions sociales ou nous permettre de nous identifier à notre corps, en lui donnant une localisation dans l'espace.

Cependant, malgré le grand intérêt scientifique que cette région de l'espace autour du corps a suscité au cours des quarante dernières années, une comparaison directe de ses fondements neuronaux chez les primates non humains et les humains fait toujours défaut. Pour cette raison, dans le premier chapitre de cette thèse de doctorat, nous rapporterons les résultats d'une étude IRMf, menée sur des participant·e·s humain·e·s et macaques, qui a identifié les patterns de réponse neuronale à des stimulations proches ou éloignées de différentes parties du corps, tout en essayant de minimiser les différences entre les protocoles expérimentaux utilisés chez les deux espèces. Pour la première fois le PPS est investigué chez deux espèces différentes mais avec le même protocole expérimental, mettant en évidence des similitudes et des différences entre le circuit PPS humain et simien, mais aussi entre les patterns de réponse associés à la stimulation de différents secteurs corporels.

À partir du deuxième chapitre, nous concentrerons plutôt notre intérêt sur la représentation de l'EPP chez l'être humain, pour essayer d'éclaircir un problème de définition qui a confondu la représentation EPP avec l'espace atteignable (EA). Ce dernier, considéré comme l'espace autour du corps que l'on peut atteindre en étendant le bras, a souvent été utilisé au fil du temps comme synonyme de la représentation de l'EPP, conduisant à définir l'EPP comme EA ou à tester les deux représentations spatiales avec les mêmes protocoles. Cependant, les différentes bases neuronales et les différentes caractéristiques de l'encodage des stimuli au sein de ces deux régions de l'espace suggèrent leur distinction. Dans le Chapitre II, pour tester l'hypothèse d'une différence entre EPP et EA, nous présenterons une série de cinq expériences comportementales qui ont étudié leurs différences et similitudes en utilisant des paramètres expérimentaux similaires et des tâches différentes. Les résultats permettent d'étayer une distinction entre ces deux représentations spatiales, mettant en garde contre les interprétations possibles de résultats issus de tâches spécifiques pour l'étude de l'EPP ou de l'EA.

Enfin, dans le troisième et dernier chapitre de ce manuscrit, nous nous concentrerons sur une fonction spécifique de l'EPP, la fonction défensive. Les évidences disponibles montrent

que la proximité au corps des stimuli menaçants est capable d'influencer la représentation de l'EPP : la réponse comportementale aux stimuli menaçants est plus rapide, grâce à un codage précoce qui nous permet de planifier les réponses défensives. Souvent, cependant, ces études demandaient aux participants de garder leurs bras, leur tête ou leur corps toujours dans la même position. Nous nous sommes donc demandé si l'encodage d'une menace proche du corps était encodé en coordonnées centrées sur les parties du corps, une caractéristique clé du PPS. Pour tenter de répondre à cette question, dans ce dernier chapitre nous présenterons une étude dans laquelle, grâce à un processus d'apprentissage de la peur par conditionnement pavlovien, un stimulus initialement neutre prend une valeur menaçante suite à l'association répétée avec une stimulation électrocutanée désagréable appliqué au niveau de la main. Suite à cet apprentissage, la simple présentation du stimulus conditionné près de la main induit une modification de la conductance cutanée indiquant une réaction de peur. Les résultats montrent que l'association entre les stimuli neutres et négatifs se produit dans des coordonnées centrées sur la main, car le déplacement de celle-ci provoque également un 'remapping' de la réponse de conductance de la peau.

L'étude des bases neurales de la représentation EPP chez les primates humains et non humains rapportée dans cette thèse a souligné des résultats cohérents avec ce qui a été observé dans la littérature électrophysiologique et IRMf respectivement, mais aussi quelques incohérences. Des régions neuronales non incluses à l'origine dans le réseau fronto-pariétal de l'EPP rapportent des préférences pour les stimuli proches du corps, chez les deux espèces, conduisant à un "élargissement" de ce réseau pour inclure, entre autres, également des régions typiquement connectées à la représentation de l'EA et / ou l'exécution de mouvements complexes. Ce résultat, au regard de la distinction fonctionnelle retrouvée entre EPP et EA dans l'étude présentée au Chapitre II, soulève quelques questions. Est-il possible que ces deux représentations spatiales soient vraiment distinctes, bien qu'elles partagent une partie du réseau neuronal sous-jacent ? Comment cette distinction s'inscrit-elle par rapport à la fonction défensive de l'EPP et son lien avec les processus d'apprentissage centrés sur les parties du corps, démontrés dans l'étude du Chapitre III ? Existe-t-il un « EPP d'atteinte » par opposition à un « EPP défensif » ? Dans ce cas, dans laquelle des deux représentations relèveraient les processus d'apprentissage, de conscience corporelle et de régulation de la distance sociale, éléments apparemment associés à l'EPP?

Dans la discussion finale de cette thèse, une tentative est proposée pour redéfinir l'EPP, non pas en le considérant comme un espace, opposé ou superposé à d'autres représentations spatiales, mais comme un mécanisme pour coder la position des parties du corps, la position des stimuli et la relation existant entre ces coordonnées.

Abstract

Forty years have passed since the coining of the term "peripersonal space" (PPS, Rizzolatti et al., 1981a, 1981b), that region of space in which our daily life takes place, in which we can interact with the objects and people around us. The first electrophysiological studies of this spatial representation have observed in specific regions of the macaque's brain the existence of multisensory neurons capable of encoding tactile, visual and / or auditory stimuli according to their distance from specific parts of the body. These bi- or trimodal neurons, indeed, show tactile receptive fields centered on a specific part of the body, such as the face or hand, and visual and / or auditory receptive fields overlapping spatially with the formers. In this way, the same neurons are able to respond to tactile, visual and auditory stimulations delivered on or close to a specific body-part. Furthermore, these multisensory receptive fields are "anchored" to each other: the movement of the monkey's hand involves a coherent displacement not only of the tactile receptive fields, but also of the visual ones. This body-part centered reference frame of the coding of multisensory stimuli within PPS allows to keep the information relating to the position of the different parts of the body and surrounding objects always updated, with the aim of planning and implementing effective actions.

Neurophysiological and behavioral studies on patients suffering from extinction and neglect following brain lesions of the right hemisphere have allowed to highlight, even in humans, the existence and modularity of the PPS. Subsequent neuroimaging studies have brought support to this evidence, highlighting a network of fronto-parietal and subcortical regions capable of coding multi-modal stimulations according to their distance from the body.

The hypothetical functions of this spatial representation are manifold: mediating the relationship between the perception of external stimuli and the execution of goal-directed actions, monitoring the space around the body in order to identify potential threats and implement defensive reactions, organizing and regulating the space between us and others in case of different types of social interaction and allowing to identify oneself with their body, by giving it a position in space.

However, despite the great scientific interest that this region of space has elicited over the past forty years, a direct comparison of its neural underpinnings in non-human primates and humans is still missing. For this reason, in the first chapter of this doctoral dissertation we will report the results of an fMRI study, conducted on human and macaque participants, which investigated the neural response patterns to stimulations close to or far from different body-parts, minimizing the differences among the experimental protocols used in the two species. For the first time PPS is tested in two different species but with the same experimental protocol, highlighting similarities and differences between the human and simian PPS circuit but also between the response patterns associated with the stimulation of different bodily districts.

Starting from the second chapter we will instead focus our interest only on human participants, to try shedding light on a defining problem that has conflated the concept of PPS representation to that of a second spatial representation: the arm reaching space (ARS). The latter, considered as the space around the body that we can reach by extending our arm, over time has often been used as a synonym for the PPS representation, leading to define PPS as ARS or to test the two spatial representations with the same experimental protocols. However, the different neural bases and the different characteristics of the encoding of stimuli within these two regions of space suggest their distinction. In Chapter II, to test the hypothesis of a difference between PPS and ARS, we will present a series of five behavioral experiments that investigated their differences and similarities using similar experimental settings but different tasks. What emerges from the results supports the distinction between these two spatial representations, warning about the possible interpretations of results coming from specific tasks for the study of PPS or ARS.

Finally, in the third and final chapter of this manuscript we will focus on a specific function of the PPS, the defensive one. Evidence in the literature shows that the proximity of threatening stimuli to the body is able to influence the representation of the PPS: behavioral responses to threatening stimuli are faster, thanks to an early coding that allows us to plan defensive responses. Often, however, these studies asked participants to keep their arms, head or body still in the same position. We therefore wondered if the encoding of a threat close to the body took place in body-part centered coordinates, a key feature of the PPS. To try answering this question, in this last chapter we present a study in which, thanks to a fear

learning process through Pavlovian conditioning, an initially neutral stimulus has taken on a threatening value following repeated association with an electrocutaneous unpleasant shock applied at the level of the hand. Following this learning, the simple presentation of the conditioned stimulus near the hand induced a skin conductance response indicating a fear reaction. The results show that the association between neutral and negative stimuli occurs in hand-centered coordinates, as moving the hand also causes a remapping of the skin conductance response.

The study of the neural basis of the PPS in human and non-human monkeys reported in this dissertation highlighted results consistent with what was observed respectively in the fMRI and electrophysiological literature, but also some inconsistencies. Neural areas not originally included within the PPS fronto-parietal network report preferences for stimuli close to the body, in both species, leading to an "enlargement" of this network to include, among others, also regions typically connected to the representation of reaching space and / or the execution of complex movements. This result, in the light of the functional distinction found between PPS and ARS in the study presented in Chapter II, raises some questions. Is it possible that these two spatial representations are really distinct, despite sharing a part of the underlying neural network? How does this distinction fit with respect to the defensive function of the PPS and its link with body-part-centered learning processes, demonstrated in the study of Chapter III? Is there a "PPS-reaching space" opposed to a "PPS-defensive space"? In this case, which of the two representations would the processes of learning, body awareness and the regulation of social distance, elements apparently associated with the PPS, fall into?

In the final discussion of this dissertation, an attempt is proposed to redefine the PPS, not considering it as a space, opposed or superimposed on other spatial representations, but as a mechanism for encoding the position of the parts of the body, the position of the stimuli and the relationship existing between those coordinates.

Introduction

Dinanzi a me non fuor cose create

se non etterne, e io etterno duro.

Lasciate ogne speranza, voi ch'intrate

Dante Alighieri

We realize the pleasure that small daily activities give us only when these are lacking, or are prohibited. We quickly understood this, especially in the last year of lock down. Precisely for this reason, as soon as it was possible, we all tried to rediscover the lost pleasure, and I decided to go to the cinema, enjoy a movie and dive into the popcorn. It is incredible to think how such a "simple" activity for us has given inspiration to about sixty years of scientific literature. Even if we don't realize it, every little part of this relaxing activity represents an incessant work at a cognitive level. To get to my seat and sit down, my brain had to integrate and monitor proprioceptive, somatosensory, and vestibular information to avoid me to fall, or making me sit improperly. Watching the film, I never thought that the sound of the conversations did not really come from the actors' mouth. They are in front of me, I see them talking, so it makes sense that the sound comes from them. For my brain it is not that easy: the verbal information that reaches my eardrums must be integrated with the visual information, coming from another perceptual channel. And the brain is so busy with this task that it does not realize that in reality it has been misled. Not to mention the skill it takes to grab the popcorn, bring it to the mouth and avoid dropping it everywhere, all without even looking.

Most of our daily activities require this kind of sensorimotor and cognitive processing and a phenomenon called *multisensory integration*. It is an automatic process, whose results are fundamental for us: not only the integration of signals of different modalities helps us to better perceive the reality around us, but also allows us to plan and implement effective actions.

This thesis will therefore begin with a first chapter aimed at better understanding what multisensory integration is, how it works and where it takes place in the primate brain. This will allow us to get closer to the topic that is the basis of the main theme and the original contribution of this research: the *peripersonal space*. Often defined as an interface between perception and action, it is easy to understand its link with the aspects of multisensory integration that we are going to describe (even if, as we will see, speaking of peripersonal space does not necessarily imply multisensory stimuli). Starting from a more general framework and moving towards increasingly specific aspects of this spatial representation, in the first chapter I will describe an fMRI contribution that compares the neural basis of peripersonal space in human adults and in non-human primates, using for the first time the same protocol and stimulation conditions across the two species. In the second chapter,

delving more into the characteristics and definition of the peripersonal space in humans, I will provide evidence in favor of the distinction between the latter and another very important spatial representation for our daily actions: the *reaching space*. Finally, in the third chapter I will dive into a specific function of the peripersonal space, the defensive one, and to test if it is possible to create associative links between different stimuli within it. Once these associations established, they remain "anchored" to the body-part, being remapped in space according to the movement of the part of the body involved.

So let's go into the space around us, the “scaffold that supports everything we do” (Graziano, 2017). Spotlights on the peripersonal space.

Chapter I

Multisensory Perception in a Multisensory World

Equipped with his five senses,
man explores the universe around him
and calls the adventure Science.

Edwin Powell Hubble

1.1 Why and how a multisensory perception?

The world around us is made up of signals of multiple nature, which manifest themselves in different forms: electromagnetic waves, air vibrations, smells and so on. We are constantly immersed in this multitude of signals, which depending on the situation can prove to be of fundamental importance for our survival, indicating where to find food, shelter or possible partners, but also what could represent a danger to our safety. Evolution allowed our brain to receive and interpret these signals and integrate them with each other, providing us with a perception of the environment as precise and detailed as possible (or at least, the representation with the best energy cost-precision ratio). A fundamental process to achieve such a result is called *multisensory integration*, and its importance has been the focus of the last fifty or so years of literature not only on the study of perception (Ghazanfar & Schroeder, 2006; Stein, 2012; Stein & Stanford, 2008), but also of action (Betti et al., 2021; Fogassi & Gallese, 2004).

Indeed, multisensoriality seems to be a pervasive presence in our daily life. When we talk to our colleagues, the movement of their lips is integrated with the sound of their voice, and if inconsistencies are experimentally introduced between these two pieces of information, perception can be misled (Mcgurk & Macdonald, 1976). In the same way, the light of the alarm clock and its sound are integrated into a single percept, as well as the visual perception of its shape will allow me to plan the configuration that my hand should take to turn it off, the distance it will have to travel and the gesture that I will have to perform. And this integration of multimodal signals happens without apparent effort, in a seemingly automatic way.

But how is multisensory integration implemented at the neural level? Much of what we know about it today stems from the pioneering work of the research team of Stein, Meredith and colleagues. In their work, multisensory integration is defined as a unidirectional process in which two signals of different nature (and therefore defined as cross-modal) are integrated into a single construct, that cannot be "deconstructed " to return to them (Stein et al., 2009; but see Soto-Faraco & Alsius, 2009). At the neural level this process leads (often, but not always) to a response called "superadditive" or “sub-

additive", that is, of an intensity that is greater or lower than the sum of the responses to their single unisensory components (Stein et al., 2009; Stein & Meredith, 1993).

The early models developed in the study of perception envisaged a hierarchical structure of information processing: sensory information was first processed at a unisensory level, in areas predisposed to treat only one sensory modality (e.g., V1 for vision, S1 for somatosensation), and only later could it be transmitted to areas with an ever-increasing level of multisensory integration, called *associative areas* (e.g., V4-V5). Only starting from this processing stage multiple signals can be integrated with each other, with an ever greater degree of complexity and precision (Felleman & Van Essen, 1991; Hubel & Wiesel, 1979).

This idea derives from the first studies investigating the interconnections between the so-called "unisensory" visual, auditory and somatosensory areas (Figure 1.1), reporting that communications at this level of information processing was virtually absent (Kuypers et al., 1965). Similarly, studies on focal lesions have made it possible to highlight that damage at the level of these regions caused specific behavioral effects, with a deficit centered on a specific sensory modality (Massopust et al., 1965). These results then consolidated the idea of a hierarchical structure of sensory information processing.

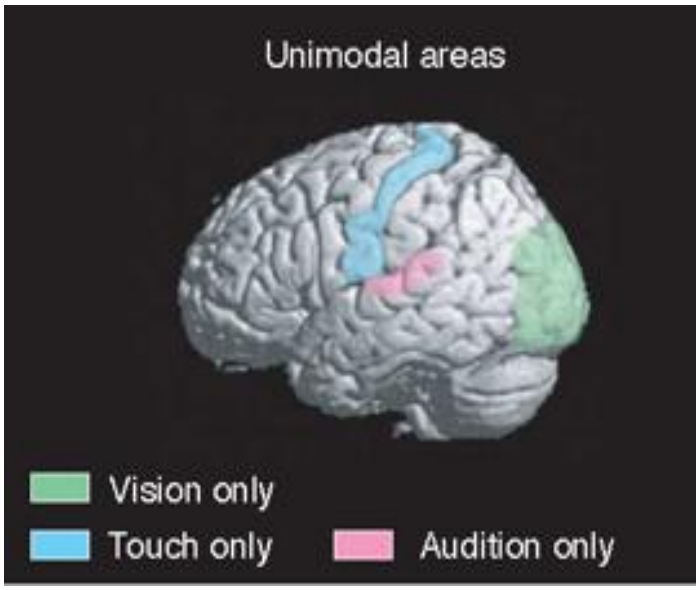

Figure 1.1 *Primary and secondary "unisensory" areas for the vision (occipital lobe), the audition (superior temporal gyrus) and the somatosensation (post-central gyrus). From Macaluso & Driver, 2005*

Today we know that this is not the entire story: even if we can affirm that the path of sensory information proceeds towards levels of ever greater complexity and multisensory integration, more recent studies have shown that cross-modal interaction processes are present even starting from those areas defined (perhaps erroneously) as unisensory. This phenomenon has been reported not only in human subjects (Calvert et al., 2004; Driver & Noesselt, 2008; Ernst & Banks, 2002; Giard & Peronnet, 1999; Macaluso et al., 2000, 2002b;

Schroeder & Foxe, 2005), but also in non-human primates (Cappe & Barone, 2005; Falchier et al., 2002; Rockland & Ojima, 2003) and cats (Binns & Salt, 1996; Stein et al., 2009; Stein & Meredith, 1993; Wallace et al., 1998), and has allowed us to understand that visual, auditory and tactile information are processed in a highly interconnected way right from the first processing steps.

Our understanding of the phenomenon of multisensory or cross-modal integration developed from the first studies on the superior colliculus of cats (Gordon, 1973; Meredith et al., 1991; Meredith & Stein, 1990; Middlebrooks & Knudsen, 1984; Stein et al., 1975, 1976). This structure not only receives information of visual, auditory and somatosensory origin, but manages to integrate these signals giving rise to multisensory maps from spatially overlapping unisensory ones. This characteristic, which seems to be species-independent (Benedetti, 1995; Bizley & King, 2008; Brett-Green et al., 2003; Chalupa & Rhoades, 1977; Dräger & Hubel, 1975, 1976; Graham et al., 1981; King et al., 1998; King & Palmer, 1985; Knudsen, 1982), is due to the existence of neurons specific for a sensory modality but which possess receptive fields in spatial co-registration with other neurons, specific for one (or more) different sensory modalities. These sensory maps are then superimposed on a motor map, thanks to which it is possible to plan movements of the head, eyes or limbs in response to external stimulations. Thanks to these co-registered maps, it is possible to have a detailed description of the surrounding environment and prepare an effective response, regardless of which combination of stimuli has been registered.

These studies have led, over time, to the definition of three fundamental principles of multisensory integration, discovered by comparing the responses of multisensory neurons to multi-modal and uni-modal signals. The first two concern the spatial and temporal aspects of stimulation: cross-modal signals, such as visual-tactile or visual-acoustic stimuli, which come from spatially close sources synchronously or with a very short temporal delay are likely to generate an enhanced neuronal response compared to uni-modal signals. This is a main feature of the multisensory integration. Cross-modal stimuli that instead occur in a more spaced way, spatially and / or temporally, will be more unlikely a source of multisensory activity (Calvert et al., 2004; Kadunce et al., 2001; Macaluso & Driver, 2005; Meredith et al., 1987; Spence & Driver, 2004). The third principle is the inverse effectiveness: the weaker the

cross-modal cues, the greater the super- or sub-additivity of the response due to their integration (provided that the first two space-time principles are respected: Calvert et al., 2000). This means that the absolute magnitude of the multisensory integration phenomenon is inversely (and non-linearly) proportional to the initial intensity of the single integrated signals (Macaluso & Driver, 2005; Stein et al., 2009; but see Leone & McCourt, 2013; Meredith & Stein, 1986b).

These principles underlie the benefits deriving from the multisensory integration process. The cross-modal signals of the environment around us are the most salient stimulations, and those that are co-registered temporally and spatially are most likely produced by the same source. Therefore, it is more parsimonious, in terms of sensory processing, to link these signals to the same source through multisensory integration processes, aimed at planning an adequate response to these stimuli. The third principle supports the first two, as it allows to amplify the intensity of weak (but not less important) cross-modal signals, and thus to foster the integration process (Kadunce et al., 2001; Meredith & Stein, 1986a; Pluta et al., 2011).

1.2 Multisensory integration in the brain

In this thesis, many of the original contributions involve visual-tactile multisensory interaction. After having clarified the neural mechanisms of this process, we will summarize the regions in which the integration between these two sensory modalities takes place, both in the humans and non-human primates.

1.2.1 Simian somatosensation

As often happens, the study of the cognitive processing of sensory signals in humans and monkeys went hand in hand, finding homologies both at the level of the involved brain regions and processes. Particular importance in my thesis is attributed to the perception of tactile and visual stimuli. In the non-human primate's brain, somatosensory stimulations coming from the external environment are first of all processed at the level of the primary (or S1, in the post-central gyrus) and secondary (SII) somatosensory cortices (Burton, 1986; Kaas, 1983; Penfield & Rasmussen, 1950; and see Ruben et al., 2001 for review), even if the distinction between primary and secondary region does not necessarily reflect serial

processing (Rossi-Pool et al., 2021). According to Broadmann's classification, the S1 of primates can be divided into three regions, called 1, 2, and 3 (Brodmann, 1909), subsequently divided into area 3a and 3b by Vogt and Vogt's classification (Vogt & Vogt, 1919). All regions appear to possess somatotopic maps of the contralateral half of the body, whether we consider non-human primates (Kaas et al., 1979; Kaas, 1983; Merzenich et al., 1978; Nelson et al., 1980; Pons et al., 1985; Sur et al., 1980) or humans (Burton et al., 1997; Francis et al., 2000; Gelnar et al., 1998; Kurth et al., 1998, 2000; Lin et al., 1996; Moore et al., 2000). The same was observed for the SII area, located in the upper bank of the lateral sulcus, and more precisely in the region of the parietal operculum: also in this case, electrophysiological studies on the monkey (Krubitzer et al., 1995; C. J. Robinson & Burton, 1980b; Whitsel et al., 1969) and neuroimaging in humans (Disbrow et al., 2000; Francis et al., 2000; Polonara et al., 1999; Ruben et al., 2001) reported neurons with somatotopically organized somatosensory receptive fields.

From these primary somatosensory regions multiple projections towards higher level areas have been identified in the monkey's brain (see Kaas, 2012 for review); the parietal ventral area (PV) is located on the rostral side of SII and forms a second somatotopic representation of the contralateral half of the body (Disbrow et al., 2000; Fitzgerald et al., 2006b), however the receptive fields of its neurons seem to be wider than those of SII. These two regions seem to share several characteristics, such as the response to features of the stimulus such as roughness (Pruett et al., 2000) or its orientation (Fitzgerald et al., 2006a). It has therefore been suggested that these areas could allow the monkey to recognize the size and shape of objects. In addition to important connections with contralateral homologous areas through the corpus callosum, these two regions show projections to areas of the posterior parietal cortex, premotor cortex and insula (Disbrow et al., 2003), where somatosensory information can be further integrated with visual, auditory, vestibular and gustatory signals.
More ventral than these two areas we can find the ventral somatosensory area (VS, Cusick et al., 1989; Krubitzer et al., 1995), in the caudal portion of which it is possible to find bimodal neurons, able to respond to both somatosensory and visuals stimuli (Krubitzer et al., 1995). Finally, in the lower bank of the lateral sulcus, on the border with VS, the caudal medial area (CM) is an important node of convergence of both somatosensory and auditory information (Smiley et al., 2007).

1.2.2 Human somatosensation

Also in humans, an fMRI study revealed the existence of a PV area homologous to the monkey's one (Disbrow et al., 2000). A difference from the latter, however, is that in humans the SII region is often considered to be wider, also including PV, VS and other surrounding areas. As already observed in non-human primates, the somatotopic organization of PV seems to reflect that of the SII area, representing the contralateral half of the body; however, both regions show greater activations in response to bilateral stimuli (Disbrow et al., 2001; Eickhoff et al., 2008). Anterior to PV and connected to it is situated the parietal rostroventral area (PR), activated during body movements and therefore probably involved during the manual exploration of objects (Hinkley et al., 2007). Caudally to the SII area, on the other hand, we find the parietal area 7b, which as we will see better later is a region of multisensory integration capable of responding to visual-tactile stimulations centered on specific parts of the body (Hyvärinen & Poranen, 1974; Jiang et al., 2013; Leinonen et al., 1979; Leinonen & Nyman, 1979).

Finally, there are numerous connections of these somatosensory regions with the insula, which different subdivisions receive multisensory afferent information. The posterior insula, for example, is a multisensory area (Mazzola et al., 2006) which also receives pain-related signals (Afif et al., 2008; Ostrowsky et al., 2002). The anterior insula, on the other hand, thanks to its connections with the frontal cortex, appears to be more involved in motor planning and in the choice of appropriate motor responses (Eckert et al., 2009).

1.2.3 Simian vision

The processing of visual information, in the monkey, follows a fairly serial path that crosses occipital, temporal and parietal areas (see Gattass et al., 2005 for review). The region to which most of the projections of the lateral geniculate nucleus, a fundamental node within the path of visual information from the retina to the cerebral cortex, reach is the striated cortex, or primary visual area (V1), located in the postero-medial occipital lobe. Here the information is still distributed according to a somatotopic organization (Sereno et al., 1994), although a magnification of the fovea is observed (Daniel & Whitteridge, 1961). From here, the information is sent to the V2 area, still at the level of the occipital lobe (Kuypers et al., 1965; Van Essen et al., 1986; Zeki, 1969, 1971), which in turn has back -projections towards

the striated cortex (Gattass, 1997). Here we find wider receptive fields than in V1, and this greater extension increases with the advancement of visual information towards areas of increasing complexity, such as the extrastriate areas V3 and V4 (Zeki, 1971, 1971). In the latter it is even possible to observe multiple representations of the visual field. All these regions have partial or complete representations of the contralateral visual hemifield, but it is starting from area V4 that we begin to observe a representation capable of covering the bilateral visual field. In addition to these areas of the occipital cortex, it is possible to observe projections at different levels towards areas of the temporal cortex, such as the MT area at the level of the superior temporal sulcus (Gattass & Gross, 1981; Van Essen et al., 1981), the TEO area (Gattass et al., 1988) or the temporal ventral posterior area, or DVT (Rosa et al., 1993; Sousa et al., 1991). The MST area, always in the temporal cortex, also receives projections from the striate and extrastriate visual areas, but the level of complexity of the information processed is greater: this area seems to be linked to the detection of stimuli in motion, and therefore needs wide receptive fields, able to cover the entire binocular visual field (Dubner & Zeki, 1971; Van Essen et al., 1981).

1.2.4 Human vision

As in non-human primates, the striate cortex occupies a large part of the posterior pole of the occipital human lobe too, and the neurons that compose it have retinotopically organized receptive fields (Holmes, 1945; Horton & Hoyt, 1991; Tootell et al., 1998). The surrounding extrastriate areas, V2 and V3, also have a retinotopic organization but with a greater representation of the peripheral visual field than V1, where instead the same super-representation of the fovea is found. Starting from these regions, it is possible to distinguish two different streams of visual information processing: a ventral stream, which reaches the temporal cortex areas and is involved in the identification of visual stimuli (the so-called "what stream") and one dorsal stream, which instead reaches the parietal lobe and is involved in the localization of stimuli (“where stream”, Ungerleider, & Mishkin, 1982; see Milner & Goodale, 2008 for review). These two paths end their course at the level of the frontal lobe: the ventral path at the level of the ventral prefrontal cortex, the dorsal path at the level of the dorsal prefrontal cortex (Pandya & Yeterian, 1996). While the ventral stream would be responsible for recognizing objects and faces, their characteristics and selecting

targets for goal-directed actions (the so-called "vision for perception"), the dorsal path would be responsible for planning and implementing such actions, locating the targets and establishing the motor plans to be implemented to act on them (the "vision for action", Goodale & Milner, 1992; see Milner & Goodale, 2008 for review). The subdivision, however, is for descriptive purposes only: broad interconnections are found at all levels of these two different paths, both in monkeys (Felleman & Van Essen, 1991) and humans (Takemura et al., 2016). As noted for monkeys, the further along these streams, the more complex the processing will be (see Slotnick, 2005 for review). As for the ventral pathway, for example, the striated and extrastriate areas project to regions such as the MT + area, homologous to macaque's MST area and dedicated to the processing of moving stimuli (Huk et al., 2002; Tootell et al., 1995; Watson et al., 1993), or the fusiform gyrus, which has sectors that respond specifically to faces or other categories of objects (Chao et al., 1999b, 1999a; Ishai et al., 1999; Kanwisher et al., 1997). More recently, the existence of a third stream of visual information processing has also been revealed, distinct from the dorsal and ventral streams (Pitcher & Ungerleider, 2021) and located more laterally on the brain surface. Thanks to this pathway, visual information is transmitted from the primary visual areas to the superior temporal sulcus (STS), passing through the MT area (see Figure 1.2). This third visual path would seem involved in the elaboration of biological movement, as faces and bodies in motion seem to enhance the responses at the STS level (Beauchamp et al., 2002; Fox et al., 2009; Grossman & Blake, 2002; Pitcher et al., 2011; Puce et al., 1998; Saxe et al., 2004). While the dorsal and ventral pathways would therefore be related to the "where" and "what" of visual perception, this third way would be more involved in the elaboration of the dynamic aspects of social perception (see Allison et al., 2000; and Hein & Knight, 2008 for reviews). This hypothesis is also supported by the fact that the STS, in addition to the visual stimuli of biological movement described, is a multisensory area selectively responding to the human voice (Belin et al., 2004), to language (Binder et al., 1997) and to situations of audiovisual integration of speech (Young et al., 2020).

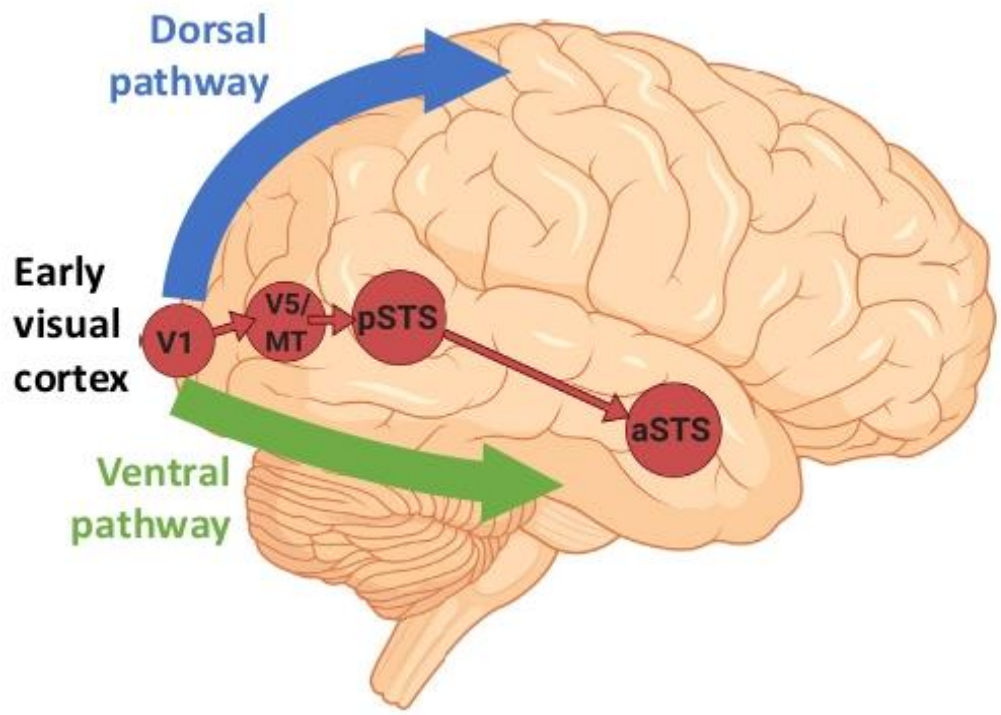

Figure 1.2 *Schematic representation of the three visual streams. They all start from the primary visual areas, but project information along three different white matter pathways. The third, more lateral, visual stream projects from the primary visual areas to the superior temporal sulcus passing through the MT area, which exhibits selective responses to moving stimuli. From Pitcher & Ungerleider, 2021.*

1.2.5 Towards an ever greater level of complexity

Visual areas also project to associative areas in the parietal lobe, such as the ventral intraparietal area (or VIP, Jones & Powell, 1969; Lewis & Van Essen, 2000) in monkeys or within the intra-parietal sulcus (or IPS, Bremmer et al., 2001) in humans, a region of the parietal lobe in which it is possible to find spatially superimposed visual, somatosensory, vestibular and auditory information (Avillac et al., 2005; Bremmer et al., 2001, 2002; Duhamel et al., 1998; Schlack, 2005).

In monkeys, neurons capable of integrating cross-modal signals have also been identified in areas adjacent to the VIP, such as in the lateral intraparietal area (or LIP), capable of integrating visual, auditory and eye-position signals (R. A. Andersen et al., 1997; Gifford & Cohen, 2004; Gross & Graziano, 1995), or in the temporo-parietal junction (or TPJ), on the border between the visual, auditory and somatosensory cortices and capable of integrating

these types of information (Leinonen et al., 1980; Passarelli et al., 2021). Interestingly, the bi- and trimodal neurons of these regions show tactile receptive fields on specific parts of the body and visual and / or auditory receptive fields spatially overlapping with them, protruding a few centimeters in the space around the body. This has led to think that this parietal complex is of fundamental importance for the creation of a detailed map of the body and of the space around it, allowing us to evaluate the spatial relationships existing between external stimuli and our body and thus helping us to plan effective response actions.

Another region in which multisensory integration between visual, somatosensory and auditory signals occurs is the frontal cortex, and in particular the premotor cortex (PM, also called F4 or polysensory zone in monkeys). Electrophysiology studies on non-human primates (Fogassi, et al., 1996; Fuster et al., 2000; Graziano et al., 1994; Graziano & Gross, 1995; Rizzolatti et al., 1981a, 1981b) and fMRI studies on healthy subjects (Bremmer et al., 2001; and see Macaluso & Driver, 2001; Macaluso & Maravita, 2010 for review) have indeed demonstrated the existence in this area of bi- or tri-modal populations of neurons capable of integrating cross-modal signals. Furthermore, these neurons seem particularly sensitive to stimuli approaching the body, thus being able to carry out a defensive function.

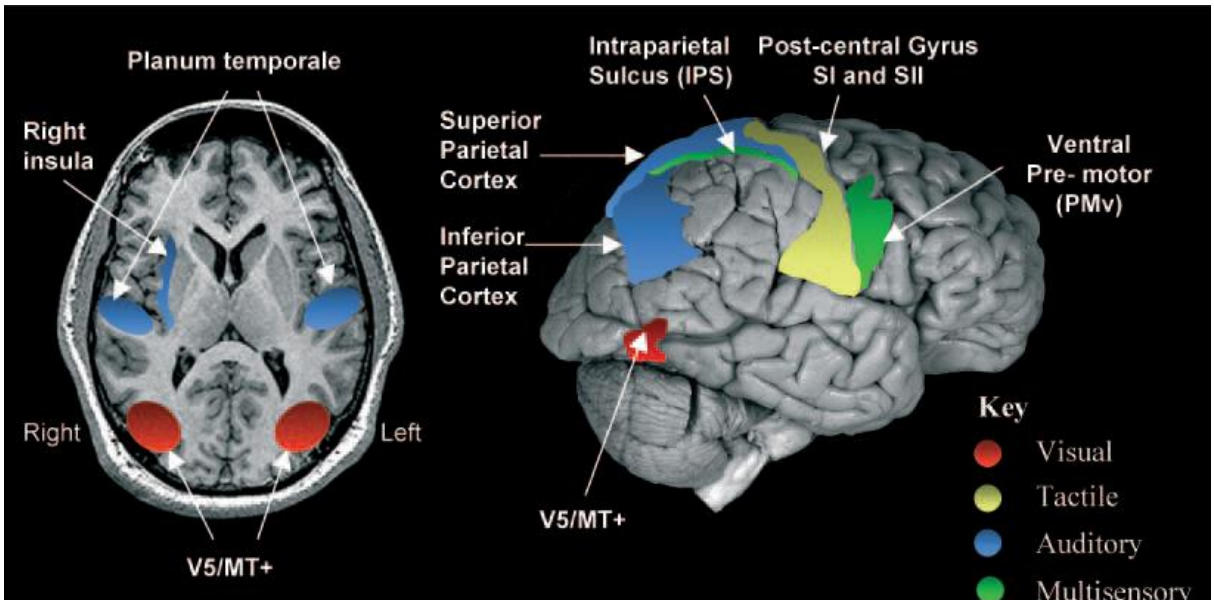

Figure 1.3 *Horizontal section (left image) and right lateral view of a whole brain. The unimodal visual (red), auditory (blue) and somatosensory (yellow) areas and two areas of multisensory integration of these signals (green) are shown in a simplified way: the intraparietal sulcus (IPS) and the ventral premotor cortex (PMv). From Soto-Faraco et al., 2004*

The interconnection between the parietal complex and the premotor region is such as to form an extensive fronto-parietal network which, as we will see later, allows the creation of a representation of the space and objects around us, allows us to constantly monitor the stimuli present in the environment and favors the planning of adequate motor responses.
However, as introduced in the previous paragraph, these so-called associative or high-level areas are not the only ones where visual-tactile multisensory interaction takes place. In fact, multiple studies in humans have identified neural responses to somatosensory stimulations in areas considered to be related only to the processing of visual information (Amedi et al., 2001; James et al., 2002; Macaluso et al., 2002a, 2002b, 2005; Pietrini et al., 2004; Sathian et al., 1997; Sathian & Zangaladze, 2002; Zimmer & Macaluso, 2007). Similarly, numerous evidence can be found in the literature regarding the presence of visual responses in low-level areas of somatosensory information processing, both in monkeys (Cappe & Barone, 2005; Zhou & Fuster, 2000) and humans (Macaluso & Driver, 2005; and see Eimer & Driver, 2001 for review). This therefore demonstrates that, even at an early level of information processing, the different transmitted signals are not treated in a completely distinct way.
In addition to these multisensory responses in "unisensory" areas, it is necessary to consider that the distinction between cortices with predominantly unisensory responses is not so clear: Wallace and colleagues have demonstrated the existence in rat's brain of patches of neurons on the border between visual, auditory and somatosensory areas which are not only able to respond to stimuli of different modalities, but are also able to integrate these signals (Wallace et al., 2004). Then, neurons on the border between the visual and auditory cortex showed increased or inhibited responses when stimuli of these modalities were presented simultaneously. However, the proximity of these patches to the unisensory areas does not seem to be the only factor determining the multisensory response: in human superior temporal sulcus (STS), located between auditory and visual areas, responses to somatosensory stimuli are observed, which therefore do not follow the rule of proximity (Beauchamp et al., 2004).

If the multisensory integration at the level of the associative areas can be explained through a phenomenon of convergence of multiple unimodal signals, from lower level areas towards an ever greater level of integration (Figure 1.4A), this mechanism cannot explain the presence of multisensory responses at the level of the purely visual, auditory or

somatosensory cortices. Areas such as the superior colliculus, the parietal complex, the superior temporal sulcus or the premotor cortex show indeed an amplified response to multisensory stimuli thanks to direct projections from different unisensory areas. For low-level areas, on the other hand, two possible mechanisms have been described. The first one is based on the existence of direct projections between the primary sensory areas (usually considered as the occipital areas for sight, the post-central gyrus region for somatosensation and the superior temporal region for hearing): once cross-modal stimuli are perceived separately, the information would not be transmitted only vertically, towards the associative areas, but also horizontally, between the low-level ones (Figure 1.4B). This hypothesis has been supported by evidence from both monkeys (Falchier et al., 2002; Fu et al., 2003; Lakatos et al., 2007) and humans (Foxe et al., 2000; Giard & Peronnet, 1999; Molholm et al., 2002; Murray et al., 2005). The second mechanism is a retrograde feedback: the associative areas, in addition to integrating the cross-modal signals received through feedforward convergence paths, can also influence the activity of the "unimodal" areas through back-projections (Figure 1.4C, Calvert et al., 1997; Kennett et al., 2001; Macaluso et al., 2000; Sams et al., 1991; Vroomen & Gelder, 2000; and see Driver & Spence, 2000 for review). Influences of this type could explain some behavioral effects observable in case of mismatch between cross-modal information, as in the case of the McGurk effect (Mcgurk & Macdonald, 1976), ventriloquism or rubber hand illusion (Botvinick & Cohen, 1998), which we will describe below in detail.

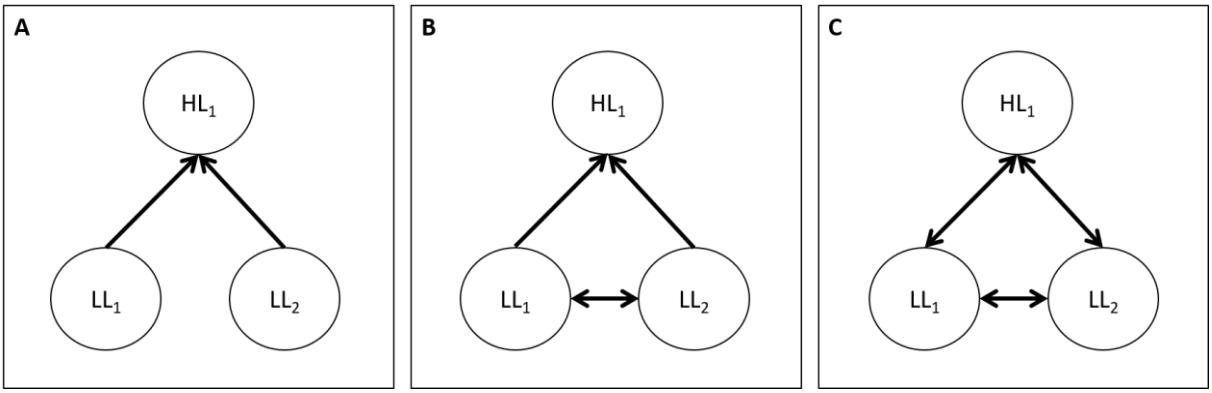

Figure 1.4 *Schematic representation of A) a process of feedforward convergence of unisensory signals, from low-level areas (LL) to high-level areas (HL); B) a process of direct horizontal communication between unisensory areas; C) a retrograde feedback process, in which low-level areas project to associative areas, as well as horizontally, and receive feedback influences from those higher-level areas.*

Considering what is described in these paragraphs, it is difficult to consider a region of the cerebral cortex as purely unisensory. However, the question remains open about the very definition of a multisensory brain region. When can a region be defined as "multisensory"? What distinguishes a high-level region from a low-level one? As the studies just mentioned have shown, this may not depend only on the presence or number of multisensory neurons, as often we do not know the real extent of multisensory patches and probably no area of the neocortex is truly unisensory (Ghazanfar & Schroeder, 2006). Waiting for future developments of this literature, with a possible turning point in the nomenclature, it is possible to consider "multisensory" those areas of the cortex in which the enhancement or suppression of the neural response for cross-modal stimuli is a predominant feature (Meredith et al., 2020).

1.3 Behavioral effects of multisensory integration

Multisensory integration, as we have already seen, is a ubiquitous phenomenon in our daily life. This has therefore generated a strong interest in studying its behavioral effects, focused above all on those situations in which the cross-modal stimuli presented are in conflict or inconsistent with each other: it is in this framework that illusions are generated. In these situations of perceptual incoherence is possible to better understand how the processing of perceptual information takes place: when multiple signals, inconsistent with each other, reach our brain, our normal perception is misled, pushing us to see, hear or feel something that goes beyond mere received signals. This shows that what we perceive is not a direct representation of what surrounds us, but rather the result of a computation and a cognitive process. The inconsistency between the signals and the illusions allow us to understand something more about how this process occurs.

One of the illusions that are before our eyes every day, even if unconsciously, is the so-called "ventriloquist effect", in which the perception of the spatial position of an auditory stimulus is altered to make it consistent with that of a visual stimulus positioned elsewhere (Driver, 1996; Spence & Driver, 2000; and see L. Chen & Vroomen, 2013 for review). Thanks to this phenomenon, we can go to the cinema or watch television and have the feeling that are the actors themselves who produce the words we hear, rather than the speakers. Although television, cinema or a ventriloquist's puppets are the most striking examples, this effect

also occurs in the case of less salient cross-modal stimuli at the cognitive level: simple light flashes associated temporally (but not spatially) with auditory stimuli can "capture" the sounds, giving the illusion that they come from the spatial position occupied by the flash itself (Lewald & Guski, 2003). Obviously, the illusion is stronger the more the stimuli are spatially and temporally coherent: by increasing too much the distance between the sources of stimulation the effect is reduced, as well as by introducing a delay between the auditory and visual onset (Lewald & Guski, 2003). This illusion could be generated by the fact that vision, being more spatially precise, dominates hearing when the two perceived stimuli are synchronous but spatially incompatible (Alais & Burr, 2004; however, this illusion may not only be due to multisensory integration: Bertini et al., 2010). A "moving" version of this illusion has already been found: having to judge the direction in which an auditory stimulus moves, we are misled if a visual stimulus is presented synchronously to it, but moving in the opposite direction (Soto-Faraco et al., 2004, 2004c). Confirming the idea of a possible dominance of vision over hearing, the opposite effect with moving stimuli does not occur (but see Alais & Burr, 2004). The same research group also tested a version of the latter illusion, but using auditory and tactile stimuli: the judgment of the direction of movement of an auditory stimulus is influenced by the direction of movement of an irrelevant tactile stimulus and vice versa, with a stronger effect of somatosensation on hearing (Soto-Faraco et al., 2004b). This is not the only case of illusion due to integration between acoustic and somatosensory signals: in the parchment-skin illusion, artificially altering the sound produced by the rubbing of the hands, it is possible to observe an alteration of the tactile perception concerning the roughness and the dryness of the palmar skin (Jousmäki & Hari, 1998). As with many other cases of illusion, however, these effects are strongly influenced by the synchrony between the stimuli.

A case in which, more than a dominance of sight over hearing, there seems to be an integration between the two signals is the so-called McGurk effect (Mcgurk & Macdonald, 1976; Saint-Amour et al., 2007). In this illusion there is a fusion between the incompatible visual and auditory signals to create a new percept, different from both starting signals. From the auditory perception of the syllable "*ba*" during the visual perception of a mouth that pronounces the syllable "*ga*", the result is the perception of the syllable "*da*". Even being aware of this mismatch between stimulations, we cannot avoid the illusion, which

seems to arise even before attentional control, at an unconscious level (Soto-Faraco et al., 2004d). However, multisensory integration may not be the only factor behind this illusion, which would require the activation of brain areas usually related to conflict resolution (Fernández et al., 2017). Contrary to what has been observed for the ventriloquist effect, therefore, the two sensory systems seem to interact with each other, rather than dominate, and this therefore suggests that the relationship between visual and auditory perception depends also on the context and not only on the intrinsic characteristics of the stimulus.
Furthermore, the opposite case was also observed, with an apparent dominance of hearing over vision. This is the case of the double flash illusion (or sound-induced flash illusion): a single flash is perceived as double if it is temporally accompanied by two closely spaced auditory stimuli (Mishra et al., 2007; Shams et al., 2000, 2005; and see Hirst et al., 2020; and Keil, 2020 for review). In this case, therefore, it seems to be hearing that dominates vision. To understand why this happens, it is possible to summarize what is stated by the information reliability hypothesis, which proposes the dominance of the modality providing the most reliable information (T. S. Andersen et al., 2004). In the double-flash illusion, the auditory system reports a better temporal resolution than the visual one, and therefore the auditory modality is the most reliable, dominating visual perception. Finally, a version of this illusion has also been reported using tactile stimuli instead of auditory distractors: in the tactile double flash illusion the effect of "doubling" the visual stimulus is still observed in the presence of two tactile distractors (Servos & Boyd, 2012; Violentyev et al., 2005).

One of the behavioral effects of multisensory integration investigated first, which we will later explore in detail, concerns the response speed: cross-modal stimuli often induce faster responses than those observed in the case of unisensory stimulations (Hughes et al., 1994). This type of effect has been replicated over time and adapted to very different paradigms, such as discrimination tasks. An exemplary case is that of the cross-modal congruency task, through which the illusion of visual-capture of touch has been reported and studied. In this task, participants have to focus on the tactile stimulus applied to the index or thumb of both hands, kept hidden from view; their goal is to discriminate stimulations on the index ("up") from those on the thumb ("down") as quickly as possible. At the same time, a visual distractor, completely task irrelevant, is displayed in an either congruent (higher when the tactile stimulation is on the index finger, lower when it is on the thumb) or incongruent

position (the opposite pattern), corresponding to that of the stimulated hand or in the position of the opposite one. Pavani and colleagues observed that this distractor is able to influence performance, slowing down the response in case of incongruent stimulation, especially when the visual stimulus is presented near the stimulated hand (Pavani et al., 2000). This visual-capture of touch therefore appears to be the parallel of the ventriloquist effect, but involving visual and tactile stimuli, which are mis-localized due to the visual distractor. Furthermore, the existence of an "auditory" version of this illusion has also been reported, using congruent or incongruent sounds as distractors and showing the same effects (Aspell et al., 2010), but also in the opposite direction: using tactile stimuli as distractors, sounds are mis-localized, towards the source of tactile stimulation (Caclin et al., 2002).

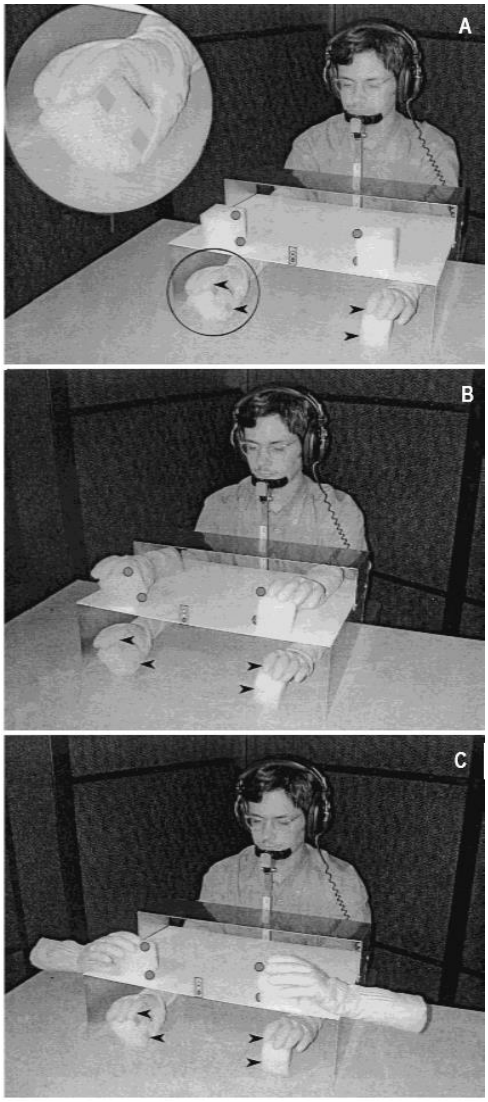

Figure 1.5 *Photographs representing the protocol used by Pavani and colleagues for the study of the "vision capture of touch" illusion. Black arrows indicate tactile stimulators, while visual distractors are represented by small gray circles. Participants had to fix the central point of fixation while discriminating the height of the tactile stimulus and ignoring the visual distractor. The setup is represented in the three experimental conditions A) fake hands absent; B) fake hands present and spatially compatible with the posture of the subject; C) fake hands present but spatially incompatible with the posture of the subject. From Pavani et al., 2000*

A very particular aspect of the visual-capture of touch reported by Pavani and colleagues is the fact that the strength of the illusion increases if the visual distractors are "held" by two fake rubber hands, but this effect only emerges if they are in a posture compatible with that of the participant's hands (Figure 1.5B), although subsequent studies have shown that direct viewing of these hands is not essential (Austen et al., 2004). By changing their posture (Figure 1.5C), this fake hand effect disappears (Pavani et al., 2000).

Considering these findings, it seems plausible to affirm that the multisensory information available during these tasks is used to integrate the fake hand within the body image, which we could simplistically define as the set of perceptions and sensations regarding the structure and the appearance of one's own body.

This is neither the only nor the first case in which an “external” hand to the body is illusory perceived as part of one's body: since the early 60's it is possible to find studies in which, through different experimental procedures, an outer limb is incorporated into the body representation, producing varied behavioral results (Nielsen, 1963).

One of the best-known and most studied cases of visual-tactile integration capable of producing alterations of the body representation is certainly the rubber hand illusion (Botvinick & Cohen, 1998; Ehrsson et al., 2008; Farnè et al., 2000; Kammers et al., 2009; Tsakiris & Haggard, 2005; van Stralen et al., 2013). In this illusion, the participant places his hand on the table, hidden from view, and a rubber hand is placed in front of him, in a posture compatible with that of his real arm (see Figure 1.6). The only visual information available to the subject is therefore that relating to the fake hand. At this point, the experimenter begins to rub the real hand and the fake hand with a brush, in a synchronous and spatially compatible way. After a few seconds, participants experience (typically to various extents) the illusion that the fake hand is actually their own hand, that it is part of their body, due to the integration between the only visual information available and the somatosensory information of the stroking. This effect does not emerge if the visually and tactually perceived strokes are asynchronous. When instantiated, the illusion is so powerful that even being aware of what will happen it is enough to avoid it. There are several effects, and thus measures, of the RHI. One effect is the proprioceptive drift: if after the establishment of the illusion the subject is asked to indicate the position of his/her real index finger, for example, he/she will tend to estimate a position shifted towards the fake hand. Other reported effects are the strong sensation that the fake limb is part of one's body, measured through questionnaires, or physiological responses, such as a sudden increase in

Figure 1.6 *Representation of a typical setup for the study of rubber hand illusion. From Kammers et al., 2006*

skin conductance (a signal of fear) when the fake hand is threatened (Ehrsson et al., 2008). The illusion was not found only using a fake "material" hand, but also using a virtual version of it (Caola et al., 2018; IJsselsteijn et al., 2006; Slater et al., 2008; Zanini et al., 2017), and all this is not limited only to the upper limb: there are now numerous studies that report the so-called full body illusion (Lenggenhager et al., 2007; Petkova & Ehrsson, 2008), in which the effect is extended to the whole body, or enfacement (Sforza et al., 2010; Tsakiris, 2008), in which the sense of body ownership is extended to an external face. Furthermore, this illusion is not limited to humans, as a similar protocol could also deceive macaques (Graziano et al., 2000) and mice (Wada et al., 2016), suggesting that body ownership is not an exclusively human concept.

Over time, numerous variables that can influence this embodiment have been explored: the type of fake hand (Caspar et al., 2015), the distance between the stimulated body part and the fake body part, the number of rubber hands used (Folegatti et al., 2012), the compatibility of the fake limb posture with that of the real limb (Costantini & Haggard, 2007). One of the elements that certainly strengthens the sense of illusion is the similarity between the fake hand and the real one, but this similarity is not strictly necessary to generate the illusion of ownership. There are indeed no many doubts about the fact that a tool, while not resembling a hand, can be incorporated and modify the body image: many evidences show the similarity between the processing of the properties of a tool and those of one's own upper limb (Heed, 2019; Martel et al., 2016; Miller et al., 2018, 2019). Studies in the literature also show that it is possible to induce the RHI simply by using colored balloons that change in size and move synchronously with the movements of the real hand (Ma & Hommel, 2015). It therefore seems possible to affirm that even an object not resembling a hand can be incorporated into one's body representation. However, multiple evidence show that it is not possible to induce the illusion of ownership by using static balloons (Kalckert et al., 2019) or wooden blocks, even if shaped as a hand (Tsakiris et al., 2009). The debate regarding the possibility of incorporating objects not resembling one's hand into one's body representation is therefore still open, due to such conflicting results. However, is it possible that, in order to modify the representation of one's body, a functional similarity is more important than an anatomical similarity?

The toolish hand illusion: Embodiment of a tool based on similarity with the hand

(Scientific Reports, 2021)

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The toolish hand illusion: embodiment of a tool based on similarity with the hand

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A tool can function as a body part yet not *feel* like one: Putting down a fork after dinner does not feel like losing a hand. However, studies show fake body-parts are embodied and experienced as parts of oneself. Typically, embodiment illusions have only been reported when the fake body-part visually resembles the real one. Here we reveal that participants can experience an illusion that a mechanical grabber, which looks scarcely like a hand, is part of their body. We found changes in three signatures of embodiment: the real hand's perceived location, the feeling that the grabber belonged to the body, and autonomic responses to visible threats to the grabber. These findings show that artificial objects can become embodied even though they bear little visual resemblance to the hand.

Our body is the means through which we interact with the external world. Little would a brain achieve without a body to execute its commands and collect information about the environment through the sensory channels. Yet our body is not just any kind of input/output machine that executes actions and provides feedback. We have a "very special regard for just one body", such that each seems to "think of it as unique and perhaps more important than any other"[1] We are not simply aware of one body; we are aware of it as being *our own* body (i.e. we have a sense of bodily ownership)[2].

Throughout evolution, interactions with the environment have become more and more complex and mediated by objects that humans built and used to overcome the limitations of their bodies. Tools expand motor capabilities and allow actions that would otherwise be dangerous or impossible. There is now little doubt that tools can be incorporated: many of their properties are processed in the same way as the properties of one's limbs[3–5]. But bodily ownership is that and more[6]. It requires experiencing tools as constitutive parts of one's own body. Though we manipulate dozens of tools during the day, could we actually feel that a fork, a toothbrush or a screwdriver belong to us in the same way our hands do? Here we investigate whether a tool can be processed as a body part not only at the spatial level (localization), but also at the physiological level (response to threats), and at the phenomenological level (feeling of ownership). For each measure, we assess the additional impact of motor experience with the tool.

Previous studies show that even ten minutes of tool-use can deeply modify the representations of both the body and the space around it[7–15]. For example, when using a long grabber tool to retrieve objects, the arm representation is updated to reflect the functional elongation of the effector. Similarly, when using pliers, digit representations change to take into account the new morphology. Tool use also modifies the visual properties of peripersonal space, recoding far space as nearer[12,16,17], and enhancing the defensive monitoring of such space[18]. However, while these previous studies showed that tool use affects sensorimotor and spatial representations, they did not address whether it affects body ownership, that is, whether using a tool makes it *feel* more like a part of one's own body.

Although we seem to have little doubt about the boundaries of our own body, it has been shown that it is relatively easy to induce the illusion of owning external fake body parts. This line of research originated with the seminal paper by Botvinick and Cohen describing what is now known as the Rubber Hand Illusion (RHI)[19]. In

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the RHI, participants are brushed on their (hidden) hand while they see a fake hand being stroked in synchrony. The temporal congruency between what is felt on their own hand and what is seen on the fake hand leads the subjects to report that the fake hand belongs to them.

Despite the ease with which such an important change in self-perception can be induced (from just a few seconds of brushing), the illusion arises only under certain conditions. First, the real and fake body parts must be synchronously brushed; introducing a delay drastically decreases the intensity of the illusion[19,20]. For this reason, asynchronous brushing has become the gold-standard control condition, even though caution is necessary in interpreting significant synchronous vs. asynchronous differences (see below). Second, the fake limb must have a posture compatible with that of the real limb, be anatomically plausible, and appear connected to the body, suggesting that the illusion is not the mere result of a multisensory integration process between what is seen and what is felt, but is also modulated by higher-level representations of body structure[21,22]. Moreover, although a discrepancy always exists between the position of the real and fake hands in the RHI setup, the vividness of the illusion decreases the further away from the body the fake hand is placed[23]. Finally, and of most relevance here, the visual resemblance between the real hand and the other brushed object has been said to be crucial. The illusion can be induced using a fake hand that is not identical to the participant's hand (e.g., using a rubber hand that is larger or has a different skin tone) and even to transplanted hands, prostheses, and virtual avatars[6,24–26]. However, previous studies reported the illusion could *not* be induced for objects such as wooden blocks, even those shaped like hands[27,28]. It has thus been assumed that a close visual resemblance to the body part is necessary for the sense of ownership, thus preventing tools to be felt as parts of one's body[29,30].

This claim, however, is controversial and has been addressed in both healthy and clinical populations. First, a sense of ownership may be reported in healthy participants for a virtual effector controlled by the subject[31] or merely a virtual balloon changing in size and color in synchrony with the movements of the participant's hand[32]. Yet, more recently Kalckert and colleagues[33] showed no illusion for a static balloon. In their study, they compared the illusion induced for a fake hand with the one induced for a balloon, as in the original study, using two measures: proprioceptive drift and a questionnaire. They observed a significantly stronger illusion when a fake hand was brushed compared to when a balloon was, as indicated by proprioceptive drift of the real hand toward the fake one (vs. the balloon). They also agreed with questionnaire statements about ownership of the fake hand and feeling touch referred to the fake hand, with such ratings being stronger for asynchronous than synchronous stroking. Although the balloon condition also elicited a *difference* between synchronous and asynchronous condition in the questionnaire, the absolute ratings did not reflect a sense of embodiment even with synchronous brushing. That is, on a Likert scale from 3 = 'strongly agree' to − 3 = 'strongly disagree' where 0 = neutral, scores for the balloon were never significantly higher than zero[34].

Taken together, the evidence suggests that objects that resemble the hand—but not those that do not—can become embodied. But what if one important factor is not visual resemblance but *functional* resemblance[35]? Perhaps what matters for the sense of ownership may be what an object can *do* rather than what it *looks* like. Evidence from special populations suggests that functional resemblance could be a key factor. Although patients with severe degenerative arthritis may still perceive a visually distorted hand as their own, amputees may feel a cosmetic prosthesis as extraneous despite its visual similarity to a real hand[36,37]. This may relate to the reasons why patients with somatoparaphrenia deny that their own hand belongs to them. They usually present with proprioceptive deficits and the so-called 'alien' hand is, in most although not all cases, generally paralyzed[38]: it can no longer either sense or do what the limb normally does. The functional criterion is in line with the hypothesis according to which one experiences as one's own any part that is incorporated into the body schema, that is, into the sensorimotor representation of the body used for action[24].

To test whether functional similarity is sufficient for embodiment, previous studies used active paradigms where the illusion was induced not by synchronous brushing, but rather by synchronous movement of the participant's hand and an object. These studies[18,31,39] show that such versions of the illusion can induce changes in action-related body parameters like perception of body location or ownership of a movement (agency), but other aspects of the illusion such as the conscious feeling of ownership, were not present. These results confirm that the illusion is a multilayered phenomenon that cannot be captured in its entirety by one single task. Importantly, since they did not use tools, they leave unanswered the question of whether tools can be embodied before being incorporated (i.e., before tool-use).

Because tools occupy such a pervasive place in human life, we hypothesized that it may be possible to induce the illusion that a tool is part of one's own body even though the illusion has previously failed with other visually dissimilar objects. We further predicted that motor experience with the functional properties of the tool would modulate the expression of the illusion. Moreover, given the multifaceted nature of embodiment, we designed a series of studies to assess the three aspects of embodiment.

First, we applied the classic RHI paradigm by brushing the index finger of the occluded right hand of participants while they were looking either at a mechanical grabber tool being brushed or a balloon (as a control object, Experiment 1). Then, in Experiment 2 we replicated the experiment using only the grabber tool, but introduced an asynchronous condition and an active period of tool use to test the role of motor experience with the tool. Finally, in Experiment 3, we tested whether the illusion was observable via physiological responses. We measured the presence of the illusion with three different tasks (Fig. 1): (1) proprioceptive drift (to determine whether the real hand was perceived as closer to the tool after the illusion was induced), (2) a questionnaire regarding the conscious sense of ownership in (Experiment 1 and 2); and (3) a measure of arousal (Skin Conductance Response, SCR[18,40]) to a threat toward the tool in Experiment 3. Each task assesses one aspect of embodiment, defined as: "Embodiment: E is embodied if and only if some properties of E are processed in the same way as the properties of one's body"[6]. In particular, one of those aspects is the conscious feeling that our body belongs to us (ownership), which can be assessed with questionnaires. A second aspect is the feeling that we are where

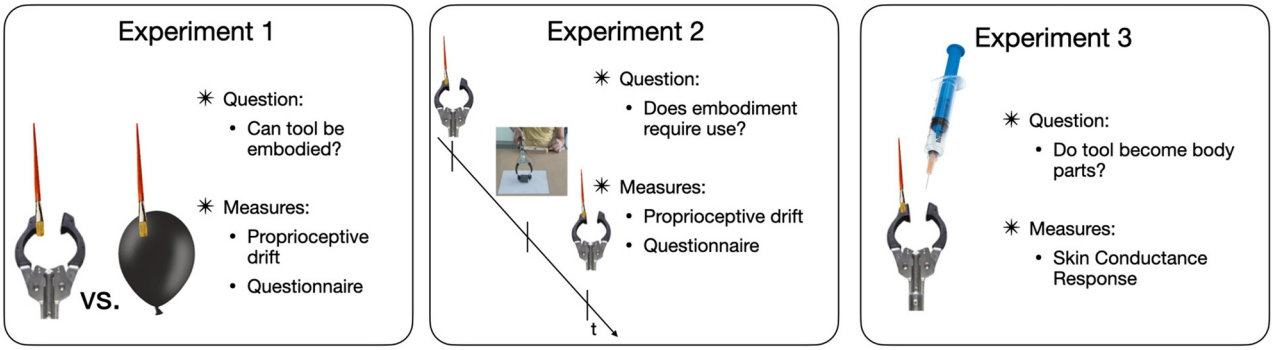

Figure 1. Study summary. Experiment 1 (N = 16) aimed to assess whether embodiment for a tool can be induced with an RHI-like setup. As a control, we used a balloon as in Ma and Hommel, 2015. We measured brushing-induced proprioceptive drift of the index finger and subjective feelings of embodiment using a questionnaire. Experiment 2 (N = 40) tested tool embodiment in a larger sample and investigated the role of functional use of the tool. The same measures as in Experiment 1 were used. Experiment 3 (N = 32) investigated the physiological correlates of embodiment, measuring skin conductance responses after threat to the embodied tool.

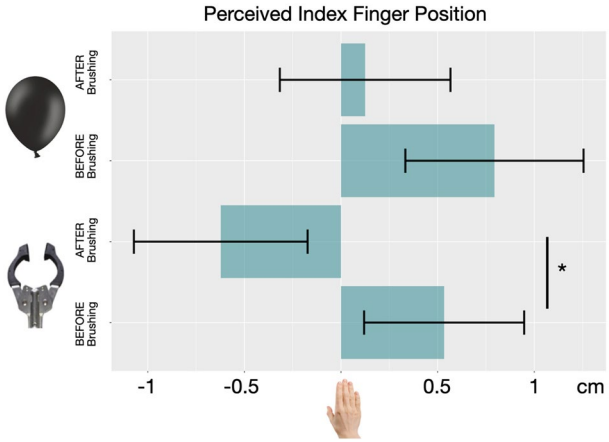

Figure 2. Perceived index finger position. In experiment 1, after 2 min of synchronous brushing, participants (N = 16) localised their index finger drifted toward the tool. The same participants did not show significant drift after synchronous brushing of the balloon. Error bars indicate 95% C.I.

our body is (which we address here with the proprioceptive drift, a measure derived by the judgement of one's position in space). The third aspect is the physiological correlates of embodiment, measured with SCR.

In addition, we examined whether there was a perceived relationship between the digits of the hand and the prongs of the tool and if it was affected by using the tool. Typically, the tactile version of the RHI is digit-specific[41]; that is, it only occurs if the same digit of the rubber and real hand are stroked. However, since the grabber tool we used here only has two "digits" (prongs), it is not immediately clear how these would be perceived to correspond to the digits of the real hand. The correspondence could be based on visuospatial matching (e.g., whether the digit is on the left or right) or functional equivalence (e.g., whether the digit functions like a thumb or an index finger). To test this, during the brushing phase of Experiment 2, half of the participants observed the tool being brushed on its left prong while the other half saw the tool being brushed on its right prong and induction of the illusion occurred twice: once at the beginning of the session and once following a short period of tool use.

Results

Experiment 1. 16 participants took part in this study (8 females, 1 left handed; age range 18–40). Participants gave written informed consent and received monetary compensation (15€).

Proprioceptive Drift. As shown in Fig. 2 the index finger of the real hand was localized significantly closer to the tool after synchronous brushing; however, there was no significant effect drift toward the balloon. Specifically, a repeated-measures ANOVA with Object (Tool vs. Balloon) and Phase (Before vs. After Brushing) as within-subjects factors revealed a significant interaction between Object and Phase ($F = 8.747$, $p = 0.01$, $\eta^2 = 0.385$). Although there was a main effect of Phase ($F = 4.740$, $p = 0.04$, $\eta^2 = 0.253$), it was driven largely by the tool condition.

Moreover, when comparing drift amplitude (finger localization pre-brushing—finger localization post-brushing) against zero (i.e., testing for the instantiation of an illusion), we found a significant difference for the tool

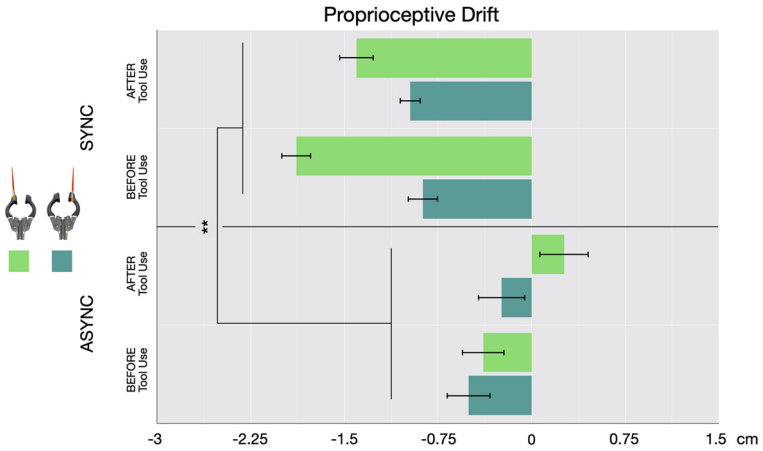

Figure 3. In Experiment 2, participants (N = 40) perceived their index finger drifted toward the tool only after synchronous (upper panel), but not after asynchronous (lower panel), brushing. Error bars indicate 95% C.I.

condition (1.2 cm; t = 2.10, $p = 0.04$) but not the balloon (0.6 cm; t = 1.69, $p > 0.05$;). Finally, 63% of participants experienced an illusion (as defined by drift > 0.5 cm) with the tool compared to 37% for the balloon.

Questionnaire. Data from the questionnaire were in line with results from the proprioceptive drift task and supported the presence of illusory embodiment for the tool, but not the balloon. Separate two-tailed t-tests revealed a significant difference between tool and balloon condition for four questions, concerning touch localization and ownership (Q1. "It felt as if the touch I was feeling was caused by the paintbrush touching the tool/balloon": t = 2.981, $p = 0.01$, d = 0.770; Q2. "It seemed like I was feeling the touch in the location where I saw the tool/balloon being touched": t = 2.335, $p = 0.03$, d = 0.603; Q5. "I felt as if the tool/balloon were my hand": t = 2.315, $p = 0.03$, d = 0.598; Q6. "I felt as if my hand began to resemble the tool/balloon in its posture: t = 2.884, $p = 0.01$, d = 0.745). For all the remaining control questions p values ranged between 0.10 and 0.80.

Experiment 2. We ran a second experiment (N = 40; 22 females, 2 left handed, age range 19–40 yo) to replicate the illusion on a separate sample of participants and investigate the role of motor experience on the different components of the illusion.

Proprioceptive drift. As shown in Fig. 3, proprioceptive drift was strongest when the tool was stroked in synchrony with hand, particularly when the left prong of the tool (compared to the right) was stroked. Specifically, an analysis of variance (ANOVA) for proprioceptive drift with three factors—Timing (Synchronous vs. Asynchronous Brushing) * Phase (Pre- vs. Post-Tool Use) as within factors and Tool Prong (Left vs. Right) as between factors revealed a main effect of Timing (stronger illusion for synchronous vs. asynchronous brushing ($F = 17.919$, $p < 0.001$, $\eta^2 = 0.131$)) as well as a significant interaction of Timing*Tool Prong ($F = 4.205$, $p = 0.04$, $\eta^2 = 0.031$; Fig. 3). Post-hoc t tests revealed that, while both groups showed higher drift for the synchronous compared to the asynchronous condition, the difference was greatest when the left prong of the tool was stroked. No significant difference was found between the two groups (1st prong group and 2nd prong group) when they both received synchronous stimulation (t = − 1.50; d = − 0.24; $p = 0.3$).

Tool use did not significantly affect the drift, as we observed a tendency for the drift to decrease after tool use (Phase: $F = 4.27$, $p = 0.07$, $\eta^2 = 0.012$), but only for the group who saw the tool being brushed on the first prong (Fig. 3).

Questionnaire. Multiple responses to the questionnaire indicated a significant degree of embodiment for synchronous stimulation, which was stronger than asynchronous stimulation. Specifically, we ran an ANOVA with Timing (Synchronous vs. Asynchronous) * Question (Q1 to Q14) * Tool Use (Before vs. After) as within factors and Tool Prong (First vs. Second) as between factor. We found a main effect of Timing ($F = 53.015$, $p < 0.001$, $\eta^2 = 0.097$) showing that participants' scores were higher (i.e. where more in agreement with a sense of embodiment) after synchronous stimulation. We also found a main effect of Question ($F = 9.846$, $p < 0.001$, $\eta^2 = 0.06$) and, crucially, a significant Timing*Question interaction ($F = 13.635$, $p < 0.001$, $\eta^2 = 0.04$). Post hoc tests revealed that six questions received higher scores in the synchronous condition compared to the asynchronous condition, including the four questions that were significant in Experiment 1 (Q1. "It felt as if the touch I was feeling was caused by the paintbrush touching the tool": t = 7.217, $p < 0.001$, d = 1.141; Q2. "It seemed as if I was feeling the touch in the location where I saw the tool being touched": t = − 9.97, $p < 0.001$, d = − 1.58; Q3. "It seemed as if I the touch I was feeling originated from a location between my hand and the tool": t = − 4.48, $p < 0.001$, d = − 0.71; Q5. "I felt as if the tool were my hand": t = − 4.90, $p < 0.001$ d = − 0.77; Q6. "I felt as if my hand began to resemble the tool/balloon in its posture: t = 2.884, $p = 0.01$, d = 0.745; Q14. "I felt as if the tool were part of my body": t = − 5.64, $p < 0.001$, d = − 0.89; all p values Bonferroni corrected; Fig. 4). Additionally, we compared scores from the significative questions to "0" (corresponding to a value of 5) and found that only Q1 and Q2 were significantly higher (respectively Q1: t = 3.34, $p < 0.001$, d = 0.53; Q2: t = 1.9, $p < 0.04$, d = 0.30) and only in the Synchronous condition. All other scores where not significantly different than 0 while all items of the Asynchronous condition scored significantly lower than 0. (all $p < 0.001$).

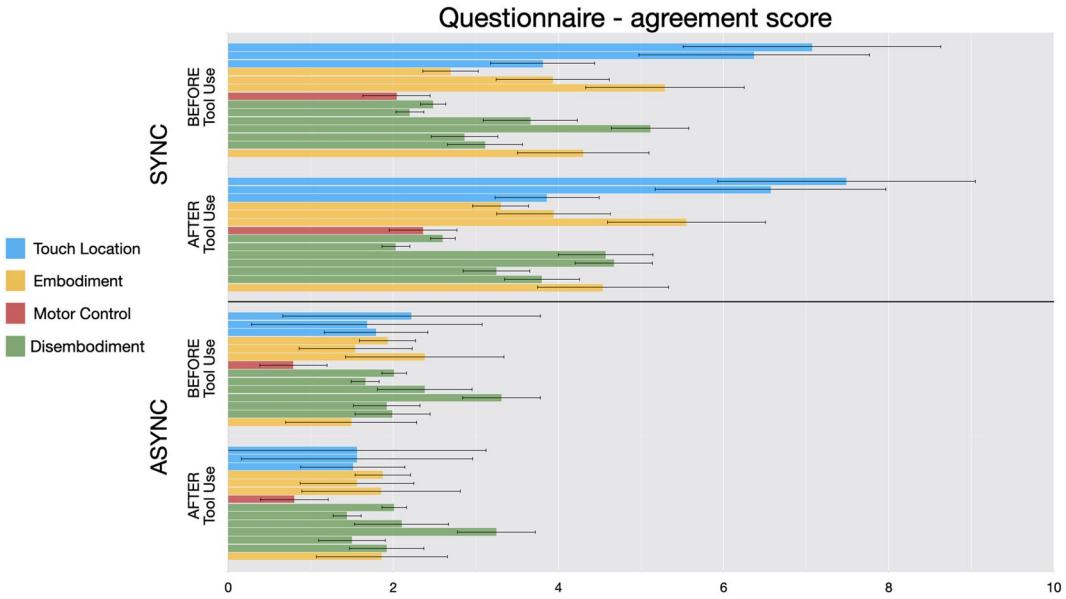

Figure 4. In Experiment 2, participants (N = 40) showed higher agreement for statement regarding changes in perceived touch location (Q1, Q2 and Q3 – light blue bars) and tool embodiment (Q5, Q6 and Q14 – yellow bars) after synchronous stimulation only. Error bars indicate 95% C. I.

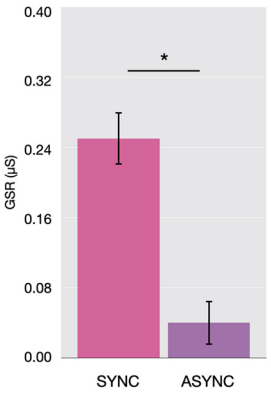

Figure 5. In Experiment 3, participants (N = 32) showed a Galvanic Skin Response to the threat of the tool after it was brushed synchronously, but not asynchronously, with their own index finger. Error bars indicate 95% C.I.

Experiment 3. Experiment 3 (N = 32, 16 females, age range: 18–30 yo) was conducted to test whether proprioceptive drift and tool ownership responses reported above were also accompanied by physiological reactions that would support the idea of the tool being embodied. We recorded SCR while threatening the tool with a syringe after one minute of synchronous or asynchronous brushing. We found that participants showed a higher SCR after synchronous brushing of the hand and the tool compared to asynchronous brushing (0.25 vs. 0.04 μS; Fig. 5). However, we did not find any significant effect of experience with the tool, as the SCR did not change after tool use. Note that while the tool is threatened, the real hand is occluded by a wooden board and is 17 cm away from the tool and the syringe and thus in no 'real' danger. Moreover, the type of threat we used (the needle) was not actually potentially dangerous for the tool (while it could have been for the hand), which could explain why the SCR values we observed are smaller than in previous studies[42].

Conclusions

Here we report the first demonstration that it is possible to induce an illusory sense of ownership over a non-biological object, namely a mechanical grabber tool, that shares functional but not visual similarity with the hand. Indeed, across three experiments, synchronous brushing of the tool and the real hand induced naive participants to demonstrate that three well-established signatures of the rubber-hand illusion also occur for a tool. Specifically, induction of the illusion with synchronous stroking induced participants to: (1) localize their hand closer to where the tool was; (2) consciously report having had the experience of the tool being their hand as well as of to feel touches as coming from the tool location; and (3) show increased arousal when the tool was threatened,

even though their own hand was in no danger whatsoever. Moreover, ownership was not present for a control object, a balloon, that shares neither visual nor functional similarity with the hand. Taken together, these results support our hypothesis that *functional* similarity can enable ownership over external objects for which there is no visual similarity to a hand. This result may have important implications for development of prostheses and/or wearable technologies. Although the full embodiment of augmentative technology is still highly problematic[36,37], our data suggest that factors other than active use may favor it.

Importantly, at odds with previous work, here we found that motor experience with the tool was not necessary to experience the illusion. Previous work converged in showing that tools need to be used actively to reveal behavioral effects of tool incorporation. Specifically, several studies reported changes in arm representation only in the active tool use – when sensory feedback, mainly proprioceptive and tactile, is provided[43–45]—but not during passive holding of the tool. Interestingly, the proprioceptive information doesn't necessarily need to arise from the tested arm. Miller and colleagues[10], using a mirror-based setup to induce the illusory experience of controlling the tool with the left arm, showed that the representation of the left arm length was modified after active use of the tool with the right arm. Moreover, tactile recalibration was not found when the tool was only passively held by the right hand (no somato-motor feedback) or when the mirror was removed (no visual feedback). Taken together, these data suggest that when it comes to tools, the criteria for integration of sensory feedback is relatively broad and allows some discrepancies: Somato-motor information from the right arm and visual information attributed to the left arm can be combined, to update both arm representations. Perhaps the tolerance for such discrepancies also enables tool embodiment despite the gap between the real hand position and the distal end of the tool, between where the sensory receptors physically are on the skin and the tool location where sensory feedback about a movement propagates from. One could then speculate that the sensory information coming from the participants' hand is being combined with the visual information from the touched tool, without the need of actual tool use.

Actually, here tool-use did not seem to play a major role in either establishing or modulating the illusion, which was already present before tool-use and not significantly impacted afterwards. That said, we did observe a trend: participants who looked at the tool being brushed on the first prong tended to reduce their drift after tool use, as if the second prong of the tool becomes functionally similar to the right index finger (which would be in a similar position during real-hand grasping). While further studies are needed, here we advance the possibility that two, non-mutually exclusive kinds of matching may exist between tool prongs and hand fingers (visual and functional), which might be modulated following tool use.

Taken together, these findings provide evidence for a new illusion, which we have named the "Toolish Hand Illusion". This illusion reveals that a tool can be perceived as an owned body part, as jointly supported by three different measures, and thus different cognitive levels, of the feeling of ownership. While the present study cannot disentangle their relative weight, we suggest the Toolish Hand Illusion may not rely solely on sensory factors, such as visual similarity, but also on motor factors, such as the potential for action. To date, our findings already show that when both are removed, as in the case of the balloon condition, no ownership is observed. Our results also indicate a novel avenue for further research on the constraints of illusory body ownership, since the way the parts of a tool are mapped onto the actual parts of the body could be modulated by the experience and the perceived functionality of the tool.

Methods

In total, 88 adult students (age range: 18–40) from Western University and Impact Lab at the Lyon Neuroscience Research Centre participated in the study (Experiment 1: N = 16, 8 females, 1 left handed; Experiment 2: N = 40, 22 females, 2 left handed, Experiment 3: N = 32, 16 females, all right handed). The number of participants to be tested was based on previous literature[31] that addressed the question of embodiment on non-corporeal objects. Moreover, for each experiment we run a post hoc power analysis using G*Power (Faul, Erdfelder, Buchner and Lang, 2009) to check that our sample size was large enough to obtain a 0.80 power, given the effect size for the different tasks. For all three experiments, the power to detect the main effect of the stimulation was higher than 0.99.

Participants received monetary compensation ($10 for those recruited at Western University, 15€ for those recruited at CRNL). All had normal or corrected-to-normal vision and no history of neurological or psychiatric disorders and had never used the grabber before. Participants were naïve about the specific goal of the study and were fully debriefed after. All participants provided informed consent and the experiment was approved by the Psychology Ethics Board of Western University (#130319) and the French (CPP SUD EST IV #11/005) ethics committee and was conducted in accordance with the ethical guidelines presented in the revised Helsinki declaration[46].

Experiment 1: Tool Embodiment and role of functional similarity. The first experiment assessed whether it was possible to induce a RHI-like illusion with a grabber tool, in place of the hand, and tested the role of functional similarity between the hand and the object in driving embodiment. The grabber tool used, used in all experiments, was a mechanical grabber tool (Unger-Global, Unger Global NN400—Nifty Nabber Pro; http://www.ungerglobal.com/en/), 52 cm long in total, composed of two rubber prongs that closed symmetrically when the participant used a power grip to squeeze the handle of the tool and a 12-cm long handle. No tool use occurred in Experiment 1.

Participants were comfortably seated at a table with their right hand and arm on the table, hidden from sight under a semi-reflecting mirror. The right hand was kept in a relaxed position with right thumb close to the rest of the hand and not protruding to the side. To further reduce cues about the participant's arm position, a large piece of black fabric was used to cover the shoulder and both upper arms. Participants were instructed to keep their left hand on their left leg.

The experiment started with a finger localization task: a ruler was placed face down over of the mirror; participants were asked to report the number on a ruler (with mm precision), corresponding to the position of their right index finger. We instructed participants to close their eyes and realign their head to the center of the body in between trials while the experimenter changed the offset of the ruler. The measure was repeated 12 times. Once the task completed and depending on the condition, a grabber tool or a black balloon were placed on the table 17 cm to the left of the participants' right hand. The experimenter then started brushing the object on the table and the right index finger for two minutes. For the tool we brushed the left tool prong. For the balloon, which was inflated so that its width would match the one of the tool prongs, we brushed the portion of its surface that corresponded to where the left prong would be. Once the brushing completed, participants were asked to close their eyes again while the object was removed and the ruler put in place to restart the finger localization task (12 trials). The difference between finger localization measured before and after the brushing phase, called 'Proprioceptive Drift", was used to quantify the illusion.

Finally, participants received a questionnaire to assess their subjective experience during the illusion induction. The questionnaire was composed by 14 statements (see Supplemental Table 1 for a complete list) addressing several aspects of the illusion experience, namely "Embodiment" (Q4, Q5, Q14), "Touch Localization" (Q1, Q2, Q3); "Disembodiment of the own hand" (Q8, Q9, Q11) and "Control Questions" (Q6 and Q7). Participants were asked to rate their agreement with each statement marking a point on a line oriented from left (I don't agree at all) to right (I completely agree).

Each participant was tested twice (once with synchronous stimulation and the other time with asynchronous stimulation) and the order of the conditions was counterbalanced across the subjects. Data from one participant were discarded as he did not complete the second session.

Experiment 2: Tool Embodiment and role of motor experience. The experiment consisted of three phases: pre tool-use, tool-use and post tool-use. In each of the pre- and post-tool-use phases, the position of the right index finger was localized before and after illusion induction to assess proprioceptive drift and a questionnaire was administered to assess subjective experience. In the tool-use phase, participants got experience using the tool to grasp and lift objects.

Participants were seated with their right forearm resting on a table. The mechanical grabber tool was placed 17 cm to the left of the participant's right hand such that the shaft was parallel to the participant's forearm and the tip of the "business end" was at the same distance as the digit tips of the hand. Throughout the experiment, a small board ($25 \times 45 \times 15$ cm) occluded the right forearm from the participant's view. To further reduce cues about the participant's arm position, a large piece of black fabric was used to cover the shoulder and both upper arms. Participants were instructed to keep their left hand on their left leg.

During measurement of proprioceptive drift, a bigger board ($100 \times 55 \times 20$ cm) covered both the smaller board and the tool. Participants were asked to judge the felt position of their right fingertip by naming a number on a measuring stick (with mm precision) placed atop the big board above their right hand. The task was repeated six times and the origin of the measuring stick was changed in between trials to prevent judgments from being influenced by previous answers. Proprioceptive localization was measured both prior to and following induction of the illusion and the difference between them, 'Proprioceptive Drift", was used to quantify the illusion.

Following the measurement of proprioceptive drift, participants filled out a questionnaire: two statements focused on touch location ("It seemed like I was feeling the touch in the location where I saw the tool being touched" and "It seemed like the touch I felt was caused by the paintbrush touching the tool"), one focused on the conscious experience of the tool being one's own hand ("I felt as if the tool were my hand") and two served as control questions.

During illusion induction, the participant could see the distal end of the tool (from the midpoint of the shaft to the tip) but not the right hand (because the large board had been removed while the smaller board remained in place). Participants were instructed to look at the tool while it was stroked with a paintbrush either synchronously or asynchronously (depending on the session) with their own (unseen) right index finger for 2 min. They were also instructed to keep their right hand and forearm still.

Participants were randomly assigned to one of the two groups. Participants in Group 1 saw the tool being brushed on its left prong while participants in Groups 2 saw the right prong of the tool being brushed.

In the Tool-use Phase participants were asked to move to a different table where a plastic parallelepiped object ($5 \times 2 \times 1$cm) was placed 35 cm from the proximal edge of the table. On the same edge, a small colored pad served as starting point. Participants were asked to keep the fingers of the same mechanical grabber tool in contact with the colored pad and wait for an auditory instruction to start the movement (reach and grasp the object, lift, replace it and then return to the starting position). Forty-eight movements were performed.

Experiment 3: Skin conductance response as a measure of sense of ownership. This experiment assessed an additional dependent measure of the sense of ownership: the skin conductance response to seeing the tool being stabbed by a needle.

Similarly to Experiment 2, Exp. 3 consisted of three phases (pre tool-use, tool-use, and post tool-use) but of four groups (with a factorial combination of left vs. right tool-prong and synchronous vs. asynchronous stroking). Skin Conductance Response (SCR) is a physiological measure of the electrical activity associated with increased secretions from the sweat glands resulting from sympathetic nervous system arousal. When one's own body is threatened, skin conductance increases.

Participants were seated at a table in an anechoic room to reduce electrical interference and acoustic noise. The room was also equipped with a ventilation system that allowed to set the temperature constant (around 21.7 °C) to avoid noise in the SCR with temperature fluctuations. Room temperature was set at the beginning of

each session and the experimenter checked, at the end, that no major change happened during each session. SCR was recorded using a Biopac System MP150 (Goleta, USA). Two electrodes were attached to the tips of the right index and middle fingers. Data were recorded at 100 Hz and processed with the software AcqKnowlege 4.0 for Windows. The right hand was then positioned palm down inside a box that was opened on the experimenter's side (as well as the participant's side) to enable brushing of the index finger. Six blocks of 60 s of brushing (synchronous or asynchronous) were alternated with a threatening block during which the experimenter briefly (~2 s) stabbed one of the two fingers of the tool (depending on the group the participant belonged to) with a syringe. The beginning of the brushing and the threat were manually flagged in the SCR acquisition file.

First, the threat-induced SCR response was identified by selecting the highest peak in a 5 s time window after threat onset. Then the peak-to-peak amplitude of such response was calculated and averaged across the six trials.

Received: 19 October 2016; Accepted: 4 January 2021
Published online: 21 January 2021

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Acknowledgements

LC is receiving funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie Grant Agreement No 754490 – MINDED project. The project leading to these results has received funding from a Fyssen Postdoctoral Fellowship (LC) and funding from the Natural Sciences and Engineering Research Council (NSERC) of Canada Collaborative Research and Training Environment (CREATE) program (44931-2014) to JCC and others. The research was funded by a NSERC Discovery + Accelerator grants to JCC (249877-2006-RGPIN), ANR-11-LABX-0042, CeSaMe ANR-10-IBHU-0003 to AF and others, Federation pour la Recherche sur le Cerveau (FRC), ANR Samenta ASD-BARN 01502 to ACR and others, ANR-16-CE28-0015-01 to AF and others and a James S. McDonnell Foundation Scholar award to AF.

Authors contributions

L.C., A.C.R. and A.F. conceived the experiment. L.C., A.Z. and R.Y. collected and analyzed the data. L.C., A.Z., A.C.R., F.V., J.C.C. and A.F. discussed the data and wrote the paper.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-021-81706-6.

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1.4 The Peripersonal Space

As described above, the environment that surrounds us and the stimulations that come from it keep our brain engaged in a continuous work of receiving, processing and monitoring information, in order to guarantee us a sensory experience that is as precise, detailed and updated as possible. If that is not enough to be grateful, it is also possible to consider the fact that we do not realize how difficult it can be to get us through a day without a hitch. Everything we do seems extremely simple and effortless to us: in the morning we get out of bed, we avoid (usually) hitting a foot, a knee or our head against the furniture in the apartment, we use a knife to cut bread, we pour the coffee into a cup from a hot coffee maker. Yet all this is a simple routine for us: we never think about how we managed to dodge the furniture in the apartment despite not paying attention to where our feet or our knees were. We are not aware of the enormous coordination and monitoring work required to cut bread without leaving a few fingers on the cutting board. Not to mention that a small miscalculation in reaching and grabbing the coffee maker could mean starting the morning with a burn.

All our interactions with the environment mainly take place in the space that surrounds our body, we could say approximately in the area we can reach by extending our arms (but regarding this definition, we will talk about it in greater detail in chapter 2). This portion of space has been defined peripersonal space (hereafter PPS), and since its "discovery" thanks to single cell investigations in the monkey, more than forty years of literature have now passed. In this section, we will try to describe the history of the study of PPS, which brain areas seem to be involved in its representation in the monkey and what are the homologues human neural correlates. To conclude, an fMRI study will be presented in which, for the first time, we tried to compare the neural basis of PPS in macaque monkeys and humans through the same paradigm.

1.5 A multisensory network in monkey's brain

The definition of peripersonal space as such derives from the pioneering studies on macaques by Rizzolatti and colleagues (Rizzolatti et al., 1981a, 1981b), who observed the existence of populations of multisensory neurons that responded preferentially to visual and / or tactile stimuli presented on the body and in the region of space close to it. Their main feature is to show tactile receptive fields (henceforth RFs) on a specific part of the body, such as the hand, arm or head, and visual RFs superimposed and anchored to the former. Multisensory neurons of this type have been observed in different brain regions, first in the monkey and later in man, which form a neural network underlying the representation of the space surrounding the body. This network includes parietal regions, in particular area 7b and the ventral intraparietal area (or VIP), and more frontal areas, in particular the F4 region of the premotor cortex (or PM), but also subcortical structures, such as the putamen (see Cléry, Guipponi, Wardak, et al., 2015 for review).

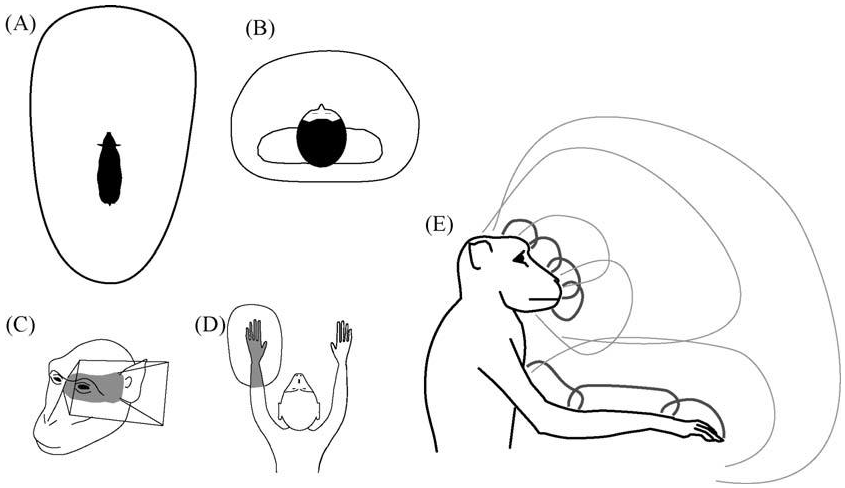


Figure 1.7 *Schematic representation of A) the "flight zone" of an animal and B) the personal space of a human. Whenever an intruder enters this space, signs of discomfort or actions of interaction or escape are put in place. C), D) and E) report examples of receptive fields of multisensory neurons linked to the representation of the peripersonal space, able to respond to visual-tactile stimuli centered on specific parts of the body, such as C) the face, D) the arm or E) more extended space regions. From Graziano & Cooke, 2006.*

As can be seen in Figure 1.8, the parietal region of the macaques can be divided into two areas separated by the intraparietal sulcus (or IPS): area 5, above IPS, and area 7, below it. Area 5 seems to be a somatosensory region, which responds in particular to complex movements and gestures (Mountcastle et al., 1975; Sakata et al., 1973). Area 7 seems to be more involved in the representation of the PPS, and receives cross-modal signals through the information convergence mechanism already described (C. J. Robinson & Burton, 1980b; D. L. Robinson et al., 1978). In particular, its rostral section, called area 7b, while showing a

majority of somatosensory neurons, has about a third of neurons that also respond to visual stimuli presented in the space surrounding the tactile RFs (Hyvärinen, 1981; Hyvärinen & Poranen, 1974; Hyvärinen & Shelepin, 1979; Jiang et al., 2013; Leinonen et al., 1979; Leinonen & Nyman, 1979). These receptive fields are then spatially co-registered and anchored to each other: bimodal neurons that respond to tactile stimuli presented on the arm and to visual stimuli presented close to it will stop responding if the arm is moved outside the visual field centred on the monkey's body-part. Moreover, it is possible to observe a somatotopic organization within this region, with neurons responding specifically to face-centered visual-tactile stimuli located in the most caudal sector, bordering area 7a. Proceeding in the lateral-anterior direction, populations of neurons are found representing the arm, the hand and finally the foot (Hyvärinen, 1981; Hyvärinen & Shelepin, 1979; C. J. Robinson & Burton, 1980a). These neurons have large RFs, usually covering the entire arm, the head and possibly extending for more than 1 m. It is important to stress that the neurons present in this area are not only involved in the perception of stimuli within PPS, but are also activated when the monkey performs actions with its arm (e.g., reaching for food) or with the muscles of the face and mouth (e.g., chewing the food grasped, Fogassi & Luppino, 2005; Hyvärinen, 1981; Hyvärinen & Poranen, 1974; Hyvärinen & Shelepin, 1979; Leinonen et al., 1979; Leinonen & Nyman, 1979; D. L. Robinson et al., 1978). This motivation led to consider PPS as an interface between perception and action, able to integrate cross-modal signals to plan response actions and understand the intentions of others.

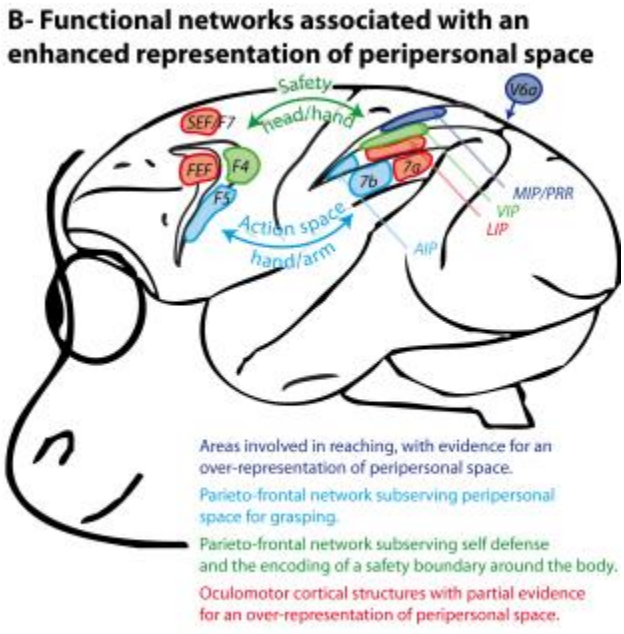


Figure 1.8 *Representation of the functional networks associated with the representation of peripersonal space in the monkey brain. In light blue, the parietal areas 7b and the anterior intraparietal sulcus (AIP), which together with the premotor area F5 create a network subserving peripersonal space for action. In green, the ventral intraparietal area (VIP) and the premotor area F4, which instead support the defensive function of the PPS. In blue and red, respectively, the areas that support reaching actions and oculomotor movements, but with an over-representation of the peripersonal space. From Cléry et al., 2014.*

Strongly interconnected with area 7b is the anterior intraparietal area (AIP), in the superior parietal lobule and anterior to the previous one. Although it is not possible to say that this area is directly involved in the representation of stimuli or actions within PPS, its anatomical interconnections and functional homologies with area 7b (Matelli & Luppino, 2001; Rizzolatti & Luppino, 2001) involve indirectly AIP within the network that subserves PPS for action purposes. In this region there are indeed neurons that respond to particular characteristics of the 3D structure of objects and to their graspability. Specifically, we observe here neurons that are activated when a grasping gesture is performed, when a graspable object is presented and / or when grasping gestures are performed towards graspable objects (Murata et al., 2000; Sakata & Taira, 1994). This type of response is therefore essential for the execution of actions within PPS.

Also area 7a, in the inferior parietal lobule and caudal with respect to area 7b, does not seem to be specifically linked to the representation of the PPS. However, this region of multisensory integration presents populations of neurons that respond preferentially to fixation points located close to the animal's body, in a range of approximately 50 cm (Sakata et al., 1980). Given its important connections with the adjacent area 7b, heavily involved in the representation of the peripersonal space for action, it is possible that area 7a also plays a role in the perception of stimuli within PPS.

A very similar argument can be made for the lateral intraparietal area (LIP), in the superior parietal lobule. Here we find again neurons that are not directly involved in the representation of the PPS, but respond differentially to visual stimuli at different distances from the body. Particularly, LIP presents a population of neurons that preferably responds to fixations in the space surrounding the body, at about 30 cm (Genovesio & Ferraina, 2004; Gnadt & Mays, 1995). As for area 7a, however, the response of these neurons is conditioned by the ocular position (Bremmer et al., 1997), contrary to what happens for neurons typically linked to the body-part centered representation of the peripersonal space.

The last parietal area strongly involved in the representation of the peripersonal space is the ventral intraparietal area (VIP). Located in the fundus of the IPS, this region features neurons capable of integrating visual, tactile, auditory and vestibular cross-modal signals following the principles of spatial and temporal coherence (Avillac et al., 2004, 2007; Schlack et al., 2002). In particular, it is possible to observe a population of visual-tactile neurons with

strong activations in response to moving stimuli within the PPS. Most of these neurons have tactile receptive fields centered on the head, while the visual receptive fields are less uniform: it is possible to detect visual responses to moving stimuli according to an eye-centered or head-centered reference frame (Avillac et al., 2004; Bremmer et al., 1999; 2001; 2002; Colby et al., 1993; Duhamel et al., 1997, 1998; Schlack et al., 2003). In particular, a subpopulation of these neurons selectively responds to stimuli in motion within the peripersonal space and/or in the direction of the head, regardless of the sensory modality (Guipponi et al., 2013). These features seem to indicate that VIP is an area where visual information still arrives in a retino-centric format, and is then transformed into body-part centered coordinates in order to monitor stimuli moving around and towards the body (Avillac et al., 2005; Duhamel et al., 1997). From this point of view, therefore, it is possible to affirm that VIP is part of a second network subserving the representation of the PPS, different (but interconnected) from the one that includes area 7b. While the first network seemed in fact more devoted to the aspects of action within PPS, the network including VIP seems to subserves its defensive function, keeping track of the stimuli present around the body (and in particular around the head) and preparing avoiding responses for possible collisions (see Cléry, Guipponi, Wardak, et al., 2015 for review).

These two different brain networks do not just include parietal areas. As can be seen in Figure 1.7, both neural systems underlying the representation of the PPS communicate with a more frontal region, the premotor area 6 (or "polysensory zone", given the several and different projections that reach this area). This area has somatosensory, visual and above all bimodal neurons organized somatotopically that can be divided into a more rostral region, close to the arcuate sulcus and called F5, and a more caudal section, called F4.

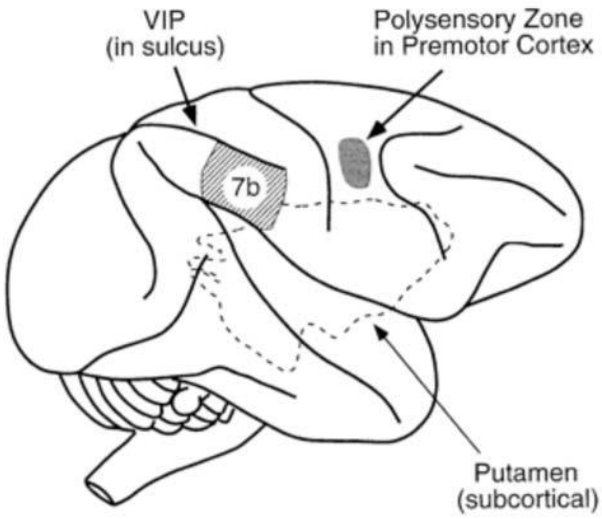
Area F5 presents neurons which appear to respond preferentially to stimuli within-reach and which exhibit a certain hand-grasping configuration (Bonini et al., 2014; Murata et al., 1997; Raos et al., 2006; and see Cléry et al., 2015 for review). These neurons receive somatosensory, visual and vestibular cross-modal afferences (Akbarian et al., 1993, 1994), with small tactile RFs located mainly on the arms, face or both (Gentilucci et al., 1988; Murata et al., 1997; Raos et al., 2006; Rizzolatti & Luppino, 2001). Visual RFs, on the other hand, seem to be more difficult to define, despite the strongest responses being recorded for stimuli within the reaching space (Gentilucci et al., 1988). This coincides with what was

observed by Gentilucci and colleagues, who report an involvement of the neurons of the F5 area for the implementation of distal gestures, as opposed to hand-to-mouth or hand-to-body gestures which instead seem to involve more the area F4 (Gentilucci et al., 1983, 1988). As suggested by Cléry and colleagues, it is therefore possible that this sector of premotor area 6 is part of the network that subserves PPS for action purposes, communicating with parietal areas 7b and AIP (Cléry, Guipponi, Wardak, et al., 2015). Moreover, F5 would not only be involved in action execution, but also in the observation of actions carried out by another actor, preferably when the latter are carried out within the animal's PPS (Caggiano et al., 2009).

Area F4, on the other hand, presents mainly visual-tactile bimodal neurons with tactile RFs centered on the arms, trunk, neck and head and visual RFs overlapping with these latter (Fogassi et al., 1996; Gentilucci et al., 1983; Graziano et al., 1994; Graziano & Gross, 1995, 1998b; Rizzolatti et al., 1981a, 1981b, and see 1997a, and 2002 for review). Thanks to the series of works by Graziano, Rizzolatti and colleagues it was possible to observe that the visual responses of these neurons are mainly independent of the gaze position (Fogassi et al., 1992, 1996; Gentilucci et al., 1983; Graziano et al., 1994; Graziano & Gross, 1998a): for a bimodal neuron with RF centered on the arm and a visual RF spatially co-registered to it, for example, a maximal response is obtained if a visual-tactile stimulus is presented in this area. If the arm is moved out of sight, maintaining the same fixation point and applying the same stimulus again, the response will be reduced, as the visual stimulus falls outside the RF of that neuron. On the contrary, if the arm is moved, but always remaining within the visual field of the animal, a visual-tactile stimulation in the new position occupied by the arm will again produce a maximum response. This fundamental characteristic allows these neurons to constantly monitor the position of external stimuli as a function of the position of the different body parts (Graziano et al., 1994, 1997a; Graziano & Gross, 1993, 1995). A further aspect is the fact that the vision of the stimulus is not necessary to activate the response of the neurons of the F4 area. Graziano and colleagues presented a stimulus inside the PPS of the monkey's face, immediately observing a response of the neurons of the F4 area coding for that portion of space. By turning off the light, and thus preventing the stimulus from being seen, they observed that the response of those neurons remained maximal, as if the stimulus were still visible (Graziano et al., 1997b). This shows a kind of "object permanence" of these neurons, which keep track of the position of the stimuli within-PPS until it is

explicitly shown that the stimulus in question is no longer in their receptive field. These multisensory neurons have been divided according to the preferential distance of the stimulus to which they respond: 54% fall into the category of "pericutaneous neurons", which respond preferentially to visual stimuli presented a few centimeters (~ 10) from the skin of the animal, while the remaining 46% is defined as "distant peripersonal neurons", responding mainly to stimuli within the reaching space, between 5 and 50 cm (Rizzolatti et al., 1981b).

In addition to these cortical areas that code for stimuli within the peripersonal space and initiate action planning, there is another subcortical structure that must be included within these networks: the putamen (Graziano & Gross, 1993, 1995; and see Graziano et al., 2012). The pioneering works of Graziano and Gross have in fact shown that in the putamen there are somatosensory, visual and bimodal neurons that follow a somatotopic organization, as happens in the parietal and premotor PPS regions. Here too, indeed, we find neurons with tactile RFs centered on the hand, arm or face that also respond to visual stimuli presented spatially close to them. Furthermore, this coding is “anchored” to the specific part of the body, just as it happens for the neurons of the 7b, VIP or F4 areas. A difference with respect to the areas described may concern the extension of these visual RFs, which seems to be slightly less extended, ranging for about 10-20 cm for the head and only 5 cm for the hand.



1.9 *Lateral view of a macaque’s brain, with representation of the parietal areas VIP and 7b, of the polysensory zone (including premotor areas F4 and F5) and the putamen, subcortically. From Graziano et al., 2012.*

1.6 PPS investigation in humans

Over time, more and more research groups have been interested in the study of that neural system capable of integrating tactile information coming from the body with visual and auditory stimulations coming from the space around it: the human PPS cerebral network.

The first studies in this direction were carried out on patients who, following brain injuries, showed a particular pathology, which is called extinction (Bender, 1952). Patients suffering from extinction are able to identify visual or tactile stimulations without any problem when these are presented individually, whether they are ipsi- or contralesional. However, in the case of bilateral stimulation, the ipsilesional stimulus "extinguishes" the contralateral one: touching the patient's two hands simultaneously (or with a short asynchrony, between ±600 ms: Di Pellegrino et al., 1997), the patient is able to report only the ipsilesional stimulus. This phenomenon, which occurs mainly following parietal lesions of the right hemisphere (Becker & Karnath, 2007; see Christopoulos et al., 2018 for review), seems to be due to a sensory competition between the stimuli, in which one of the two "wins" over the other (B. de Haan et al., 2012; Di Pellegrino & De Renzi, 1995; Jacobs et al., 2011). To understand how this competitive model works, we can consider this (simplistic) example: when we are touched on a hand, the left one for example, the simple perception of touch activates in our brain those areas destined to represent the body district involved. The same thing would happen, under normal conditions, receiving two tactile stimulations on the two hands, with consequent activation of the areas involved in their representation. However, the right parietal lesion of patients with extinction "weakens" the representation of the contralesional half of the body, and therefore, in the case of bilateral stimulation, the remaining cognitive resources are not sufficient to guarantee the detection of the two stimuli. For this reason, the stimulus presented in the under-represented spatial region is extinguished (see Làdavas, 2002; and Farnè et al., 2008 for review). As demonstrated by Mattingley and colleagues, extinction does not require unimodality: ipsilesional visual stimuli can extinguish contralesional tactile ones and vice versa (Mattingley et al., 1997). The study of these patients has allowed us to observe, however, that the extent of the deficit depends on the distance at which the stimuli are presented from the body. By presenting a tactile stimulus on the contralesional hand and a visual stimulus near the ipsilesional one, the visual

stimulus, as already described, extinguishes the tactile stimulus. However, asking the patient to move the ipsilesional hand behind the back and using a visual stimulus in the same position as the previous one, the patient proves to be able to detect the contralesional tactile stimulus. This is due to the fact that the visual stimulus in the first condition is located within the PPS (and in particular in the peri-hand space) of the patient, as well as the tactile stimulus, while in the second condition the two stimuli are in two different reference frames, since the visual stimulus is outside the PPS (Di Pellegrino et al., 1997; Làdavas et al., 1998). This proved also for humans, as already evidenced by electrophysiology studies on non-human primates, the existence of a hand-centered peripersonal space (see Làdavas & Farnè, 2004; and Di Pellegrino & Làdavas, 2015 for review regarding PPS and crossmodal extinction): when patients with extinction are asked to cross their hands, a fundamental characteristic of PPS coding immediately stands out, namely the "anchoring" of stimulations to a specific part of the body. Crossing the hands, in fact, it would be possible to expect an extinction always directed towards the left half-space, in which the right hand is now located. Yet, Di Pellegrino and colleagues demonstrated that by presenting a contralesional visual stimulus and an ipsilesional tactile stimulus on the left hand, the patient once again extinguishes the tactile stimulus, despite being in the "healthy" region of space (Di Pellegrino, Làdavas, et al., 1997). This therefore means that the spatial reference frame within which this deficit operates is not centered in a general way on the body, but is anchored to the parts of the body themselves, and remaps according to their movement. After these first results, the step was short to identify in patients suffering from extinction a visuo-tactile (Farnè et al., 2005; Làdavas et al., 1998) and an audio-tactile (Farnè & Làdavas, 2002) peripersonal space also centered around the head. As observed for the hand, an ipsilesional visual stimulation close to the face was able to extinguish a tactile stimulation applied to the contralesional cheek (see Figure 1.10). If the visual stimulation was presented ipsilesionally but away from the face, the severity of the extinction was reduced, with a higher number of tactile stimuli reported correctly. However, the “distance from the body” is not the only criterion to influence this deficit: the performance of these patients is indeed worse when the two stimuli are presented bilaterally and close to homologous body parts (i.e. tactile stimulus on the cheek / left hand and visual stimulus on cheek / right hand). If the body districts stimulated are not homologous (i.e. tactile stimulus on the left cheek and visual stimulus on the right hand), the performance is instead slightly better (Farnè,

Demattè, et al., 2005). According to what has been observed from the electrophysiological studies on monkeys, therefore, also the human being turns out to be endowed with a modular representation of space (at least at the neural level) and centered on the different body districts.

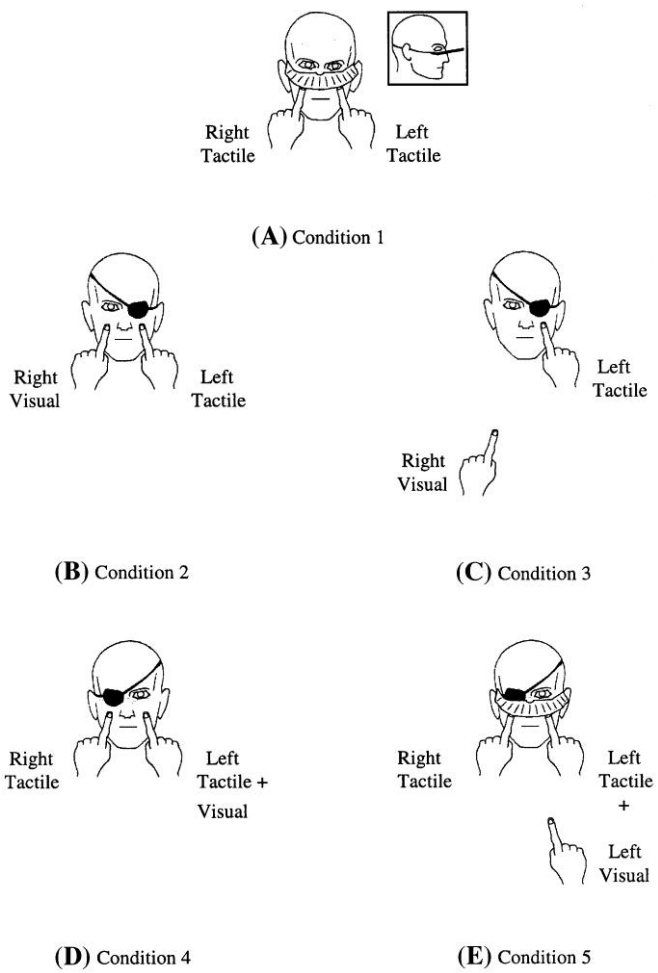


Figure 1.10 *Schematic representation of the experimental conditions in Làdavas et al. (1998). A) Tactile stimuli could be applied on both side of the face, with no vision. B) Left tactile stimulation and vision of the right near space. C) Same as B), but with visual stimuli presented in the right far space. D) Tactile stimuli applied on the right or left side of the face (or bilaterally), visual stimulus presented only in the left near visual space. E) Same as in D), but visual stimuli were presented in the far left space. From Làdavas et al., 1998.*

Almost simultaneously with the studies that investigated PPS coding in patients with extinction, several research groups have been interested in studying this same aspect in patients with a similar pathological condition: the unilateral neglect. Initially described by Brain as "an inattention to the left half of the outer space, in the absence of primary visual deficits", this disorder occurs mainly following lesions located in the right parietal lobe (Brain, 1941; Driver & Mattingley, 1998). Contrary to extinction, patients are unaware of the contralesional half of the space and of everything is presented in it, even when a stimulus is presented alone. Their deficit comes in various forms, and is often tested with tasks of objects representation or bisecting lines. In the latter task, for example, they are asked to

split a horizontal line in half using a pen: while healthy subjects tend to bisect with a slight bias to the left (a phenomenon called pseudoneglect, see Jewell & McCourt, 2000 for review), patients draw their mark too much on the right. This bias is due to the unawareness of the existence of the left half of the line, but its significance goes far beyond, negatively impacting the conscious perception of contralesional stimuli, the consideration of the contralesional half of the body and so on (see Brozzoli et al., 2006; and Schenk & Karnath, 2012 for review).

The studies by Bisiach and colleagues date back to the late 1980s, demonstrating a double dissociation between unilateral neglect for the peripersonal and extrapersonal space (Bisiach et al., 1986). The severity of the deficit of these patients is indeed influenced by the region of space in which the task is performed: some patients may be successful in a bisection task carried out in near space, with a pen in hand, and tragically fail when the same task is carried out in the extrapersonal space, for example with a laser pointer (Berti & Frassinetti, 2000; Beschin & Robertson, 1997; Bisiach et al., 1986; Guariglia & Antonucci, 1992; Halligan & Marshall, 1991; Ortigue et al., 2006), but the opposite pattern is also well documented (Bisiach et al., 1986; Cowey et al., 1994; Ortigue et al., 2006; Vuilleumier et al., 1998; and see Berti et al., 2001; and Halligan et al., 2003 for review). This dissociation between the two different spatial reference frames has also been reported in the monkey: an ablation of area 6 induced in the monkey an attention deficit towards the contralateral half of the body and of the space, which occurred both in somatosensory and visual modality. The visual impairment, in particular, appeared only for stimulations within the PPS. In contrast, the inattentive deficit caused by the ablation of the most ventral area 8 was again present for the somatosensory and visual modalities, but in this case directed towards the extrapersonal space (Rizzolatti et al., 1983). Non-invasive brain stimulation studies on healthy humans also support this segregation between a dorsal and a ventral path in the processing of visual and spatial information related to space near or far from the body. In the study by Bjoertomt and colleagues, participants in a line bisection task shift from a pseudoneglect performance to a strong rightward bias, similar to that reported by patients with unilateral neglect, following repetitive transcranial magnetic stimulation (or rTMS) applied at the level of the posterior parietal cortex or the ventral occipital lobe of the right hemisphere. In particular, the first stimulation affected the performance only when the task was performed in the near space, while disrupting the activity of the ventral occipital lobe lead to a deficit only in the far space

(Bjoertomt et al., 2002). This kind of segregation at the neural level supports the results of behavioral studies on pseudoneglect, which have shown a reversal of the direction of the bias as a function of the distance at which the line to be bisected is presented. Interestingly, healthy subjects show a bias to the left when they have to perform the task in the space near the body, while this bias tends to shift more and more rightward if the line has to be bisected in the extrapersonal space (Gamberini et al., 2008; Longo & Lourenco, 2006; McCourt & Garlinghouse, 2000; Varnava et al., 2002).
However, near and far are plastic, malleable concepts: what happens to far space, defined as inaccessible and beyond my reach, if I hold a tool in my hand that allows me to act at a greater distance? Despite the pungent interest that this question evokes, we will have to wait for Chapter II to satisfy this curiosity.

The idea of a representation of space fragmented into multiple reference frames centered on different body districts but at the same time perceived as a single continuum has since then increasingly developed, inspiring the interest of more and more research groups. PPS was no longer just the domain of electrophysiology, but becomes a subject of study at the human level, both in patients and in healthy subjects, thanks to both behavioral and neuroimaging studies.
Having reviewed the neural basis of PPS in the monkey, therefore, we can now try to understand which are the regions of the human brain that code for the space closest to the body.

1.7 Neural bases of humans' PPS

As we have already seen, early electrophysiological studies in monkeys have allowed to highlight an extensive fronto-parietal network of areas dedicated to coding the space surrounding the body and its various parts. It is therefore evident that the results on patients and healthy subjects have led to investigate also in the human being what are the neural underpinnings and the functioning mechanisms of PPS. Two precautions must be taken before entering into the comparison between electrophysiology studies in non-human primates and those of neuroimaging on humans. Firstly, caution has to be taken about the level of spatial definition that we can expect: although technical developments in

neuroimaging and increasingly precise analyses can allow us to improve our level of detail, it is not yet possible to obtain the representation of the activity of single neurons without using invasive registration techniques. Considering the presence of intermingled populations of neurons specialized in the response to different regions of the PPS within the same brain area, this could affect the activations reported in the different studies. The second aspect to consider is that, although similar, our brains and that of our closest relatives are not identical, and different homology relationships between the associative brain areas may exist.

The (recent) history of neuroimaging on PPS begins precisely from a homology. At the turn of the new millennium, Bremmer and colleagues investigated the pattern of neural responses to tactile stimulations applied to the face and visual and auditory stimulations moving towards the head. What the authors observed is an overlap of these responses at the level of the superior parietal cortex, particularly in the deeper part of the superior intraparietal sulcus (IPS), of the ventral premotor cortex (PMv), and of the inferior lateral part of the postcentral gyrus. Thanks to the characteristics of the response of its neurons, the IPS has thus (erroneously) considered as the human homologue of the VIP area of the macaques, located at the bottom of the IPS and strongly involved in the coding of the PPS (Bremmer et al., 2001; Grefkes & Fink, 2005). This homology is confirmed a few years later by the studies of Sereno and Huang, who extended Bremmer's results showing that IPS neurons are capable of encoding external stimuli in face-centered coordinates and that they possess visual-tactile maps of the space around the head aligned with each other. In this way, the same neurons in this area respond not only to tactile stimuli applied to the face, but also to visual stimuli spatially adjacent to them (Sereno & Huang, 2006), as already observed in monkey's VIP (Bremmer et al., 2002; 2001).

Nevertheless, only a year later the first inconsistencies in the results began to appear. Quinlan and Culham presented static, looming or receding visual stimuli from the face at three different distances: near (13-17 cm), at medium distance (33-43 cm) or away from the face (73-95 cm). In this case, IPS appears not to be sensitive to the distance of the stimulus, responding in a similar way to the three conditions. However, another region of the superior parietal cortex, the dorsal parieto-occipital sulcus (dPOS) shows responses with a near-to-far gradient, with a strong preference for stimuli closer to the face and an increasingly weak

response with the increase in distance (Quinlan & Culham, 2007). This possible inconsistency could be due to the fact that the "human VIP-homologue area" may need the combination of multiple depth signals to bring out its preferential response, something not investigated in this study. dPOS, on the other hand, would be involved in the encoding of the distance of a stimulus, collecting information relating to eye convergence and / or pupillary dilation / constriction (see Cléry, Guipponi, Wardak, et al., 2015). These aspects would make dPOS an important source of information regarding depth perception for all areas of the dorsal visual stream, including those related to the representation of the PPS.

A result that instead confirms, though partially, Bremmer's results is that obtained by Holt and colleagues, who present visual stimuli approaching (looming) or moving away (receding) from the face to investigate the connectivity between the dorsal sector of the IPS and PMv, two of the regions mainly involved in PPS coding according to Bremmer. Visual stimuli used included human faces, cars or simple spheres, and also in this case a preferential response of the investigated areas to looming stimulations is observed. However, this occurs only in response to faces, and not in the case of other visual stimuli (Holt et al., 2014).

Subsequent studies have found and confirmed the role of the superior parietal region in the coding of the space around the body, and not only as regards the peri-head space. Huang and colleagues tested visual-tactile multisensory integration around different body districts, including head, shoulders, hands, fingers, legs and toes. Thanks to this in-depth study, a somatotopic mapping was observed at the level of the posterior superior parietal cortex, with the face represented at the level of the IPS, the lower part of the body more medially and laterally and the upper limbs in the lateral-anterior direction (Huang et al., 2012; and see Huang & Sereno, 2018 for review on human parietal lobe).

The modularity of the representation of the PPS, as we have been able to understand, is one of its fundamental aspects. The very essence of the peripersonal space is to "wrap" the body and its various parts constantly, through a continuous updating and remapping according to the movements of the body. Furthermore, as we will see better in the next chapter, PPS coding is not only linked to perceptual aspects, but is intrinsically involved in the planning and execution of actions. Considering the vastness of actions and manipulations that we can carry out with our hands, both in quantitative and qualitative terms, the study of the PPS centered on the hands, or peri-hand space, certainly has a special place in this literature.

It is Makin and colleagues who lead the way in this line of research, with an experimental design in which the participants, inside the fMRI scanner, have a direct view of their right hand, resting on a support. Using as a stimulus a simple ball attached to the end of a stick, which could be moved towards the hand or away from it, the authors observed activations very similar to those observed by Bremmer and colleagues for the face: IPS, PMv and the lateral occipital complex (LOC) show preferential responses to looming stimuli near the hand. These responses were not only dependent on the type of movement of the stimulus: by displacing the hand and hiding it from the subject's view, these three regions no longer showed any response (Makin et al., 2007). These results are confirmed and expanded a few years later by Brozzoli and colleagues, through an fMRI adaptation paradigm. In this type of paradigm it is possible to obtain a greater level of spatial detail thanks to the repetition of the same stimulus, which induces a suppression of the response of those neurons specific to one of its characteristics (Grill-Spector et al., 2006). Profiting by this advantage, the authors used a protocol similar to that of Makin and colleagues identifying activations in IPS, supramarginal gyrus (SMG), dorsal and ventral premotor cortices, cerebellum and putamen specific for stimulations presented within the peri-hand space (Brozzoli et al., 2011). Furthermore, the hand-centered nature of these activations is highlighted: maintaining the same fixation point and the same absolute position of the external stimulus, the presence of the hand close to the stimulus induces a response from the PPS network, while its displacement in a position far away does not generate such a response. By moving the object closer to the new hand position, the PPS network response reappears (Brozzoli et al., 2012a). These regions not only encode for the space around the hand, but are also capable of integrating multisensory signals (Gentile et al., 2011), as demonstrated by the presence of super- and subadditive responses (Stein & Meredith, 1993), similar to what has already been observed in animals (Avillac et al., 2005; Stein & Stanford, 2008). Particularly, the correct integration of these multisensory signals would be at the basis of the response features of these regions: by altering the temporal and / or spatial congruence of the visual-tactile stimuli applied to the hand and close to it, the sensation of ownership of the visually perceived limb is missing, dragging with it the answers related to the PPS coding (Gentile et al., 2013).

These latest results therefore seem to demonstrate that the regions involved in the coding of the peripersonal space do not only use sensory information coming from external

stimulations, as in a bottom-up process, but are also influenced in a top-down direction by higher-level cognitive processes, such as those related to body ownership. Recognizing a part of the body as being part of one's own body could induce a PPS encoding for stimuli presented near it. This supports the results of studies in the literature that obtained activations of the PPS-network by stimulating the space around a fake hand, rather than around the subject's hand, both in humans (Brozzoli et al., 2012a; Makin et al., 2007 and see 2008 for review) and non-human primates (Graziano et al., 2000). Furthermore, it must not be forgotten that PPS is not only a space to act, but also to *inter-act* with others (Patané, 2018). This social function, which we will see in more detail in the next chapter, seems to be supported by the fact that the activity of PMv is not only linked to the presentation of stimuli within one's own peri-hand space, but also within the peri-hand space of another person (Brozzoli et al., 2013). This "shared" aspect of PPS, already observed in the F5 premotor area of monkeys (Caggiano et al., 2009; Ishida et al., 2010), also seems to extend to a brain region less frequently identified in this literature: the primary somatosensory area, or S1. Schaefer and colleagues revealed the presence of neurons in S1 and S2 with a preferential response to stimuli within the peri-hand space. The interesting aspect is that these neurons respond both when the hand is perceived from a first person perspective, as if it were one's own hand, and when the perspective passes into the third person, looking at a hand that cannot be part of one's body (Schaefer et al., 2012). Thanks to mirror responses of this type, it would be possible to lay the foundations of a shared peripersonal space, within which events, actions and stimulations can be encoded in a single reference frame.

The present description of the fronto-parietal-cerebellar network that represents the basis of the PPS coding, albeit extensive, is far from being exhaustive (see Di Pellegrino & Làdavas, 2015; Serino, 2019; and Bogdanova et al., 2021 for more extensive review). Other brain areas probably cooperate with those described in order to keep the representation of our body and the space that surrounds it operational and always updated. An example could be the superior temporal sulcus (STS), which seems to preferably respond to audio-visual stimuli looming towards the body (Tyll et al., 2013). To try to clarify what is the core of the neural underpinnings of the PPS, Grivaz and colleagues conducted an extensive meta-analysis of the literature available to date. What emerged reveals a fronto-parietal network composed of seven activation clusters, located at the level of the superior parietal (right IPS),

temporo-parietal (bilateral SMG and S1) and premotor cortices (bilateral PMv, Grivaz et al., 2017).

These activations, therefore, seem to converge with those observed in non-human primates, thanks to electrophysiology studies (see Cléry, Guipponi, Wardak, et al., 2015 for review). However, the experimental paradigms and stimulations used for the two species are often very different, making direct comparison difficult. For this reason, we conducted the first fMRI study with an adaptation paradigm to investigate the neural basis of the representation of the peripersonal space in human subjects (n = 2) and in non-human primates (n = 2), taking advantage of the same experimental protocol, in order to make a direct comparison between the two species.

Peripersonal space representation in humans and monkeys: a cross-species and between body-parts fMRI comparison

(In preparation)

Peripersonal space representation in humans and monkeys: a cross-species and between body-parts fMRI comparison

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Conflict of Interest: The authors declare that they have no conflict of interest.
Acknowledgements: This work was funded by the French National Research Agency ANR-15-CE37-0003 grant MySpace to FHB.

Funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abstract

Human and non-human primates are supposed to be endowed with similar neural mechanisms for coding the space closely surrounding their body, termed peripersonal space (PPS). Independent investigations through electrophysiological studies in the macaques and fMRI studies in humans have identified a set of fronto-parietal regions showing enhanced activations in response to stimuli close to the body compared to far ones. Despite the overall coherence of the findings, the differences between the two techniques have so far prevented a direct comparison between the two species. Thus, we used a similar unimodal visual stimulation protocol, recording BOLD fMRI adaptation, to reveal the existence of neuron subpopulations specific to near space coding, in both human and non-human primates. The findings demonstrate for the first time an overlap in the neural underpinnings of the PPS representation across both species within the fronto-parietal network, with activations found in premotor areas (F4-F5-PMdc/PMd-PMv), putamen and parietal regions (VIP-MIP-LIP-area 7 and their human homologues). Furthermore, in humans, we presented stimuli close to three different body parts -hand, face and trunk- in order to investigate the commonality and specificity in the neural basis of the body-part-centered reference frame of the PPS. The results points toward a common network within the fronto-parietal-supramarginal PPS network, regardless of the body-part stimulated. Importantly, we also identified specific activations for hand-, trunk- and face-based PPS representations along this network. These results provide a bridge between the results of electrophysiology in the monkey and neuroimaging in humans and broaden the knowledge about the neural basis of body-part-based PPS representations.

Abbreviations

6d/6r/6a/6mp/6v = dorsal/rostral/anterior/medial-posterior/ventral area 6

7Al/7Am = lateral/medial area 7

AIP = anterior intraparietal area

DVT = dorsal transitional visual area

FEF = frontal eye fields

LIPd/LIPv = dorsal/ventral lateral intraparietal area

LOP = lateral occipital parietal area

I6-8 = inferior 6-8 transitional area

IFJ = inferior frontal junction area

IP1/2 = intraparietal area 1/2

IPL/SPL = inferior/superior parietal lobule

IPS = intraparietal sulcus

MIP = medial intraparietal area

OP1 = S2 (secondary somatosensory area)

PEF = premotor eye fields

PIP = posterior intraparietal area

PMC = primary motor cortex (M1)

PMd/PMv = dorsal/ventral premotor cortex

PMdc = premotor dorsal caudal cortex

POS = parieto-occipital sulcus

PSL = perisylvian language area

RI = retroinsular cortex

S1 = primary somatosensory area

SMG = supramarginal gyrus

STV = superior temporal visual area

TPOJ = temporo-parieto-occipital junction

VIP = ventral intraparietal area

Vm_IPS/lat_IPS = ventro-medial / lateral IPS

1. Introduction

The peripersonal space (PPS) is the multisensory representation of objects in the region close to the body allowing us to interact with them. Its definition steams from single-unit electrophysiological studies in macaque monkeys which identified a set of neurons in the posterior periarcuate regions, within the ventral premotor cortex (PMv; F4), that responded preferentially to objects presented in the region of space close to the body (Rizzolatti et al., 1981a, 1981b). Subsequently, studies have shown that activity of single neurons in premotor (Graziano et al., 1994) and parietal cortices (Colby et al., 1993) and the putamen (Graziano and Gross, 1993) displayed similar neural properties.

In the parietal cortex, several subregions displayed selective coding for PPS, namely the ventral intraparietal (VIP) area (Colby and Duhamel, 1991; Colby et al., 1993), the medial intraparietal (MIP) area (Colby and Duhamel, 1996) and area 7b (Graziano and Cooke, 2006; Leinonen et al., 1979; Robinson et al., 1978). In addition, the visual receptive fields of area VIP formed a map of the visual space around the face (Colby and Duhamel, 1991; Colby et al., 1993), presenting a somatotopic organization with separate face, arm and hand representations (Hyvärinen and Shelepin, 1979; Leinonen et al., 1979). Also neurons in F4 were characterized by relatively large tactile RFs, located on the monkey's face, neck, arm, hand or both hands and face (Graziano et al., 1994; Matelli and Luppino, 2001; Raos et al., 2006). These neurons were multisensory, reporting visual RFs extending for few centimeters from the skin (Rizzolatti et al., 1981b) and "anchored" to the tactile ones, following the movement of the arm (Graziano et al., 1994). Visuo-tactile neurons were also recorded in the rostral subregion F5 of area 6, RFs being located around the face, the hand or both (Rizzolatti et al., 1998). In the putamen, visual and tactile RFs were somatotopically organized on the arm, hand and face, large portion of face neurons responding best to visual stimuli presented close to the face (10-20 cm, Graziano and Gross, 1993). Altogether, these findings demonstrated that neurons in premotor-parietal-subcortical PPS network have visuo-tactile responses with a hand/arm-centered, head- or trunk-based representation. Based on these properties, it was suggested that these regions play a key role in visually guided actions, and that they would more particularly be engaged in the preparation of appropriate motor plans, especially given their anatomical position, at the interface with motor regions (Rizzolatti et al., 1997a, 1997b).

More recently, studies have investigated PPS representation in humans using functional magnetic resonance imaging (fMRI). These experiments have measured sensitivity to either

unisensory or multisensory dynamic visual stimuli presented in the space near the hand, the face or the trunk (Bremmer et al., 2001; Brozzoli et al., 2011, 2012, 2013; Ferri et al., 2015; Gentile et al., 2011, 2013; Holt et al., 2014; Huang et al., 2012; Makin et al., 2007; Schaefer et al., 2012; Sereno and Huang, 2006), identifying regions within parietal and premotor cortices that displayed enhanced or selective activation when stimuli were close to the body, without a clear and direct comparison between PPS representations depending on the part of the body stimulated (but see Grivaz et al., 2017). Brozzoli and coworkers identified through fMRI adaptation a reduction of neural activity following the repetition of near visual stimuli close to the hand within a parieto-premotor network including supramarginal gyrus (SMG), intraparietal sulcus (IPS) and dorsal and ventral premotor cortices (PMd, PMv, Brozzoli et al., 2011). Other investigations relying on different fMRI paradigms converge to indicate the involvement of this network in coding stimuli in close space in humans (Bremmer et al., 2001; Brozzoli et al., 2011, 2012; Gentile et al., 2013; Holt et al., 2014; Makin et al., 2007; Quinlan and Culham, 2007) reporting further activations in the insula (Gentile et al., 2011; Schaefer et al., 2012a) and, subcortically, in the putamen (Brozzoli et al., 2011; Gentile et al., 2011). A recent meta-analysis (Grivaz et al., 2017) also points toward a common denominator subserving PPS representation, which includes the postcentral gyrus, IPS, SMG and precentral gyrus (i.e. PMv). How does the network revealed in humans using fMRI relate to that observed in monkeys through single-cell recordings? Can we identify specificities in the neural correlates of PPS representation depending on the body parts stimulated in the same individual?

In light with the first question and to the best of our knowledge, only one study has attempted to unveil the neural correlates of PPS representation in monkeys using fMRI. Cléry et al. (2018) used a naturalistic 3D environment where a cube was presented either close or far from the monkey's body and also found the involvement of a parieto-premotor network in the processing of stimuli near the body (VIP and premotor area F4, Bremmer et al., 2013; Duhamel et al., 1998; Graziano et al., 1994; Rizzolatti et al., 1981a, 1981b). Yet, the network described in their study was far more extended than that previously described by both electrophysiological studies in macaques and fMRI studies in humans, also including regions in posterior and medial parietal areas, area SII and the STS. Single-unit electrophysiological studies in macaque monkeys have focused on specific predefined regions (putamen, premotor and parietal cortices), thus failing to observe the activity of an entire network and its interactions with other brain regions, even with multi-site recordings. Their advantageous

spatial resolution comes thus at the expenses of a reliable comparison with the neuroimaging results available in humans, which have the advantage to provide more holistic information on the whole-brain network of areas involved in PPS representation. Furthermore, electrophysiological recordings provide a direct measure of neural activity of a single neuron, whereas whole brain fMRI approach provides an indirect measure of brain activity, sampling the responses of thousands of neurons (i.e. BOLD signal). To compare human fMRI and monkey electrophysiology suffers of discrepancies which are also due to the different experimental paradigms (Boynton, 2011). Applying fMRI to both species, employing the same protocol of stimulation for investigating PPS, the first aim of the current study is to bridge the gap between these two major sources of knowledge about the primate brain. To develop two experimental protocols as similar as possible, considering the different positions of the human (lying in the scanner) and non-human participants (sphinx in an fMRI-compatible chair), the visual stimulation used for the comparison between species was presented only close to the face. In this way, it was possible to ensure the equal distance between face and stimulation and the absence of any physical barrier between the stimulus and the body part, which is not possible in stimulations near the trunk or hand of the macaques, due to technical constraints with the presence of the chair the animals are tested in.

In addition, in humans, where the direct access to different body parts was possible, we sought to investigate the neural underpinning of body-part-centered coding of stimuli in the near space within the fronto-parietal network underlying PPS representation. We thus adapted the fMRI adaptation protocol to address this issue by presenting stimuli close to three different body parts -hand, face and trunk. Based on the previous findings described above in particular in monkeys, we predicted a somatotopically organized reduction of BOLD signal in response to repeated presentations of visual stimuli near to the hand, the trunk or the face.

2. Methods

2.1 Participants

For this study, we included two monkeys (two females rhesus monkeys, *Macaca mulatta*, 21-9 years old, hereafter M1 and M2 respectively), to minimize the use of animals, in line with the 3Rs requirements. The monkeys have been trained daily in a mock scanner to maintain fixation on a central point with their head fixed, while seated in a sphinx position in a plastic primate chair. Animals were maintained on a water and food regulation schedule,

individually tailored to maintain a stable level of performance for each monkey. All procedures follow the guidelines of European Community on animal care (European Community Council, Directive No. 86–609, November 24, 1986) and were approved by French Animal Experimentation Ethics Committee #42 (CELYNE).

Human participants (N=2, 24-30 years old, hereafter H1 and H2) were healthy volunteers with no history of neurologic or psychiatric disorders and with normal or corrected-to-normal vision (through eye-lenses). Participants were screened for MRI safety and only after meeting the previous requirements they were enrolled in the study. Written informed consent was obtained from all participants prior to participation. The study follows the Declaration of Helsinki standards and was approved by the Institut National de la Santé et de la Recherche Médicale (INSERM) Ethics Committee (SUD EST IV, ID RCB: 2010-A01180-39).

2.2 Apparatus and procedures

Human participants

During the scanning sessions, participants were lying down comfortably on the scanner bed and foam paddings have been used around their head and knees. A head coil was positioned around their head and stimuli were perceived using a mirror system attached to the scanner head coil. Participants were being told about the importance of keeping still in the scanner. Ear plugs have been used to reduce scanner noise. An MR-compatible stand for the hand (23x16 cm) was mounted on the bed above the participants' waist and was adjusted to allow them to place their (right) arm and hand comfortably at the same position across sessions. An infrared MR-compatible camera (MRC Systems) was mounted on the stand at around 60 cm of the eyes of the participants to monitor eye-movements. The task was controlled by the Presentation® program. Participants were asked to fixate at the camera while a 3D visual stimulus was presented at different distances from their face, trunk or hand (see 2.3 Experimental set-up and task), which could be placed on the stand or alongside the body, in a retracted posture.

Macaque monkeys

Macaque monkeys were surgically implanted with a MR-compatible head post under anesthesia and sterile conditions. During the surgical procedure, the animals were intubated

with a mixture of O_2 and air and their head was immobilized in a stereotactic apparatus. After an incision of the skin along the skull midline, the head fixation device was positioned on the skull, and put in place using ceramic sterile screws and dental cement following approved procedures based on the guidelines of European Community on animal care (European Community Council, Directive No. 86–609, November 24, 1986). After the surgery, monkeys recovered for at least one month. Monkeys were then trained daily to sit in a sphinx position in a plastic chair with their heads fixed, in a mock scanner mimicking the actual MRI environment. Before the scanning sessions, monkeys will undergo training every week day for 2 to 3 hours.

During the scanning sessions, the monkeys seated in a sphinx position in a plastic chair. Their head was restrained using the surgically implanted head post and they were required to fixate a LED placed at 60 cm away from their face, at eye level, aligned with their sagittal axis. Eye position was monitored at 1000 Hz during scanning using an eye-tracking system (Eyelink 1000 Plus Long Range). The horizontal (X) and vertical (Y) eye positions in degrees have been recorded from the right eye of each monkey in each run. The calibration procedure involved the central LED and 4 additional LEDs (10° eccentricity), placed in the same plane as the fixation LED. All five LEDs were sequentially switched on and off and the monkey was rewarded for orienting and maintaining its gaze towards the illuminated LED. Monkeys were rewarded with splashes of juice dispensed by a computer-controlled reward delivery system (Crist®) through a plastic tube placed in their mouth. The reward volume increased as fixation duration increased. When the animal stop fixating, the reward was suspended to encourage the monkey to keep the gaze onto the fixation point. Fixation was considered successful if the eyes remained within a window of 4° around the fixation point. The mean percentage of gaze time spent within the fixation window across runs was respectively 86% and 57% for M1 and M2. The task and all behavioral parameters were controlled by the Presentation® program.

2.3 Experimental set-up and task

Humans and monkeys were instructed or trained to maintain their gaze during all scanning sessions. One experimenter stimulated the space around the participant by moving a visual stimulus either close (at 2 cm) or far (at 100 cm) from the body-part or the stand, depending on the experimental condition. These distances correspond to those used in single-

cell recoding experiments in monkeys (Rizzolatti et al., 1981b) and in fMRI studies on humans (Brozzoli et al., 2011). The visual stimulus consisted of two fluorescent plastic balls (2 cm diameter) mounted on the tip of two carbon sticks (150 cm long for the close ball and 100 cm for the far ball). Real physical objects were used, rather than artificial computer-generated stimuli, to increase the similarity between our protocol and those used in electrophysiological studies. As humans or monkeys maintained central fixation, the ball appeared in their right peripheral visual field. Only the last portion of the carbon stick and the ball attached to it were visible to the subjects. For the monkeys, because of their sphinx position, a curtain was attached at the edge of the scanner bore to allow the vision of only the last part of the stick and the ball, equaling the experimental conditions of human participants. The experimenter listened to audio instructions regarding the location of the forthcoming stimuli and to a metronome set to a pace of 1 Hz, to guide him to perform up and down movements of 5 cm amplitude of the ball at each position. Ball's movements were video-recorded to check for the accuracy of stimulation offline.

During the scanning session, at the beginning of each run, the position of human participants' right hand was adjusted to keep it on the stand or to retract it along the right side of the body. The experimenter moved the ball either close to the hand on the stand (HAND condition), the face (FACE condition, hand retracted and non-visible) or the empty stand (TRUNK condition, hand retracted and non-visible), in order to assess hand, face and trunk-based PPS representations, respectively. To investigate the neural underpinnings of these PPS representations, looking for both overlaps and possible differences, the three stimulation conditions were compared in human participants. Monkeys maintained their hands retracted inside the chair, and the experimenter could only move the ball close to or far from the face (FACE condition). This type of protocol allowed us to investigate the hand-, trunk- and face-based PPS representations in healthy humans and, at the same time, to compare the human's and non-human primate's face-centered PPS.

The fMRI adaptation protocol we adopted included four combinations of visual stimuli: Near-Near, Near-Far, Far-Near, and Far-Far, each combination lasting a total of 6 s divided into a first and second part of equal length. Therefore, each stimulation period lasting 3 s was modelled with 8 separate regressors: Near before Near, Near after Near, Near before Far, Far after Near, Far before Near, Near after Far, Far before Far and Far after Far (Figure 2). Each run was composed of these 4 combinations of stimuli repeated 12 times (48 stimuli per run).

Consecutive trials were separated by a jittered inter-trials baseline interval (3 to 11 s) with no stimulation (see Figure 1). During these baseline periods, humans and monkeys should maintain their gaze on the central fixation point. In each human session, a total of 6 runs were collected: 1) two runs with the right hand visible and visual stimulation close to or far from it, 2) two runs with hands retracted and visual stimulation close to or far from the stand 3) two runs with hands retracted and visual stimulation close to or far from the face. The order of the 3 different types of runs was counterbalanced across sessions. For monkeys, a total of 17 and 15 runs, respectively for M1 and M2, with the visual stimulation close to or far from the face have been collected across different sessions.

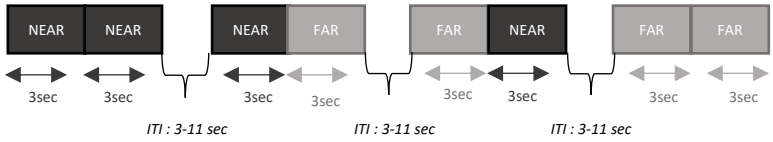


Figure 1: Task design. The four combinations of stimuli adopted in the study: Near-Near, Near-Far, Far-Near and Far-Far. Each combination was split into two parts of 3 sec each for a total duration of 6 sec. One run was composed of these 4 combinations of stimuli repeated 12 times. Conditions were separated by a jittered inter-trial interval (ITI, 3-to-11 s) with no stimulation.

2.4 MRI Data acquisition

Neuroimaging data have been collected using a 3T Siemens Magnetom Prisma scanner. In humans, we used a Siemens 64-channel head coil. An anatomical MRI has been collected for each participant at the beginning of the experiment using a T1-weighted MPRAGE 3D (voxel size=1x1x1 mm; 192 slices, TR=3000 ms, TE=3.34 ms, TI=1100 ms, flip angle=8°, matrix: 224x256). For each fMRI volume, 40 slices covering the whole brain hava been collected in an ascending order (BOLD-sensitive T2* weighted echo planar sequence, TR=2200 ms, TE=29 ms, flip angle=90°, FOV=546x546mm, matrix size=78x78, voxel size=2.7 mm^3). Each run consisted of 320 volumes for a total of 2100 volumes per session.

In monkeys, MRI images have been collected with a custom-made 8 channels receive surface coil, positioned around the head. A circular transmit coil was positioned above the head (Mareyam et al., In: Proceedings of the 19th Annual Meeting of ISMRM, Montreal, Canada, 2011). For each fMRI volume, 38 slices covering the whole brain have been collected in an ascending order (BOLD-sensitive T2* weighted echo planar sequence, TR=2500 ms, TE=30 ms, flip angle=90°, FOV=588x532 mm, matrix size=84x76, voxel size=1.25 mm^3). Each run

consisted of 350 volumes for a total of 1980 volumes per session. The anatomical MRI data have been collected at the beginning of the experiment in high-resolution T1-weighted MPRAGE 3D in the sagittal plane (voxel size=0.5 mm^3 thickness, TR=3000 ms, TE=3.62 ms, FOV=320 x 210).

2.5 MRI Data preprocessing

fMRI data have been preprocessed with SPM12 software (Wellcome Department of Cognitive Neurology). For humans, functional images have been realigned to correct for head movements and underwent slice timing correction. The anatomic and functional volumes have been coregistered with the high-resolution structural scan from each individual participant and normalized to Montreal Neurological Institute (MNI) standard brain space. The anatomical images have been segmented into white matter, gray matter, and CSF partitions and also normalized to the MNI space. For monkeys, the same preprocessing has been applied to anatomical and to all functional volumes except for the normalization. The functional images have been then spatially smoothed with an 8 and 4 mm FWHM isotropic Gaussian kernel, in humans and monkeys, respectively, based on the respective voxel size for each species.

2.6 Regions of Interest

The regions of interest (ROIs) of the e humans ROIs, the following regions of the AAL3v1 atlas (Rolls et al., 2020) were considered bilaterally: precentral gyrus, postcentral gyrus, superior and inferior parietal lobule, supramarginal gyrus and putamen (Bremmer et al., 2001; Brozzoli et al., 2011, 2012; Gentile et al., 2011, 2013; Holt et al., 2014; Makin et al., 2007; Quinlan and Culham, 2007; Schaefer et al., 2012b; and see Grivaz et al., 2017 for a meta-analysis). To refine the localization of the activation peaks, we then used the Glasser multi-modal Atlas parcellation (Glasser et al., 2016), carried out on four different features, including both anatomical and functional criterion: cortical thickness, myelin maps, task fMRI and resting state fMRI (Glasser et al., 2016). Similarly, the results from the literature on the neural basis of the monkeys' PPS suggested bilateral extraction of the premotor area, S1, ventro-medial and lateral IPS, area 7 and area 5 (Bremmer et al., 2013; Colby and Duhamel, 1991, 1996; Colby et al., 1993; Graziano and Cooke, 2006; Graziano et al., 1994; Leinonen et al., 1979; Rizzolatti et al., 1981b; Robinson et al., 1978) ROIs from the fourth level of the CHARM atlas (Jung et al., 2021). Furthermore, from the fourth level of the SARM atlas (Hartig et al., 2021) the ROI of the putamen was extracted at bilateral level (Graziano and

Gross, 1993). As for human participants, a more detailed localization of activation peaks was achieved thanks to the 6 levels of the CHARM and SARM atlases, which also feature fined-grained anatomical and functional descriptions of brain areas.

3. Imaging Data Analyses

Our aim is to identify brain regions that are sensitive to the presentation of visual stimuli in near space (i.e. PPS) in humans and macaques within the ROIs mask. We performed first-level univariate and adaptation analyses on smoothed data, by defining a general linear regression model to all runs concatenated across sessions, depending on the body-part stimulated. We further performed multi-voxel pattern analyses (MVPA) on the unsmoothed data (see description below). Furthermore, we performed conjunction and disjunction analyses on both univariate and MVPA results on human participants to investigate both overlapping and specificities of the three body-part-based PPS representations. Details about adaptations analyses, tables and results could be found in Supplementary Materials.

3.1 Univariate fMRI analysis: neural correlates of near space processing in macaques and humans

First, in order to identify brain regions implicated in near space processing independently of the body part stimulated we defined regressors of interest corresponding to near or far space in each run: Near-before-Near, Near-after-Near, Near-before-Far and Near-after-Far for the near space processing and Far-before-Far, Far-after-Far, Far-before-Near and Far-after-Near for the far space processing. These 8 regressors have been modeled with the standard SPM12 hemodynamic response function. In addition, 6 regressors of no interest have been modeled, corresponding to the head movement parameters in each run. In the first level analysis, we compared near stimulations (combining Near-before-Near, Near-after-Near, Near-before-Far and Near-after-Far regressors of interest) with far stimulation (combining Far-before-Far, Far-after-Far, Far-before-Near and Far-after-Near regressors of interest) including all conditions (i.e. 6 runs per session in total: face, hand and trunk, which means a total of 30 runs per subjects) (**Table 1**). The results from this analysis provided beta estimates, ined by contrasting these two groups of conditions for each subject. We first thresholded the activations at $p<0.001$ uncorrected and reported only the clusters surviving a significance

cluster threshold of $p<0.05$, corrected using Family-wise error rate (FWE) implemented in SPM12.

3.2 Multi-voxel pattern analysis: specific activation patterns for representations of space centered on different body parts

It is possible that the differences between near and far stimulations are represented by patterns of activations within the selected ROIs, rather than specific and punctual variations of activation within these areas. In the first case, a general linear model could not capture these differences, and even adaptation analyses (see Supplementary Materials), despite the greater spatial resolution power of the reported signal, could not provide information regarding the spatial distribution of specific activations. For this reason, we conducted MVPA at the single subject level. For this purpose, the acquired images were subjected to the same preprocessing described above, but without proceeding with the final smoothing.

Firstly, we calculated the β weights of the eight stimulation conditions (Near before Near, Near after Near, Near before Far, Near after Far and vice versa for far stimulations) for each run of each humans and non-human primates participant, within the ROI mask previously described. In this way, 30 β weights were obtained for each condition for each human participant and 17 and 15 β weights respectively for M1 and M2. To investigate the difference between stimulations close to and distant from specific body-parts, we selected the four Near conditions (Near-before-Near, Near-after-Near, Near-before-Far, Near-after-Far) and the four Far conditions (Far-before-Far, Far-after-Far, Far-before-Near, Far-after-Near) of each body district (HAND, FACE, TRUNK) and for each voxel within the ROI mask we defined a spherical neighborhood of 100 voxels (searchlight). Considering the different extension of the investigated surface in human participants (7519 voxels) and in non-human primates (1697 voxels), the extension of the searchlight was also adapted according to the species: 100 voxels in human participants, 20 voxels in monkeys (the results of the analyses conducted with a searchlight of 100 voxels in the two macaques were in line with those that will be reported here). We then conducted a searchlight analysis using the linear discriminant analysis (LDA) classifier implemented in CoSMoMVPA (Oosterhof et al., 2016) with a leave-one-out approach (see Table 1): the accuracy map was then obtained by training the classifier on the near versus far difference in n-1 runs (n=10 for humans participants, 17 and 15 for monkeys) and testing this difference on the remaining run. To compare the accuracy map of the classification thus obtained against the chance level, we performed a threshold-free cluster

enhancement (TFCE) analysis (through cosmo_montecarlo_cluster_stat, implemented in CoSMoMVPA) defining a mean of 0.5 under the null hypothesis and comparing the initial accuracy map versus 1000 maps with permuted targets (the Near and Far conditions used in training and test). Finally, we reported the voxelwise corrected statistical map ($z=1.65$; $p<0.05$, one-sided t test) for each participant and each spatial district investigated.

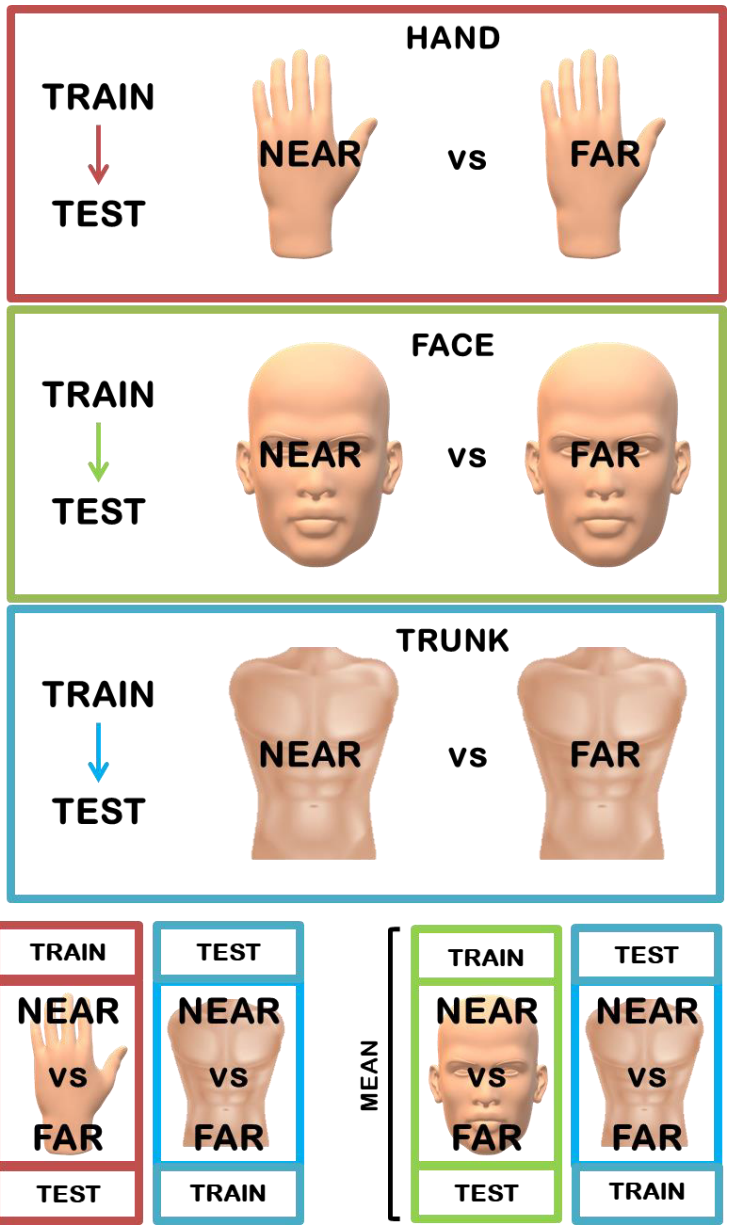
Complementary to the MVPA analysis described above, we conducted cross-validation analyses to investigate the discriminability of the activation patterns linked to the specific body districts stimulated. As in the previous analysis, the β weights of each condition in each run were introduced into an LDA classifier with a leave-one-out cross-validation approach (see Table 1). In this method, the classifier is trained on n-1 runs of the conditions of one of the investigated body districts (i.e., the face) and tested on the remaining run of another district (i.e., the hand). A searchlight including 100 voxels (20 voxels for non-human primates) around the central voxel was then conducted for each voxel in the ROI mask. In addition to the statistical map obtained in this way, another 1000 maps were obtained by randomly permuting the training and testing runs. As previously described, these maps were subjected to a TFCE analysis with a mean of 0.5 under the null hypothesis, in order to report the voxelwise-corrected maps for each participant ($z=1.65$; $p<0.05$, one-sided t test).

3.3 Conjunction analysis in humans: common and specific representations of space centered on different body parts

To test our second hypothesis, concerning the possible specificities at the level of brain activations for the different body parts, we conducted disjunction analyss between the HAND, FACE and TRUNK conditions using the AFNI *3dcalc-step* function, using as input the thresholded maps of these three conditions obtained through the univariate analyses. In this way, it is possible to observe the specific activations of each condition, with the hypothesis that stimuli close to different body-parts induce spatially distinct activation peaks within the same ROIs. Furthermore, we studied the conjunction between the different conditions, highlighting the common activations induced by stimulations close to the hand, the face and the trunk, regardless of the body-parts.

Table 1: **Summary of the planned fMRI analysis.** On the left, univariate analysis to compare near and far stimulations, for all conditions (HAND, TRUNK and FACE). On the right, MVPA classifier within condition, trained and tested on the near vs far difference with a leave-one-out method. In the lower panel, cross-validation MVPA, training the classifier on the near vs far difference in one condition and testing it on a different condition, with a leave-one-out method.

	Univariate Analyses
Selectivity for NEAR stimulations	**Near Condition**
	Near-Before-Near
	Near-After-Near
	Near-Before-Far
	Near-After-Far
	versus
	Far Condition
	Far-Before-Far
	Far-After-Far
	Far-Before-Near
	Far-After-Near



4. Results

4.1 First Aim: cross-species comparison of head-based PPS

Human's univariate and MVPA fMRI analyses

First-level analyses of brain responses associated to stimuli near to or far from the face stimulations on human participants highlighted the broadest network of activations. Comparing the Near versus the Far regressors, it was possible to find five different clusters in the subject H1, three in the right hemisphere and two in the left one. In the right hemisphere, such clusters include SMG, S1 (k=269, t_{peak}=16.21), the IPS (k=519, t_{peak}=14.45) and several

portion of the premotor cortex, including PMd and PMv (k=220, t_{peak}=8.83). The two clusters on the left cover the homologous contralateral areas: the IPS (k=394, t_{peak}=12.2), S1 and large portions of both the SMG and the premotor cortex (k=1331, t_{peak}=9). The activations observed for subject H2 are consistent with those observed for H1, with two significant clusters per cerebral hemisphere. The two right-hemisphere clusters include broad regions of the SMG, IPS, S1 (k=1436, t_{peak}=15.74) and premotor cortex (k=292, t_{peak}=10.94). The left clusters include the contralateral homologous areas: IPS (k=421, t_{peak}=14.35), SMG, S1 and a large part of the premotor cortex (k=1120, t_{peak}=12.02). An exhaustive list of the clusters of activation can be found in Table 2A, significant clusters are also displayed in Figure 2A.

The results obtained by the LDA classifier used to investigate the discriminability between stimulations near and far from the face revealed activation patterns similar to those observed for the hand and the trunk (displayed in Figure 3A). In particular, a bilateral pattern of activations is observed for both H1 and H2, with a cluster in the left hemisphere (k=1851, z_{peak}=3.09 and k=2107, z_{peak}=3.09 for H1 and H2 respectively) including wide portions of the SMG, the premotor region, the IPS and the postcentral gyrus. In the right hemisphere, both subjects show activation clusters (k=2064, z_{peak}=3.09 and k=2411, z_{peak}=3.09 for H1 and H2 respectively) that include the same areas described for the left hemisphere: SMG, PMd, PMv, S1 and IPS among the others. The exhaustive list of the areas involved in this broad activation pattern is reported in Table 3A.

To summarize, the results obtained with the univariate and MVPA analyses (as well as with the adaptation analyses, see Supplementary Materials) on human participants are consistent with each other in showing a fronto-parieto-supramarginal activation network underlying the encoding of visual stimuli close to the head.

Monkey's univariate and MVPA analyses

Consistent with what has been observed for humans, brain responses to stimulation near the face involve a large bilateral network in monkeys. In M1, three significant clusters ($p<0.05$ FWE corrected) are observed, two of which lateralized to the left and including the areas F4, F5, PMdc (k=97, t_{peak}=11.02) and the putamen (k=100, t_{peak}=6.68). The remaining cluster is very large (k=727, t_{peak}=16.29) and covers both hemispheres, reporting activation peaks in

multiple PPS-related areas, such as MIP, VIP, LIPd and area 7 bilaterally plus area 5, the putamen and somatosensory areas 1-2 in the right hemisphere.
Also for the second monkey, close-to-the-face stimuli activate a large bilateral network. Four significant clusters are found, of which only one on the left (k=624, t_{peak}=17.15) and including LIPv, VIP, areas 7a and 7b, premotor areas F4, F5 and PMdc, areas 1-2 and the putamen. The three clusters of the right hemisphere, in turn, cover premotor areas, such as F5 and PMdc (k=107, t_{peak}=10.93), parietal areas, such as LIPv, VIP and the right area 3a/b (k=241, t_{peak}=8.93) and the putamen (k=136, t_{peak}=8.69). Results of this analysis are reported in Table 2B and displayed in Figure 2B.

As observed in human participants, also in monkeys the activation pattern related to the Face condition is very extensive, and reports activation peaks in both hemispheres, both at cortical and subcortical level. For M1, a pattern consisting of two clusters in the left hemisphere and two in the right one is observed. In both hemispheres one of the clusters is located frontally, including the entire premotor cortex (F4, F5, PMdc and PMdr) on the left (k=108, z_{peak}=3.09) and the premotor cortex (F4, F5) plus the putamen on the right (k=55, z_{peak}=3.09). The other cluster of each hemisphere is located in a more posterior position, at the parietal level; on the left (k =204, z_{peak}=3.09) it involves PPS-related areas such as VIP, MIP, area 5, different portions of area 7 (7b, 7a, 7_OP) and the lateral section of the IPS (AIP, LIPv, LIPd). On the right (k=105, z_{peak}=3.09) we find activations consistent with the contralateral cluster, with the exception of AIP. M2 also shows an activation pattern sensitive to the difference between close-to and far-from the face stimulations involving PPS-related fronto-parietal areas of both hemispheres. A large cluster in the left hemisphere (k=738, z_{peak}=3.09) reports activation peaks at the subcortical level (putamen), frontal cortex (premotor regions such as F4, F5 and PMdc, but also somatosensory regions such as areas 1, 2 and 3a/b) and parietal cortex (large portions of area 7, area 5 and the lateral and ventro-medial regions of the IPS). On the right, the pattern consists of two different clusters, one subcortical (putamen, k=71, z_{peak}=3.09) and one cortical (k=506, z_{peak}=3.09), including premotor regions F4 and F5, somatosensory areas and parietal areas located in area 5, area 7 and in the lateral and ventromedial portions of the IPS. These results are reported in Table 3B and illustrated in Figure 3B.

To summarize, univariate and MVPA analyses on non-human primates also identified a fronto-parietal network of areas associated with the encoding of stimuli close to the head. These results, in addition to being in line with what has been observed in the literature (see

Cléry et al., 2015a for review), are similar to those observed in human participants (see Discussion).

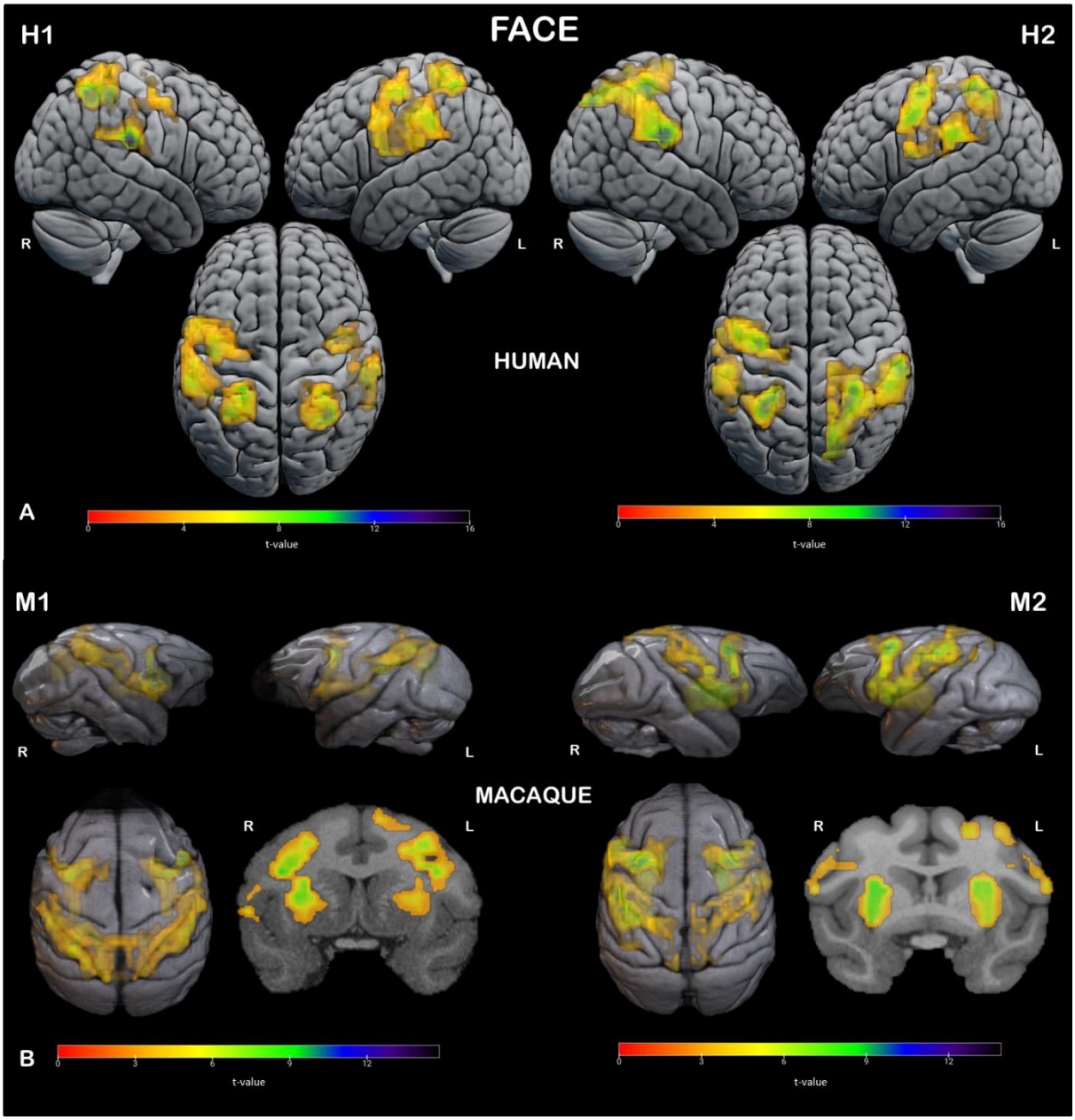


Figure 2. Results from univariate analyses comparing visual stimuli close to or far from the FACE in humans (A) and non-human primates (B). t-maps of significant clusters ($p<0.05$, cluster-based FWE corrected) for Near vs Far stimulations for H1 (upper left), H2 (upper right), M1 (lower left) and M2 (lower right).

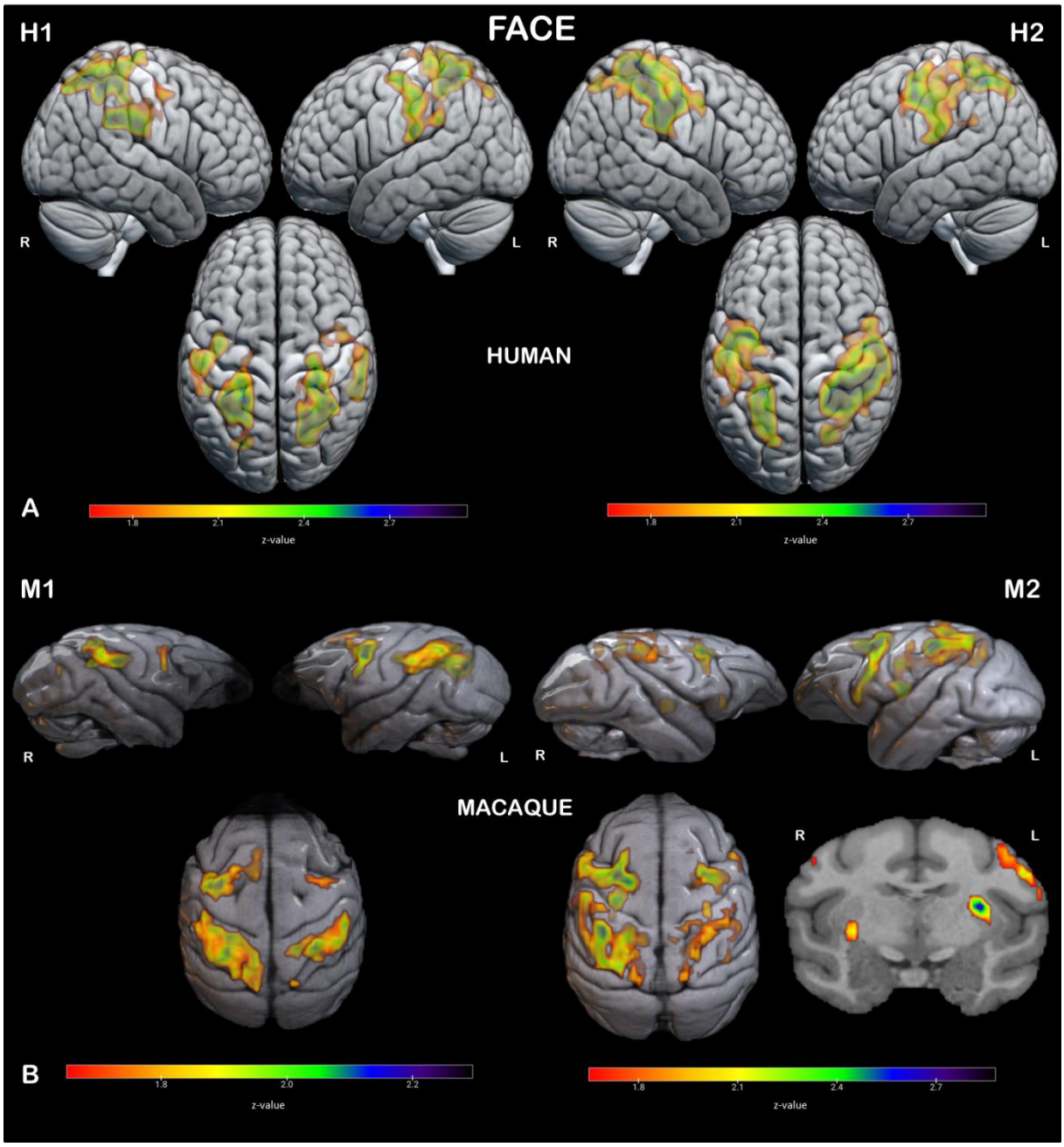


Figure 3. Results from MVPA comparing visual stimuli close to or far from the FACE in human (A) and non-human primates (B). z-maps of significant clusters (z<1.65, one-sided t test) for Near vs Far stimulations for participants H1 (upper left), H2 (upper right), M1 (lower left) and M2 (lower right). For illustrative purposes, z-maps were smoothed after statistics (6 and 2 voxels smoothing for humans and monkeys respectively).

4.2 Second Aim: between body-parts-based PPS comparisons in humans

Visual stimulation presented near the face showed activation clusters consistent with what has been observed in the literature (see Grivaz et al., 2017), including a network of fronto-parietal areas involving the dorsal and ventral premotor cortices, large portions of bilateral SMG, IPS and adjacent parietal regions. To compare the specific and common neural activations for the

three body districts investigated, we conducted univariate, adaptation and MVPA analyses (the last two approaches reported in Supplementary Materials) also on the responses observed following stimulations presented near to or far from the hand and trunk.

Univariate fMRI analysis: Hand

We performed a first-level analysis by defining a general linear regression model to the data. We compared all Near regressors with all Far regressors**,** corresponding respectively to visual stimulation near to and far from the hand. For H1, the univariate contrast between near and far hand stimulations revealed two significant activation clusters, one in the left hemisphere (k=1627, t_{peak}=18.56) including several peaks of activation in all the ROIs (SMG, IPL, SPL, Precentral and Postcentral gyri), and a smaller one in the right hemisphere (k=309, t_{peak}=13.54), including SMG and the postcentral gyrus. H2 reported an activation cluster at the level of the right SMG (k=168, t_{peak}=10.41) and three clusters in the left hemisphere, including several IPS portions and S1 (k =426 t_{peak}=16.3), the SMG (k=366, t_{peak}=14.53) and the premotor region (k=137, t_{peak}=8.78). These results are displayed in Figure 4; peak of activations and the respective MNI coordinates are reported in Table 4.

Univariate fMRI analysis: Trunk

As already described for the hand, first-level analyses were conducted to compare the Near versus the Far regressors in the trunk condition. In H1, the contrast shows two significant clusters, one in the left hemisphere (k=959, t_{peak}=11.37), including areas in the SMG, the IPS and S1, the other in the right hemisphere (k=150, t_{peak}=9.58), involving several portions of the SMG ROI. The second participant, on the other hand, reports a significant cluster (k=316, t_{peak}=11.93), lateralized to the left and including several portions of the IPS and S1. These results are displayed in Figure 4; peak of activations in MNI coordinates are reported in Table 5.

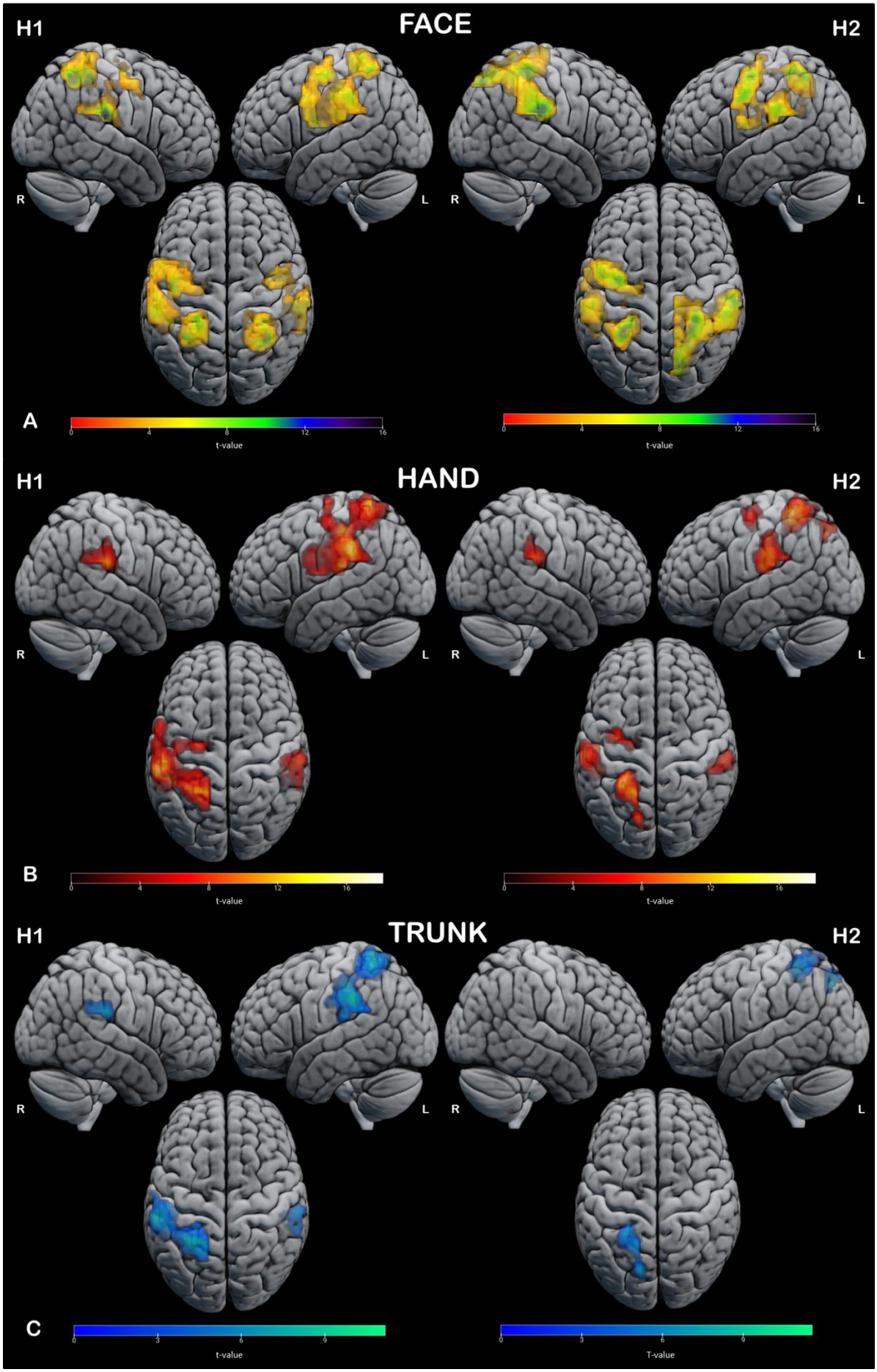


Figure 4. Results from univariate analyses comparing visual stimuli close to or far from the FACE (A), the HAND (B) or the TRUNK (C) in human participants. t-maps of significant clusters ($p<0.05$, cluster-based FWE corrected) for Near vs Far stimulations for H1 (left side) and H2 (right side).

Cross-classification between different body-parts

In search of an activation pattern sensitive to the difference between close-to or far-from the body stimulations, regardless of the stimulated body-part, we conducted cross-classification MVPA analyses between the three conditions (HAND, TRUNK and FACE). By training the classifier on the activation associated with stimulations near or far from a specific part of the body and testing it on the pattern related to this difference but associated with a different body-part (see Table 1), it is indeed possible to investigate common activations across body sectors.
The results relating to the three different dyads tested (Hand-Trunk, Hand-Face and Trunk-Face) are shown in Table 6. The activation loci are reported in MNI coordinates.

By training the classifier on the near-far difference associated with the Hand condition and testing it on the Trunk one, it was possible to observe a pattern of activations common to these body districts in both H1 and H2. The pattern of responses common to these two conditions is quite broad in both participants, and involves a bilateral network of fronto-parietal areas. In H1 a large cluster is observed in the left hemisphere (k=2664, z_{peak}=3.09) with activations in all the ROIs tested and in particular in PMd, PMv, and several portions of the IPS (VIP, LIPd, LIPv) and of the PF complex. These activations are also found in the right hemisphere, divided into three different clusters (respectively k = 842, z_{peak} = 3.09; k = 211, z_{peak} = 3.09; k = 36, z_{peak} = 2.17). Moreover, both hemispheres reported activations in somatosensory areas as 1, 2, 3a and 3b. Similarly, a left cluster (k = 2313, z_{peak} = 3.09) is found in H2 response pattern including the same areas described for participant H1, and including also MIP and AIP regions within the IPS. Finally, the two clusters observed in the right hemisphere reported peaks of activation in the same areas (respectively k = 1918, z_{peak} = 3.09 and k = 9, z_{peak} = 1.94).

The common response pattern to hand and trunk conditions appears to be the largest, in both participants. However, the other two dyads tested also report common responses. Regarding Hand-Face cross-validation, for example, H1 reports two clusters in the left hemisphere including SMG (PFcm, PFop, PFt and PSL), premotor regions (PMd and PMv), several portions of postcentral gyrus such as S1 and M1 (k = 884, z_{peak} = 3.09) and a small cluster in the IPS (k = 10, z_{peak} = 1.91). In the right hemisphere, common activations are divided into a cluster at the SMG level (k = 341, z_{peak} = 3.09), including a broad portion of the PF complex,

and one in the postcentral gyrus (k = 45, z_{peak} = 2.47), including areas 2 and 3b. Also for H2 the activation pattern is distributed bilaterally, with a left cluster (k = 836, z_{peak} = 3.09) including SMG, PMd, PMv, M1, S1 and IPS (LIPv and AIP) and a right cluster (k = 960, z_{peak} = 3.09) involving PMd, IPS (VIP and AIP), area 7 in the superior parietal lobule, the PF complex and different portions of S1 (areas 2, 3a and 3b).

The third dyad investigated, Trunk-Face, is the one that reported the least extensive pattern of common activations. However, a strong overlap of activations in PPS-related areas is observed. H1 reports indeed an activation cluster at the level of the right SMG (k = 254, z_{peak} = 3.09), including a large part of the PF complex, and three clusters in the left hemisphere, located at the level of the SMG (k = 551, z_{peak} = 3.09), of the postcentral gyrus (k = 98, z_{peak} = 3.09), including areas 1 and 3b, and IPS (k = 58, z_{peak} = 3.09), particularly VIP and LIPv. The clusters at the level of SMG and IPS in the left hemisphere are also found in H2 (respectively k = 168, z_{peak} = 3.09 and k = 173, z_{peak} = 3.09), to which however a small more frontal cluster is added, at the level of PMd (k = 22, z_{peak} = 2.87). In the right hemisphere, activations in SMG are confirmed and an activation peak in premotor region is added (k = 480, z_{peak} = 3.09).

To summarize, the cross-validation analyses carried out between the three different dyads of body parts investigated allowed us to observe that, although important similarities are present, the fronto-parieto-supramarginal networks involved in the encoding of stimulations near different parts of the body have some differences. These results, treated in more detail in the Discussion, are consistent with the body-part-centered reference frame of the PPS highlighted in the literature.

Conjunction analyses: a common pattern of activations for hand-, face- and trunk-based PPS representation

In order to compare the activation pattern in response to stimuli close to the body elicited by the three experimental conditions (HAND, FACE and TRUNK), we then conducted conjunction analyses on the human participants using the thresholded maps of activations obtained through the univariate analyses of each condition.

Consistent with the MVPA results, these analyses revealed the existence of a common activation cluster, in both subjects, at the level of the superior and inferior left parietal lobules. In particular, both H1 and H2 reported activations in different portions of the left IPS, such as LIPv, the lateral section of area 7a and area 7PC. Within this activation cluster, a peak is also found in the postcentral gyrus, within area 2 (S1). However, the activations common to

HAND, FACE and TRUNK conditions are not limited to this region for H1, whose left hemisphere cluster also includes other regions of the superior (medial 7A, area 5 and VIP) and inferior parietal lobule (PFt and PFcm) and a large part of the supramarginal gyrus (including the areas OP4, PFop, PFt, PF and PSL). Moreover, H1 also reports activations in the right hemisphere, again at the level of the supramarginal region including the two sections of the PF complex, PFop and PFcm, the perisilvian region (PSL) and the superal temporal visual area.
These results therefore confirm the existence of a core of brain areas that seem to respond to the distance of stimulations from the body independently of the body-part involved.

In addition to this overlapping between the neural response to close to the hand, the face and the trunk stimulations, we investigated brain regions that reported preferential responses only to stimuli presented near the hand or face. Evidence in the literature reports, especially at the premotor level, the existence of neurons active in response to stimulations close to the hand or to the mouth (Rizzolatti et al., 1981a, 1981b), or able to respond to stimulations near the face and movements of the hand towards the mouth (Gentilucci et al., 1988). We therefore wondered if it was possible, through our experimental protocol, to observe brain regions in human participants capable of responding to close to the hand or to the face stimulations.
We observed areas in which the response to stimulations close to the two different body districts overlaps, especially at the level of the left precentral and supramarginal gyrus, for both participants. Indeed, both H1 and H2 report an activation cluster in the left premotor cortex, including different portions of area 6 (including its dorsal, ventral, anterior and medial-posterior parts). It is interesting to observe that this cluster seems to interpose itself between premotor regions with preferential response to close to the hand stimuli and regions with face-specific preferential responses, in both participants. The same appears to be true in left SMG, where both participants report an activation cluster that includes several portions of the PF complex, including PFt and PFop. In this case, however, the activation cluster of H1 are less extended and more lateralized than that of H2, but this is due to the greater extension in H1 of the supramarginal cluster in which the conjunction of the responses to the three stimulated parts of the body is found. . In both subjects, however, this cluster of response to close to the hand or the face stimuli is localized between the hand-specific areas at the postcentral / precentral level and the more posterior and superior supramarginal areas, where in H2 specific responses are found for stimuli within the peri-head space and in H1 nonspecific responses for all stimuli close to the body. Finally, both subjects show a small

cluster at the level of the SPL, where the conjunction between the three parts of the body takes over, centered in both cases in the most dorsal section of the 7Al area.

In the right hemisphere, on the other hand, overlapping clusters between hand and face are found only in the SMG, including the more anterior and posterior portions of the PF complex in H1, bordering the area in which the triple conjunction takes place, and the central portion in H2, which did not displayed triple conjunction in this hemisphere. In this second case, hand-face activations were surrounded by face-specific response regions.
Results of these conjunction analyses are reported in Table 7 and displayed in Figure 5.

Specific neural activations for hand-, face- and trunk-based PPS

Besides to the common activations for stimulations within different body-part-based PPS representation, our initial hypothesis concerns the possible differences, at the neural level, of these latter. For this reason, we identified regions that selectively responded to visual unimodal stimulations presented near the face, hand or trunk. The activation peaks for each body part are reported in Table 8 and displayed for both participants in Figure 8. Qualitatively, the results show that the representation of each body part stimulation has a different spatial pattern and extension, with a more restricted territory for trunk representation. The representation of the space around the head and hand shows more extensive and bilateral activations, especially at the supramarginal and premotor level. It is in these two regions that the greatest overlaps are found between the activations associated with these two body districts, while the neural responses associated with stimulations close to the trunk are more represented at the parietal level, and particularly in the left hemisphere.

Specifically, the trunk (represented in light blue in Figure 5) appears to be the body part with less specific activation: H2 does not exhibit any significant activation and in H1 only a small cluster can be observed at the parietal level, including the posterior part of area 7PC and the central portion of the VIP.
The second specific network body-part, in order of extension, is the one related to the hand (depicted in orange in Figure 5). In this case, indeed, bilateral specific activations are observed for H1, which in the left supramarginal gyrus include the most rostral part of the OP4 area and the section of OP1 bordering the previous one, but also the most superior section of the PF complex. Still in the left hemisphere, but at the level of the IPL, hand-

specific activations are found in the sections of the AIP and the 7PC areas bordering area 2, but also in the upper part of the latter and, in the postcentral gyrus, in area 1. Finally, the last activation cluster of the left hemisphere is found more frontally, in the most dorsal part of area 55b. In the right hemisphere, H1 displays specific activations for close-to-the-hand stimulation at the SMG level, in particular in the border region between the PFt and PF area and in that between the PF and PSL area. Finally, more ventrally, an activation cluster is observed at the level of the temporo-parietal-occipital junction. H2 also reports multiple activation clusters specific to stimulations within the peri-hand space. In the left hemisphere, coherently with what was observed for H1, activations are found at the level of the SMG, in the central section of the OP4 area and in the anterior superior one of the PF complex. Still in the SMG, but more dorsally, activation clusters are found at the level of the upper portion of the PFt area and, on the border between SMG and IPL, of the most posterior part of area 1, at the limit with PFt. Finally, in the SPL, foci of hand-specific activation are found in area 7PC, in the most dorsal part of the VIP area and in area 5, bordering the lateral section of area 7A.

The last and largest specific network is that relating to stimulation within the peri-head space (represented in green in Figure 5). The two participants reported in this case multiple overlapping, in both hemispheres. At the level of the left precentral gyrus, H2 shows a large cluster of activation in the region of the posterior inferior frontal junction, which occupies the entire junction up to occupy the ventral part of the PEF, in which it is possible to find face-specific activation also for H1, and the dorsal portion of the rostral area 6. This cluster also extends to the ventral part of area 6 (PMv), where specific activations are also found for H1. Furthermore, both subjects reported activations in the left 55b area (H1 at the intersection with the most frontal area 8C, H2 more laterally and dorsally) and in PMd, bordering area 6a. Finally, with regard to the precentral gyrus, H1 reports activations of the dorsal part of the anterior region 6 and of the FEF, while H2 reports an activation cluster on the border between FEF and the precentral part of area 4.

Only the second participant reports specific activations for the face in the left postcentral gyrus, at the level of the ventral area 4 and at the intersection between areas 3a and 3b. However, at the margin between the postcentral and supramarginal gyrus, H2 reports a face-specific activation cluster slightly more anterior and ventral than observed for the hand network, at the junction between areas 2 and PFt. H1 also reports different specificities in this region, with specific activations for the face in the PO4 area more lateral than those observed for the hand.

The last clusters of H1 activation in the left hemisphere are found between IPL and SPL, at the junction between area 2, AIP and the intraparietal area, and between the postcentral gyrus and dorsal SPL, at the boundary between areas 1 and 5. On the other hand, the parietal cluster of H2 is wider, with head-specific activations in the IPL, which include the intraparietal areas 1 and 2, PFm, the ventral part of the 7PC area and the most ventral portion of the posterior aspect of the LIP area.

Also in the right hemisphere the specific activations for stimuli within the peri-head space are found at the premotor, supramarginal and parietal level, for both participants.

In this case, the clusters of the precentral gyrus are less extensive than in the left hemisphere, and not overlapping between the two participants: H1 reports activations in the lateral sector of the FEF and at the border between PMd and the precentral portion of the primary motor cortex, while H2 reports only one cluster, always in PMC, but more dorsally.

In the postcentral gyrus, contrariwise, a focus of activation common to the two participants is observed, located in the most lateral portion of the opercular part of the PF complex. The face-specific network of H2 also presents activations that also extend to the contiguous PFt and PF areas, resulting in the right SMG. It is here that we found another activation cluster common to the two participants, located in the most ventral part of the PFm area, bordering the STV area and the PSL area, sites of further face-specific activation for H2. The most dorsal part of PFm, in the IPL, is part of another H2 activation cluster, which includes this region and expands into the intraparietal area and the superior parietal lobule, in which the largest overlaps between the two participants are found. These face-specific activations seem to reflect the areas of activation common to the three body districts observed in the left hemisphere and described in the previous paragraph, including the dorsal and ventral portion of the LIP area, the anterior, medial and ventral intraparietal area and several portions of area 7 (lateral and medial 7A, 7PC). Finally, both participants report a final activation cluster in the most dorsal part of the junction between SPL and postcentral gyrus, on the border between areas 5 and 2.

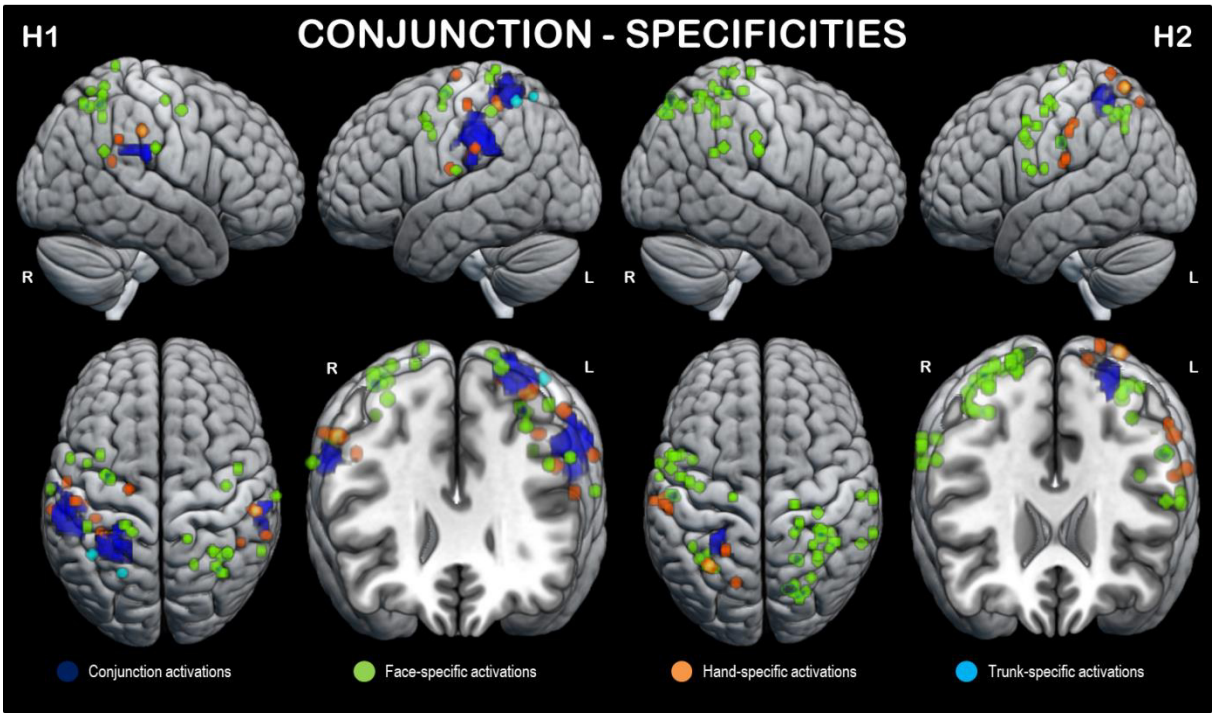


Figure 5. Peak-activation voxels reported for visual stimuli close to the face (green), the hand (orange) or the trunk (light blue) in the first (left side) and second (right side) human participants. Regions of conjunction between the activations of the three body parts are illustrated in dark blue.

5. Discussion

In our study, two human participants and two non-human primates underwent a similar experimental protocol, in which 3D visual stimuli could be presented near to or far from different body parts during fMRI recording of the respective neural responses. Main findings obtained concern the comparison of the peri-head space network between the two species and the identification of specific and common response patterns for different body-part-based PPS representations in humans.

5.1 Peri-head space underpinnings in human and non-human primates

Our study represents the first attempt to directly compare the PPS network of human and non-human primates, using the same neuroimaging technique and a similar experimental protocol. A precaution to be taken into consideration in this type of comparison concerns the possible discrepancies between the brain anatomies of the two species. A clear example concerns the intraparietal sulcus and the regions of the SPL, including the VIP. This region, strongly involved in the encoding of stimuli within the PPS, is located on the ventral fundus of the IPS in the macaque (Colby et al., 1993), while in humans various studies have located the putative

human VIP (hVIP) in different portions of the superior parietal lobule (see Foster et al., 2021). To optimize comparison, we used brain atlas that features parcellation based both anatomical and functional criteria (see methods). In particular, we found a clear overlap of the neural patterns related to the decoding of the distance of the visual stimulations used. The MVPA classifier conducted on the Near-Far difference in the two species, indeed, brings out a network of bilateral areas which, in human and non-human primates, includes important portions of the premotor cortex (both ventral and dorsal), IPS (and, more generally, of the surrounding parietal cortex) and putamen. The same activation clusters in the SMG are also observed for human participants. For the first time, therefore, fMRI data allow to observe an extensive network of subcortical and fronto-parietal cortical areas coding for the presence of a stimulus as a function of its distance from the body, both in macaques and in humans.

In monkeys, coherently with Cléry and coworkers' results (Cléry et al., 2018) and expanding the set of PPS-regions typically investigated by electrophysiological studies, we found specific responses for near visual stimuli also at the level of the premotor area F5. This area seems to be an important site for the processing of reachable stimuli and for the execution of grasping and reaching actions (Bonini et al., 2014; Murata et al., 1997; Raos et al., 2006; see Cléry et al., 2015a for review and discussion). Furthermore, its visual-tactile neurons have small receptive fields also centered on the face (Gentilucci et al., 1988; Murata et al., 1997; Raos et al., 2006; Rizzolatti and Luppino, 2001). Always in keeping with previous work, our results allow us to include within the network underlying the representation of the peri-head space also the dorsal portion of area 6 (PMdc) and the somatosensory areas 1 and 2.
The pattern of activation highlighted by the MVPA not only converge with the results obtained from the univariate analyses, but also reported the rostral dorsal premotor region (PMdr) and area 5, in particular AIP and PE, as part of the network of brain areas whose activity encodes the distance of the visual stimulus from the face. AIP, like 7a, does not seem to be directly involved in the PPS representation, but the interconnections and homologies with area 7b (Matelli and Luppino, 2001; Rizzolatti and Luppino, 2001) and the preferential response to the presentation of graspable objects (Fogassi et al., 2001; Gallese et al., 1994; Murata et al., 2000; Sakata and Taira, 1994) might explain its activation in the present study. We also found preferential activations for stimuli close to the face found at the level of the dorsal and ventral portions of the lateral intraparietal area (LIPd and LIPv). Here, close-to-the-face stimulation, but not stimulations far away, induced bilateral LIP responses. This result appears to be in agreement with the preferential response of neurons in this region to

visual stimuli presented between the monkey's body and a fixation point within the animal's reaching distance (Genovesio and Ferraina, 2004): in our experimental setting, the stimulation near the monkey's face was located within its central visual field (for which LIP neurons show a preferential response, Ben Hamed et al., 2001) and intermediate between its head and the fixation LED. Considering the similar experimental setup of Cléry and colleagues, the difference in the results could be related to the distance of the stimulation used: about 15 cm compared to about 2 cm in our study. It is interesting that, while the univariate analyses and the MVPA reported consistent results, the two adaptation analysis approaches reported small activation clusters or not sufficiently solid to resist the statistical correction. This could be due to the experimental setup used here: trials of 3 + 3 seconds may not be sufficient to induce a reduction of the response in the areas within the ROI mask adopted. It is possible that a block design (Cui and Nelissen, 2021) or a more prolonged repetition of stimulations (Kilner et al., 2014) are more suitable for eliciting this type of response, obtaining results in line with what has been observed in the other two statistical approaches.

The large network of activations described for the two monkeys is reflected in the results of the human participants, in which stimulation near the face reported the largest clusters of response that included activations at the level of the ventral premotor cortex, IPS, the primary somatosensory area and the supramarginal gyrus (Bremmer et al., 2001; Huang et al., 2012; Quinlan and Culham, 2007; Sereno and Huang, 2006), as well as more widespread activations at the level of the superior and inferior parietal cortex (which could explain any discrepancies between the coordinates of the activation peaks reported in the cited studies). The most interesting aspect, however, concerns the important overlaps of the responses observed in the two species. As for the two non-human primates, indeed, also for the two human participants the univariate analyses revealed significant activation clusters at the level of the ventral premotor cortex (homologous region of the F4 and F5 sections of the premotor area of the macaques) and of the dorsal one (reflecting the activations of the simian PMdc area). Proceeding caudally, the activations at the parietal level of the human participants are widespread, and cover large portions of the IPL and SPL, particularly in the region of the IPS. Despite the different anatomical localization compared to the putative homologous regions of the macaques, both the ventral and the dorsal sections of the LIP area are activated, confirming what has been observed in non-human primates, and this coherence of neural responses is also confirmed for the rostral section of the simian area 7 (area 7b), activated at the level of the left hemisphere of M2. Indeed, H1 and H2 show activations of the PF/PFt

complex (putative homologues region of 7b, Caspers et al., 2011) not only lateralized to the left, but also in the contralateral hemisphere. As for area 7a, activated in the left hemisphere in M2, the comparison with human participants seems more complex. The region anatomically homologous to the simian area 7a is the PFm area, which in H1 and H2 is activated only in the right hemisphere, contralaterally with respect to what is observed in M2. However, no clear homology between the two areas has so far been confirmed, and the simple rostral-caudal contiguity between PF and PFm in humans may not reflect the arrangement of 7b and 7a in macaques. Another conflicting result concerns the VIP area, activated bilaterally in the two non-human primates but absent in the activation clusters of the two human participants, at least at the level of the univariate analyses, and MIP, also activated bilaterally in M1 and M2 but found only in the right hemisphere of H2. In addition to these activations, the head-based human PPS network also extends to other regions, especially at the SMG level (multiple portions of the PF, PSL, STV and OP4 complex in particular) and parietal, in which activations of the area 7 (lateral and medial 7A and 7PC), of AIP and area 5L (putative homologue of the PE area, Scheperjans et al., 2005a, 2005b). The statistical approach of adaptation on humans allows to fill some of the inconsistencies found between the two species, reporting activations in bilateral VIP for both participants and in bilateral MIP for H2. Similarly, subcortical activations at the putamen level also emerge in human participants only through this approach, completing the comparison between the two species. However, this result is observed only through the repetition of a close-to-the-face stimulus, while the comparison between a Near-after-Near and a Near-after-Far does not report any significant result, in either human participant, following the FWE correction. Also, with regard to close-to-the-hand and to the trunk stimulations, this second adaptation approach reported clusters of activations that are less extensive than the first approach. As regards the face, in particular, it is observed that Near stimuli presented after a Far stimulus report stronger activations than a repeated Near stimulus, but this difference is not sufficiently solid to resist the correction of significance. It is possible that the first level analyses we conducted do not have sufficient power to bring out this difference, unlike the second level analyses conducted in a similar experimental paradigm (Brozzoli et al., 2011, 2012).

5.2 Body-part based PPS underpinnings in humans

In addition to near-face stimulation, human participants in our study were tested using visual stimuli presented near two other body districts, namely the right hand and the trunk. After the

study by Huang and collaborators (Huang et al., 2012), ours is the first attempt to compare the neural basis of human PPS representations based on different body parts.

As previously described, the visual stimulations presented near the head, the trunk and the hand allowed to observe neural responses consistent with what has been reported in the literature (Bremmer et al., 2001; Brozzoli et al., 2011, 2012; Gentile et al., 2011, 2013; Makin et al., 2007). Although with some peculiarities related to the stimulated body district, the involvement of a fronto-parieto-supramarginal network is evident, including premotor (especially PMd), intraparietal, superior parietal and supramarginal regions (in particular large portions of the PF complex). Univariate and adaptation analyses, however, failed to report activations in the putamen, previously observed in associations with visual stimulations close to the hand (Brozzoli et al., 2011; 2012).

The MVPA classifier allowed us to deepen these results by investigating the pattern of areas involved in decoding the distance of visual stimulations close to or far from the hand. The observed results are consistent with what was described by the univariate and adaptation analyses, but with a wider bilateral involvement of PMd and extra-IPS parietal areas. Furthermore, the network included the PMv (in H1), FEF, PEF, the anterior and medial-posterior portions of the premotor area 6 (6a and 6mp) in the left hemisphere of both participants, but also the anterior segment of the IPS (AIP) bilaterally for H2 and in the right hemisphere for H1.

Ours is the first study investigating the effects of visual unimodal stimuli close to the trunk. Huang and colleagues overlapped brain activations in the posterior parietal cortex resulting from visual and tactile stimulations close to different body parts, such as the face, lips, shoulders, fingers, legs and toes (Huang et al., 2012), but they did not investigate further the neural network involved in this coding. The stimulus distance decoding pattern observed by our MVPA classifier seems similar to that observed for the previously described body parts, with bilateral involvement at the level of SMG, of the posterior parietal areas and, at least for H2, of the intraparietal and premotor areas. In H1, in these last two cases, it seems that the decoding pattern involves only the left hemisphere.

For this reason, we conducted cross-classification analyses between the patterns found for the three different parts of the body stimulated. We wondered if it was possible to train the classifier on the network of areas involved in decoding the distance of a stimulus from the hand, for example, and then test it in decoding the distance of the stimuli from the trunk. The same was done for all possible dyads: hand-face and trunk-face. The goal was to understand whether all or part of the fronto-parietal-supramarginal network described so far is involved

in the decoding of the distance of a visual stimulus regardless of the part of the body involved. The areas of this network would be, more generally, sensitive to the distance of a stimulus from the body. In all dyads tested, the reported pattern covers both hemispheres, particularly for H2. H1, as reported above, appears to have a pattern more lateralized to the left. The dyad showing the broadest shared activation is that of the hand and trunk, in which the closer or farther stimuli induce activations in ventral and dorsal premotor areas, in the PF supramarginal complex, in the postcentral area S1 and in several areas at the level of the superior and inferior parietal lobules, all bilaterally. The same is observed, for H2, in the hand-face dyad, in which however the participant H1 does not report activations in PMv and lateralizes the described pattern to the left hemisphere only, with the exception of the right SMG. Finally, the pattern shared face and trunk stimulations seems to be narrow: also in this case the only region involved bilaterally by both participants is the supramarginal PF complex, with the bilateral addition of S1 and PMd for H2. H1, on the other hand, reports activations in S1 and in the region of the left IPS.

These results support the idea of a fronto-parieto-supramarginal network capable of decoding the distance of a stimulus from the body regardless of the body-part involved. The greater lateralization to the left could be due, in our experiment, to the presentation of visual stimuli, slightly lateralized in the right visual hemispace. It is interesting to observe the smaller extension of the common activation network between face and trunk; this sub-representation may be connected to less frequent interaction between these body district: if it is easy to think of hand movements in relation to the trunk and head (approaching or moving objects away from the face or trunk, for example), in which the distance of a stimulus from the two parts of the body counts, it is more difficult to imagine similar situations involving movements of the head towards the trunk or vice versa. However, this hypothesis remains only a speculation in light of the lack of motor aspects within our experimental setup, and can provide interesting insights for future studies.

5.3 Commonality and differences between the neural responses underlying the different body-part based PPS representation

After investigating the decoding patterns of the distance of a stimulus common between the three parts of the body, we tried to understand if there were areas, within the PPS fronto-parietal network, having a preferential response for stimuli close to the body, regardless of which part of the body was closest. The areas belonging to this network would represent the central "core" of the PPS representation, capable of encoding the distance of a stimulus from

the body, considered in this case as a whole. Grivaz and colleagues, in their meta-analysis, sought to highlight the neural basis of this PPS-core by integrating the results of 18 neuroimaging studies that tested the hand-, trunk- or face-based representation of PPS. What is reported is a response network that includes PMv at the frontal level, the areas PFop, PFcm, OP1 and OP2 in the SMG, the areas PFt, IP2 and 5 respectively in the IPL and SPL and, finally, the areas 1, 2, 3b (all included in S1) and 4 (M1 or PMC) in the postcentral gyrus (Grivaz et al., 2017). However, most of the studies involved in this meta-analysis stimulated the face (Bremmer et al., 2001; Cardini et al., 2011; Holt et al., 2014; Huang et al., 2012; Quinlan and Culham, 2007; Sereno and Huang, 2006; Tyll et al., 2013; Wittmann et al., 2010) or the hand (Brozzoli et al., 2011, 2012, 2013; Ferri et al., 2015; Gentile et al., 2011, 2013; Huang et al., 2012; Makin et al., 2007; Schaefer et al., 2012a). Only one of these also stimulated the trunk (Huang et al., 2012), and in that case the stimulation was applied to the shoulders, and not the lower abdomen. Of these studies, less than half used visual unimodal stimulation (see Grivaz et al., 2017, Table 1). The characteristics of our study, and the consequent differences with respect to this literature, may be at the basis of the inconsistencies observed between our results and those just mentioned: considering the areas common to the three body districts and to both human participants, the core of the whole-body PPS seems to include mainly regions of the parietal cortex, both within the IPS (LIPv, in the left hemisphere) and in the surrounding area (lateral portion of area 7 and area 7PC, always in the left hemisphere). Finally, the last area presented by both H1 and H2 is one of those listed by Grivaz: area 2, at the level of the left postcentral gyrus. However, it is possible to confirm some of the regions described in the literature by better observing the results of the participant H1, who, in addition to the aforementioned network, also includes the supramarginal regions PFop and PFcm, the inferior parietal area PFt, the superior parietal area 5 and the somatosensory area 1. In addition, the participant also reports activations in the medial parietal area 7A, in VIP and in different portions of the SMG, including PSL and OP4, all lateralized to the left. In the right hemisphere, only the PSL area and the superior temporal visual area, both on the border between the SMG and the temporal lobe, differ from the activations reported by Grivaz. The absence of clusters at the level of the premotor cortex stands out: no portion of area 6 seems to be part of the core of the whole-body PPS. However, as already mentioned, most studies in the literature have tested the hand-centered (Brozzoli et al., 2011, 2012, 2013; Ferri et al., 2015; Gentile et al., 2011, 2013; Huang et al., 2012; Makin et al., 2007; Schaefer et al., 2012a) or head-based PPS representation (Bremmer et al., 2001; Cardini et al., 2011; Holt et al., 2014; Huang et al., 2012; Quinlan and Culham, 2007; Sereno

and Huang, 2006; Tyll et al., 2013; Wittmann et al., 2010). Indeed, by considering the conjunction of specific response networks for the hand and for the face, this gap with respect to literature is bridged. We observed that both participants show a cluster of joint activation in the left precentral gyrus, which includes different portions of the premotor area 6, including PMd, PMv (in H1), the anterior and medial-posterior portions and the precentral section of the area 4 (M1 or PMC). In addition to this more frontal cluster, other specific activations are found in the SMG (bilaterally), in the SPL and in the postcentral gyrus. It therefore seems that the most frontal part of the PPS network is associated only with the encoding of stimuli near the hand or the face, indifferently. This is in line with the results from electrophysiology, which report premotor neurons characterized by multisensory receptive fields centered on the hands and face (Rizzolatti et al., 1981a, 1981b) or involved in hand-to-mouth movements (Gentilucci et al., 1988).

Another aspect that deserves attention concerns the disparity of the core-network between the two participants, caused by a left-parietal cluster only for H2 and by bilateral SMG activations for S1. This disparity seems to be due to an under-representation of the trunk at the supramarginal level by H2 (or its over-representation by H1): where H1 reports, in left SMG, a conjunction between the activation clusters associated with the hand, the face and at the trunk, H2 shows an overlap only between hand and face. Future studies, using larger samples and group-level analyses, could define in more detail the extension and localization of the PPS-core-network.

Finally, our hypothesis regarding the neural-level specificities of body-part-based PPS representations finds support in the results of the disjunction analyses. As can be seen in Figure 8, the areas of conjunction between two or more body districts are surrounded by specific body-part activations. Less extensive are those associated with the trunk, located only at the left intraparietal level in H1. It therefore seems that the stimuli presented near the trunk induce responses mainly in non-specific areas, but associated with one or more other parts of the body. As for the hand and the face, however, the specificities are more widespread and observable in all the ROIs investigated. In particular, the underrepresentation of the trunk in H2 involves larger portions of parietal (7PC, 7Pl, VIP and area 5) and postcentral (S1, PFop, PFt) areas of the left hemisphere specifically associated with close-to-the-hand stimulations. The same is also observed for H1, in which these peaks are found at the edges of the left SMG and superior parietal cluster of the PPS core network, in both cases in the antero-ventral direction, and in the posterior and dorsal regions with respect to the right SMG cluster of

conjunction already described. Finally, the last hand-specific activation is found in the most dorsal portion of the 6mp premotor area.
Lastly, the specific activations for close-to-the-face stimulations report the largest network of activations, bilaterally, for both participants. At the level of the left hemisphere, it is evident that the specific activations for the face of H1 and H2 are localized in the precentral and premotor areas more anterior than in the hand-face junction region; on the contrary, the specificities of the hand seem to be reported more posteriorly with respect to this cluster, occupying the post-central region. On the left superior parietal level, however, there does not seem to be a clear and distinct subdivision, with specific areas for face or hand intermingled with areas of conjunction. Also at the level of the right hemisphere, consistent results emerge between the two participants, with superior parietal and SMG areas associated to the encoding of stimuli close to the face. The apparent greater extent of face-specific activations in H2 actually appears to be associated with the underrepresentation of the hand in this participant's right hemisphere.

This greater extension of the network of face-specific brain regions could be due to the greater importance, in defensive terms, of the region of space surrounding the head. The stimulations used in our study also moved vertically towards the participant's face, lying on the scanner bed. In this position, the head-centered PPS representation tends to extend upwards, taking into account the gravitational cues that influence the movement of the stimuli towards the head (Bufacchi and Iannetti, 2016). Furthermore, stimuli close to the face were characterized by oscillations on the vertical axis that led to micro-movements of looming and receding directly towards the participant, as opposed to what happens for close-to-the-hand stimulation, slightly localized on the right of this body part. The possibility of impact and the prediction of contact with the body influence the encoding of stimuli within PPS (Cléry et al., 2015b, 2017; Kandula et al., 2017), and this factor could therefore also have played a role in the over-representation observed here. Future studies can investigate this aspect, involving dynamic stimuli directed towards different body-parts in order to evaluate the consequences on the specific and joint activations reported here.

Tables

	H1								H2							
	k	Hemisphere	AAL3v1 ROI	Glasser Area	X	Y	Z	t	k	Hemisphere	AAL3v1 ROI	Glasser Area	X	Y	Z	t
Univariate Analyses Face	269	Right	SMG	PFop	67	-25	22	16.21	1436	Right	SPL	IPS1	19	-76	48	15.74
				PF								DVT				
				PFcm								V6A				
				PFt								MIP (IPS)				
				PSL								7Am				
				OP4								7Al				
				RI								7Pl				
				STV								VIP (IPS)				
				PFm								5mv				
			Postcentral	PFop	67	-14	20	4.8				5L				
				1 (S1)							Postcentral	2 (S1)	25	-45	53	14.22
				PFt								3b (S1)				
	519	Right	IPL	PF	33	-53	53	14.45				4 (PMC)				
				AIP (IPS)								PFt				
				IP2							SMG	PF	58	-28	22	13.71
			Postcentral	2 (S1)	28	-39	53	13.14				PSL				
				7PC								PFm				
			SPL	LIPv (IPS)	33	-50	59	9.9				PFcm				
				LIPd (IPS)								Pfop				
				5L								STV				
				7Al							IPL	AIP (IPS)	36	-45	50	6.37
				VIP (IPS)								7PC				
				7Am								PFm				
	394	Left	SPL	2 (S1)	-23	-39	64	12.2				LIPv (IPS)				
				7Al								LIPd (IPS)				
				7PC					421	Left	SPL	7Al	-28	-48	56	14.35
				LIPv (IPS)							IPL	IP1	-34	-59	39	3.97
				VIP (IPS)								IP2				
				5L								LIPd (IPS)				
			Postcentral	2 (S1)	-26	-36	64	10.65				LIPv (IPS)				
			IPL	LIPv (IPS)	-33	-50	55	7.3				AIP (IPS)				
				7PC								7PC				
	1331	Left	SMG	PF	-56	-34	36	9				PFm				
				PFcm							Postcentral	2 (S1)	-29	-43	54	9.84
				PFop					1120	Left	Precentral	FEF	-34	-6	56	12.02
				PSL								PEF				
			Postcentral	4 (PMC)	-45	-11	56	8.85				6d (PMd)				
				OP4								6a				
				3a (S1)								6mp				
				3b (S1)								55b				
				1 (S1)								8Av				
				2 (S1)								i6-8				
				43							SMG	PFcm	-51	-31	22	10
				PFt							Postcentral	PFt	-56	-20	28	6
			Precentral	6d (PMd)	-42	-8	56	7.6				4 (PMC)				
				6v (PMv)					292	Right	Precentral	FEF	44	-3	48	10.94
				6r								PEF				
				6a								6v (PMv)				
				6mp								6r				
				FEF								8C				
				PEF								55b				
				8C								6a				
				i6-8								6d (PMd)				
			IPL	PFt	-54	-31	42	6.18								
				AIP (IPS)												
				IP2												
	220	Right	Precentral	6d (PMd)	42	-8	56	8.83								
				PEF												
				6v (PMv)												
				8Av												
				8C												
				55b												
			Postcentral	2 (S1)	50	-20	48	3.8								
				3b (S1)												

Table 2A. Significant clusters from univariate analyses for H1 and H2 by comparing stimulations close to or far from the FACE. The significant clusters ($p < 0.05$, cluster-based FWE correction) are reported with the relative activation peaks in MNI coordinates and the relative t-score.

	M1					M2				
	k	**Hemisphere**	**CHARM/SARM 4 ROI**	**CHARM 6 Area**	**t**	**k**	**Hemisphere**	**CHARM/SARM 4 ROI**	**CHARM 6 Area**	**t**
Univariate Analyses Macaques	**727**	**Left**	**vm_IPS**	**MIP**	**16.29**	**624**	**Left**	**lat_IPS**	**LIPv**	**17.15**
				VIP	12.75			vm_IPS	VIP	12.81
			Area 7 in IPL	Area 7_OP	12.64			Area 7 in IPL	Area 7b	12.21
			lat_IPS	LIPd	9.61				Area 7a	5.92
		Right	**Premotor**	**F5**	**13.64**			S1	Areas 1-2	10.32
			Putamen	Putamen	8.91			Premotor	PMdc	11.75
			Area 7 in IPL	Area 7_PO	8.58				F4	10.1
			S1	Areas 1-2	5.99				F5	7.94
			vm_IPS	MIP	7.69			Putamen	Putamen	7.62
				VIP	5.91	**107**	**Right**	**Premotor**	**F5**	**10.93**
			lat_IPS	LIPd	5.98				PMdc	4.12
	97	**Left**	**Premotor**	**F5**	**11.02**	**241**	**Right**	**S1**	**Area 3a/b**	**8.93**
				PMdc	7.85			lat_IPS	LIPv	7.75
				F4	5.24			vm_IPS	VIP	6.08
	100	**Left**	**Putamen**	**Putamen**	**6.68**	**136**	**Right**	**Putamen**	**Putamen**	**8.69**

Table 2B. Significant clusters from univariate analyses for M1 and M2 by comparing stimulations close to or far from the FACE. The significant clusters ($p < 0.05$, cluster-based FWE correction) are reported with the relative t-score.

	H1								H2							
	k	Hemisphere	AAL3v1 ROI	Glasser Area	X	Y	Z	z-score	k	Hemisphere	AAL3v1 ROI	Glasser Area	X	Y	Z	z-score
MVPA Near vs Far Face	1851	Left	SMG	PFcm	-54	-25	14	3.09	2107	Left	SMG	OP4	-54	-25	14	3.09
				OP4								PFop				
				PFop								PSL				
				PFt								PFcm				
				PSL							Postcentral	3b (S1)	-51	-17	45	3.09
			Postcentral	2 (S1)	-25	-36	62	3.09				2 (S1)				
				1 (S1)								3a				
				3a								PFt				
				3b (S1)							Precentral	FEF	-34	-6	56	3.09
				5L								6v (PMv)				
			SPL	7PC	-34	-45	59	3.09				6d (PMd)				
				IPS1								4 (PMC)				
				7Al								6r				
				VIP (IPS)								IFJp				
				LIPv (IPS)								PEF				
				LIPd (IPS)								8C				
				MIP (IPS)								55b				
				DVT								8Av				
			IPL	7PC	-37	-42	48	3.09				6mp				
				PFt							SPL	7Al	-26	-56	64	3.09
				PFm								DVT				
				IP2								IPS1				
				AIP (IPS)								7Pl				
				PF								VIP (IPS)				
			Precentral	FEF	-42	-3	56	3.09			IPL	2 (S1)	-45	-28	42	3.09
				4 (PMC)								AIP (IPS)				
				6mp								LIPv (IPS)				
				6d (PMd)								LIPd (IPS)				
				8Av								MIP (IPS)				
				6a								IP2				
				55b					2411	Right	Postcentral	OP4	64	-17	14	3.09
	2064	Right	Postcentral	OP4	67	-17	14	3.09				2 (S1)				
				4 (PMC)								3a				
				1 (S1)								3b (S1)				
				PFt							SMG	PF	55	-30	44	3.09
				3a								Pfop				
				7Al								PFcm				
				5L								PSL				
			Precentral	55b	50	-3	40	3.09				RI				
				FEF								STV				
				6v (PMv)								PFt				
				6a								AIP (IPS)				
				6d (PMd)							IPL	PFm	47	-56	48	3.09
			SMG	PSL	56	-39	28	3.09				IP2				
				PFop								IP1				
				PF								IPS1				
				PFcm								LIPd (IPS)				
				PFm								7PC				
				RI							SPL	LIPv (IPS)	28	-53	59	3.09
				STV								MIP (IPS)				
			SPL	LIPv (IPS)	22	-62	53	3.09				DVT				
				LIPd (IPS)								VIP (IPS)				
				DVT							Precentral	4 (PMC)	39	-17	62	3.09
				7Pl								PEF				
				7Am								6v (PMv)				
				MIP (IPS)								6d (PMd)				
				VIP (IPS)								8Av				
			IPL	IP2	39	-48	45	3.09				FEF				
				AIP (IPS)								6a				
				IPS1								55b				
				IP1												
				7PC												

Table 3A. Significant clusters from MVPA on human participants training and testing the LDA classifier on the difference between near and far stimulations in the FACE condition. The significant clusters (z<1.65, one-sided t-test) are reported with the relative activation peaks in MNI coordinates and the relative z-score.

	M1					M2				
	k	Hemisphere	CHARM/SARM 4 ROI	CHARM 6 Area	z-score	k	Hemisphere	CHARM/SARM 4 ROI	CHARM 6 Area	z-score
MVPA Near vs Far Macaques	**204**	**Left**	**V6**	**V6**	**3.09**	**738**	**Left**	**Putamen**	**Putamen**	**3.09**
			vm_IPS	MIP	3.09				F4	3.09
				VIP	3.09			Premotor	F5	3.09
			Area 5	PEa	3.09				PMdc	3.09
			lat_IPS	LIPv	3.09			S1	Area 3a/b	3.09
				AIP	3.09				Areas 1-2	3.09
				LIPd	3.09				Area 7_OP	3.09
			Area 7 in IPL	Area 7b	3.09			Area 7 in IPL	Area 7b	3.09
				Area 7_OP	3.09				Area 7a	3.09
				Area 7a	3.09			Area 5	Pea	3.09
			S1	Areas 1-2	3.09				AIP	3.09
	108	**Left**	**Premotor**	**F5**	**3.09**			Lat_IPS	LIPv	3.09
				F4	3.09				LIPd	3.09
				PMdc	3.09				LOP	3.09
				PMdr	2.57				VIP	3.09
	55	**Right**	Premotor	F5	3.09			vm_IPS	MIP	3.09
				F4	3.09				PIP	3.09
				PMdc	3.09			V6	V6Ad	3.09
			Putamen	Putamen	1.85	**71**	**Right**	**Putamen**	**Putamen**	**3.09**
	105	**Right**	**vm_IPS**	**MIP**	**3.09**	**506**	**Right**	**Premotor**	**F4**	**3.09**
				VIP	3.09				F5	3.09
			lat_IPS	LIPv	3.09			S1	Area 3a/b	3.09
				LIPd	3.09				Areas 1-2	3.09
			area 5	PEa	3.09			Area 5	PEa	3.09
				PE	3.09				PEc	3.09
			Area 7 in IPL	Area 7b	3.09			Lat_IPS	AIP	3.09
				Area 7_OP	3.09				LIPv	3.09
				Area 7a	3.09			vm_IPS	VIP	3.09
			S1	Areas 1-2	3.09				MIP	3.09
									Area 7_OP	3.09
								Area 7 in IPL	Area 7b	3.09
									Area 7a	3.09

Table 3B. Significant clusters from MVPA on macaques training and testing the LDA classifier on the difference between stimulations close to and far from the face. The significant clusters (z<1.65, one-sided t-test) are reported with the relative z-score.

	H1								H2							
	k	Hemisphere	AAL3v1 ROI	Glasser Atlas	X	Y	Z	t	k	Hemisphere	AAL3v1 ROI	Glasser Atlas	X	Y	Z	t
Univariate Analyses Hand	**1627**	**Left**	**SMG**	**PFcm**	**-51**	**-28**	**20**	**18.56**	**426**	**Left**	**SPL**	**7Al**	**-28**	**-45**	**52**	**16.3**
				PFt								LIPv (IPS)				
				PFop								POS_2				
				PF								7Pl				
				PSL								7 PC				
			IPL	**1 (S1)**	**-55**	**-28**	**47**	**13.63**				5L				
				7PC								VIP (IPS)				
				LIPv (IPS)							**Postcentral**	**2 (S1)**	**-28**	**-39**	**67**	**5.2**
			SPL	**7Al**	**-20**	**-50**	**67**	**12.29**	**366**	**Left**	**Postcentral**	**OP1**	**-51**	**-20**	**20**	**14.53**
				7Am								OP4				
				VIP (IPS)								1 (S1)				
				5L								2 (S1)				
			Precentral	**6d (PMd)**	**-40**	**-14**	**56**	**7.88**				PFt				
				6a							**SMG**	**PFcm**	**-48**	**-31**	**22**	**13.6**
				6mp								PFop				
			Postcentral	**2 (S1)**	**-59**	**-16**	**34**	**8.11**				PF				
				1 (S1)								PSL				
				3b (S1)					**168**	**Right**	**SMG**	**PFcm**	**47**	**-31**	**25**	**10.41**
				4 (PMC)								PFop				
	309	**Right**	**SMG**	**PFop**	**67**	**-25**	**22**	**13.54**				PF				
				PFcm								PSL				
				PF								RI				
				PFm					**137**	**Left**	**Precentral**	**FEF**	**-34**	**-6**	**59**	**8.78**
				PSL								6d (PMd)				
				PFt								6a				
				STV								6mp				
			Postcentral	**PFt**	**53**	**-22**	**45**	**3.78**								
				1 (S1)												

Table 4. Significant clusters from univariate analyses for the two human participants by comparing stimulations close to or far from the hand. The significant clusters (p <0.05, cluster-based FWE correction) are reported with the relative activation peaks in MNI coordinates.

	H1								H2							
	k	Hemisphere	AAL3v1 ROI	Glasser Atlas	X	Y	Z	t	k	Hemisphere	AAL3v1 ROI	Glasser Atlas	X	Y	Z	t
Univariate Analyses Trunk	959	Left	SMG	PFcm	-45	-36	28	11.37	316	Left	SPL	POS2	-12	-76	45	11.93
				PF								7Al				
				PFt								7Pl				
				PFop								7Pm				
				OP4								IPS1				
				OP1								DVT				
				PSL							Postcentral	2 (S1)	-25	-45	56	9.53
			SPL	7Al	-25	-50	70	9.9			IPL	LIPv (IPS)				
				LIPv (IPS)								LIPd (IPS)				
				VIP (IPS)												
				7Am												
				5L												
			Postcentral	2 (S1)	-25	-36	62	6.88								
				1 (S1)												
				3b (S1)												
			IPL	PFcm	-56	-28	48	7.9								
				AIP (IPS)												
				1 (S1)												
				IP2												
				PF												
				7PC												
	150	Right	SMG	PFop	67	-25	22	9.58								
				PF												
				PSL												
				PFcm												
				RI												
				STV												

Table 5. Significant clusters from univariate analyses for H1 and H2 by comparing stimulations close to or far from the TRUNK. The significant clusters ($p < 0.05$, cluster-based FWE correction) are reported with the relative activation peaks in MNI coordinates and the relative t-score.

	H1								H2							
	k	Hemisphere	AAL3v1 ROI	Glasser Area	X	Y	Z	z-score	k	Hemisphere	AAL3v1 ROI	Glasser Area	X	Y	Z	z-score
Near vs Far Hand-Face MVPA	884	Left	SMG	PFcm	-54	-25	14	3.09	836	Left	Postcentral	3a (S1)	-59	-8	20	3.09
				PFop								3b (S1)				
				PSL								2 (S1)				
				PFt								OP4				
			Postcentral	2 (S1)	-48	-26	48	3.09				55b				
				55b							SMG	PF	-56	-34	28	3.09
				OP4								PFt				
				3b (S1)							Precentral	FEF	-34	-6	56	2.58
				4 (PMC)								PEF				
			Precentral	6d (PMd)	-42	-8	58	2.17				6v (PMv)				
				6v (PMv)								6d (PMd)				
			IPL	PF	-59	-36	40	3.09				6a				
	341	Right	Postcentral	OP4	64	-16	14	3.09				6r				
				PFt								4 (PMC)				
				1 (S1)								i6-8				
			SMG	PFop	64	-22	25	3.09			IPL	2 (S1)	-32	-42	51	3.09
				PF								IP2				
				PSL								LIPv (IPS)				
				PFm								AIP (IPS)				
				PFcm							SPL	7PC	-37	-45	62	3.09
				RI								7Al				
				STV					960	Right	Postcentral	OP4	61	-17	17	3.09
	10	Left	SPL	IPS1	-25	-81	48	1.91				2 (S1)				
	45	Right	Postcentral	2 (S1)	25	-39	53	2.87				55b				
				3b (S1)								3b (S1)				
												3a (S1)				
											SMG	PFop	64	-22	31	3.09
												PF				
												PFcm				
												PFt				
												PSL				
												RI				
											IPL	IP2	48	-36	52	3.09
												AIP (IPS)				
											SPL	7PC	33	-53	64	2.75
												7Al				
												VIP (IPS)				
											Precentral	55b	53	-8	45	3.09
												6d (PMd)				
												FEF				
												4 (PMC)				

	H1								H2							
	k	Hemisphere	AAL3v1 ROI	Glasser Area	X	Y	Z	z-score	k	Hemisphere	AAL3v1 ROI	Glasser Area	X	Y	Z	z-score
Near vs Far Hand-Trunk MVPA	**2664**	**Left**	**SMG**	**PFcm**	**-54**	**-25**	**14**	**3.09**	**2313**	**Left**	**SMG**	**PFcm**	**-54**	**-25**	**14**	**3.09**
				PFt								PFop				
				PFop								PL				
				PF							**Postcentral**	**2 (S1)**	**-25**	**-36**	**62**	**3.09**
				PSL								3b (S1)				
			Postcentral	**4 (PMC)**	**-53**	**-11**	**40**	**3.09**				OP4				
				OP4								3a (S1)				
				1 (S1)								PFt				
				3b (S1)								55b				
				3a (S1)							**Precentral**	**FEF**	**-34**	**-3**	**56**	**3.09**
				2 (S1)								6v (PMv)				
			Precentral	**6r**	**-54**	**6**	**36**	**3.09**				6d (PMd)				
				6d (PMd)								6mp				
				6V (PMv)								4 (PMC)				
				6mp								6r				
				FEF								6a				
				PEF								IFJ				
				i6-8								PEF				
				6a								8C				
				55b								i6-8				
			SPL	**7Al**	**-20**	**-48**	**64**	**3.09**			**SPL**	**7Al**	**-23**	**-50**	**64**	**3.09**
				7Pl								7Pl				
				7PC								VIP (IPS)				
				IPS1								MIP (IPS)				
				5L								DVT				
				VIP (IPS)							**IPL**	**AIP (IPS)**	**-45**	**-36**	**41**	**3.09**
				LIPv (IPS)								IP2				
				DVT								LIPv (IPS)				
			IPL	**LIPd (IPS)**	**-28**	**-50**	**45**	**3.09**				7PC				
				PFm					**1918**	**Right**	**Postcentral**	**OP4**	**64**	**-17**	**14**	**3.09**
				PF								2 (S1)				
				IP2								1 (S1)				
				PGs								3b (S1)				
	842	**Right**	**Postcentral**	**OP4**	**67**	**-17**	**14**	**3.09**				5L				
				2 (S1)								7PC				
			SMG	**PFop**	**64**	**-22**	**28**	**3.09**			**SMG**	**PFcm**	**53**	**-36**	**28**	**3.09**
				PF								PF				
				PSL								PFt				
				RI								PSL				
				STV								PFop				
				PFt							**IPL**	**PFm**	**50**	**-42**	**53**	**2.88**
			IPL	**PFm**	**53**	**-48**	**48**	**2.58**				AIP (IPS)				
			Precentral	**3b (S1)**	**47**	**-11**	**53**	**3.09**				IP2				
				PEF							**SPL**	**7PC**	**42**	**-48**	**59**	**3.09**
				6v (PMv)								7Al				
				6d (PMd)								7Am				
				FEF								VIP (IPS)				
	211	**Right**	**SPL**	**LIPv (IPS)**	**30**	**-56**	**62**	**3.09**			**Precentral**	**6d (PMd)**	**32**	**-14**	**61**	**3.09**
				VIP (IPS)								6v (PMv)				
				7Am								PEF				
				7Al								FEF				
				5L								6a				
			Postcentral	**2 (S1)**	**22**	**-42**	**64**	**1.87**				8Av				
	36	**Right**	**Postcentral**	**3b (S1)**	**25**	**-31**	**62**	**2.17**				4 (PMC)				
									9	**Right**	**SPL**	**DVT**	**19**	**-76**	**48**	**1.94**
Near vs Far Trunk-Face MVPA	**551**	**Left**	**SMG**	**PFcm**	**-54**	**-25**	**14**	**3.09**	**168**	**Left**	**SMG**	**PFcm**	**-51**	**-25**	**17**	**3.09**
				PSL								PFop				
			Postcentral	**3b (S1)**	**-46**	**-22**	**55**	**2.58**			**Postcentral**	**PFt**	**-56**	**-19**	**28**	**2.75**
				OP4								OP4				
			IPL	**1 (S1)**	**-54**	**-25**	**50**	**3.09**	**480**	**Right**	**SMG**	**PF**	**58**	**-28**	**36**	**3.09**
				PF								AIP (IPS)				
				PFt							**Postcentral**	**3a (S1)**	**38**	**-24**	**50**	**3.09**
				PFm								2 (S1)				
	254	**Right**	**Postcentral**	**2 (S1)**	**59**	**-15**	**41**	**3.09**				1 (S1)				
			SMG	**OP4**	**62**	**-25**	**31**	**3.09**				PFt				
				PFop							**Precentral**	**FEF**	**36**	**-6**	**48**	**2.29**
				PF								6a				
				PFt							**IPL**	**IP2**	**50**	**-32**	**48**	**2.22**
				PSL								7PC				
				STV								PFm				
	58	**Left**	**SPL**	**LIPv (IPS)**	**-34**	**-59**	**59**	**3.09**			**SPL**	**7Al**	**30**	**-51**	**64**	**2.41**
				7PC								VIP (IPS)				
				VIP (IPS)					**173**	**Left**	**IPL**	**LIPd (IPS)**	**-31**	**-48**	**42**	**3.09**
	98	**Left**	**Postcentral**	**1 (S1)**	**-31**	**-36**	**67**	**3.09**				LIPv (IPS)				
				3b (S1)								7PC				
				55b								AIP (IPS)				
			Precentral	**4 (PMC)**	**-26**	**-24**	**70**	**2.58**			**Postcentral**	**2 (S1)**	**-31**	**-39**	**59**	**3.09**
												1 (S1)				
												3b (S1)				
									22	**Left**	**Precentral**	**4 (PMC)**	**-40**	**-14**	**59**	**2.87**
												6d (PMd)				

Table 6. Significant clusters from cross-validation MVPA on human participants training and testing the LDA classifier on the difference between near and far stimulations in different dyads of conditions. The significant clusters ($z<1.65$, one-sided t-test) are reported with the relative activation peaks in MNI coordinates and the relative z-score.

	H1						H2					
	Hemisphere	**AAL3v1 ROI**	**Glasser Area**	**X**	**Y**	**Z**	**Hemisphere**	**AAL3v1 ROI**	**Glasser Area**	**X**	**Y**	**Z**
Univariate Hand-Face Conjunction	**Right**	**SMG**	PFop	62	-20	25	**Right**	**SMG**	PF	63	-29	27
			PF	64	-27	36			PFop	64	-23	25
			STV	61	-49	26			PSL	61	-35	28
	Left	**Precentral**	6v (PMv)	-59	5	27			PFcm	57	-35	30
			6d (PMd)	-32	-15	69			RI	51	-31	24
			4 (PMC)	-58	0	23	**Left**	**SMG**	PF	-64	-32	33
			6r	-56	4	23			PFop	-60	-23	28
			6a	-32	-13	59			PFt	-58	-30	35
			6mp	-23	-17	70			PFcm	-55	-27	17
		Postcentral	1 (S1)	-46	-20	58			PSL	-51	-38	25
			2 (S1)	-59	-17	40		**Precentral**	6d (PMd)	-34	-9	62
			4 (PMC)	-64	-2	23			6a	-31	-13	56
			3a (S1)	-62	-5	16			6mp	-21	-17	70
		SMG	PFop	-62	-25	24		**SPL**	LIPv (IPS)	-34	-58	61
			PFt	-62	-21	38			7AI	-23	-44	67
			OP4	-56	-20	25		**Postcentral**	2 (S1)	-26	-40	58
		IPL	IP2	-49	-37	51						
		SPL	7AI	-31	-43	72						
			5L	-19	-46	74						
Univariate Hand-Face-Trunk Conjunction	**Right**	**SMG**	PF	68	-27	27	**Left**	**Par Inf**	LIPv (IPS)	-30	-49	53
			PFop	67	-26	26		**Par Sup**	7AI	-27	-48	65
			PSL	66	-30	30			7PC	-31	-45	65
			PFcm	56	-32	27		**Post**	2 (S1)	-25	-41	62
			STV	60	-42	25						
	Left	**Par Sup**	7AI	-27	-48	65						
			7Am	-16	-60	66						
			7PC	-31	-45	65						
			5L	-16	-53	76						
			VIP (IPS)	-22	-61	65						
		Par Inf	LIPv (IPS)	-30	-49	53						
			PFt	-47	-28	37						
			PFcm	-48	-36	26						
			2 (S1)	-51	-23	37						
		Post	2 (S1)	-25	-41	62						
			1 (S1)	-57	-25	43						
		SMG	PFcm	-49	-35	26						
			PSL	-48	-45	26						
			PF	-55	-39	35						
			OP4	-57	-21	21						
			PFt	-57	-25	30						
			PFop	-57	-27	24						

Table 7. Overlapping areas of activations for stimuli close to the hand and to the face (upper table) or close to one of the body part tested, indifferently (lower table). The reported MNI coordinates do not refer to peaks of greater activation but are only representative of the portion of the area involved in which the overlap occurs.

	H1						H2					
	Hemisphere	**AAL3v1 ROI**	**Glasser Area**	**X**	**Y**	**Z**	**Hemisphere**	**AAL3v1 ROI**	**Glasser Area**	**X**	**Y**	**Z**
Univariate Face Specificity	**Right**	**Postecentral**	PO4	65	-17	14	**Right**	**SMG**	PFop	66	-19	27
		SMG	PF	69	-19	29			PF	66	-21	35
			PFm	60	-51	27			PSL	66	-41	29
		Precentral	FEF	46	-3	51			STV	59	-47	26
			4 (PMC)	39	-13	57			PFt	59	-19	29
		SPL	7PC	40	-52	60			AIP	33	-39	44
			7Al	31	-51	65		**IPL**	IPS_2	43	-46	43
			PFm	40	-53	54			AIP	40	-40	44
			MIP	37	-64	55			PF	43	-46	51
			AIP	33	-52	47			7PC	40	-50	55
			LIPv	37	-54	54		**Postecentral**	2 (S1)	35	-39	60
			LIPd	33	-60	53			1 (S1)	22	-35	73
			VIP	20	-59	62			4 (PMC)	19	-24	73
			5L	16	-44	77			7PC	35	-44	62
	Left	**SPL**	5L	-17	-40	76			5L	19	-41	73
		Postecentral	1 (S1)	-21	-36	71		**SPL**	LIPv	33	-54	59
			2 (S1)	-44	-37	51			LIPd	33	-57	52
			PO4	-66	-15	16			Tal	30	-48	65
		Precentral	6a	-30	-9	63			7Am	19	-56	58
			6d (PMd)	-33	-7	61			MIP	29	-67	53
			FEF	-33	-6	54			IPS_1	26	-75	48
			PEF	-44	0	37			V6A	22	-79	49
			55b	-36	5	47			VIP	22	-57	60
			6v (PMv)	-54	3	42			DVT	19	-76	53
									7Pl	15	-74	58
							Left	**Postecentral**	4 (PMC)	-62	0	16
									2 (S1)	-55	-18	33
									3a (S1)	-62	-8	17
									PFt	-53	-20	32
								Precentral	6r	-55	4	19
									6v (PMv)	-55	5	37
									6d (PMd)	-44	-11	57
									PEF	-55	-3	42
									55b	-53	4	45
									FEF	-49	-8	51
									IFJ	-42	2	32
									6mp	-18	-20	75
								IPL	7PC	-42	-49	52
									PFm	-38	-56	50
									IPS_1	-33	-60	40
									IPS_2	-33	-53	47
									LIPd	-33	-60	47
								SPL	LIPv	-29	-61	52
Univariate Hand Specificity	**Right**	**SMG**	PSL	63	-42	34	**Left**	**Postcentral**	PFop	-65	-22	23
			PF	58	-28	39			PO4	-59	-20	20
			PFt	55	-27	42			PFt	-59	-24	39
			TPOJ	48	-46	21			1 (S1)	-56	-27	44
	Left	**SMG**	PO1	-47	-24	25		**SPL**	7PC	-33	-59	65
		Precentral	6mp	-19	-15	73			7Pl	-16	-70	56
		Postcentral	2 (S1)	-33	-42	54			VIP	-31	-61	65
			1 (S1)	-51	-22	55			5L	-22	-51	73
			PO4	-56	-11	17						
		SMG	PF	-65	-27	29						
		IPL	7PC (IPS)	-36	-40	57						
			AIP (IPS)	-39	-32	38						
Univariate Trunk Specificity	**Left**	**IPL**	7PC (IPS)	-41	-53	57						
		Par Sup	VIP (IPS)	-23	-64	60						

Table 8. Specific activation areas for stimulations close to the face (upper table), the hand (middle table) and the trunk (lower table). The reported MNI coordinates do not refer to peaks of greater activation but are only representative of the portion of the area involved in which specificity is present.

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Supplementary Materials

S1. Adaptation analysis: brain regions selective for objects within face- and hand-based PPS in macaques and humans

We then examined neuronal adaptation by defining regressors of interest separately according to the stimulation period (i.e. first 3 sec of stimulation and second 3 sec of stimulation) and the type of body-part stimulated in each run (i.e. hand, face or trunk). Each regressor has been modeled with the standard SPM12 hemodynamic response function. We also added 6 regressors of no interest, corresponding to the head movement parameters of each run. **Table S1** provides an overview of the different analysis we performed. As in the univariate analysis, we reported clusters surviving an FWE correction ($p<0.05$).

To test our first hypothesis, namely the reduction of BOLD signal in PPS-related areas in humans and monkeys, we contrasted the conditions where the presentation of the stimuli near the hand or the face was repeated. First of all, we compared the first and the second part of the Near-Near trials, keeping separated HAND, FACE and TRUNK conditions. The repetition of the visual stimulus near the same body district should induce a reduction of the BOLD signal in areas selective for the space near this specific body-part. We then compared the activations associated with Near stimulations presented immediately after another Near stimulus (Near-after-Near condition) versus the activations associated with Near stimulations following a Far stimulus (Near-after-Far condition, see Brozzoli et al., 2011, 2012 for a similar procedure). Given the different spatial localization of the two stimuli, Near-after-Far will not undergo adaptation, thus reporting greater activations than Near-after-Near. (See Table 1, on the right, first row). In monkeys, the same contrasts were carried out on the FACE condition. As described in the introduction, we predict that different brain regions in premotor and parietal cortices and in the putamen are involved in the processing of visual stimuli presented in near space. Therein, we hypothesize a reduced BOLD signal, signature of the neuronal adaptation, when the near stimulation is repeated, suggesting that these regions contain neurons sensitive to PPS representation. Furthermore, with regard to within-face-PPS stimulation, we expect spatially coherent activations between the two species, in line with the idea that the representation of the PPS, in humans and non-human primates, involves homologous structures.

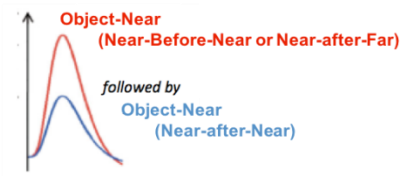
	Univariate Analyses	Adaptation Analyses	
		Near Repetition	Second Part
Selectivity for NEAR stimulations	**Near Condition**		
	Near-Before-Near	Near-Before-Near	Near-After-Far
	Near-After-Near	*versus*	*versus*
	Near-Before-Far	Near-After-Near	Near-After-Near
	Near-After-Far		
	versus		
	Far Condition		
	Far-Before-Far		
	Far-After-Far		
	Far-Before-Near		
	Far-After-Near		

Table S1: Summary of the planned fMRI analysis. On the left, the univariate analysis will compare near and far stimulations, regardless of the order of presentation for all type of runs (HAND, TRUNK and FACE). On the right, the adaptation analysis will compare: 1) the fMRI signal in the first (Near-before-Near) and second (Near-after-Near) repetitions of the Near condition (Adaptation Near Repetition approach) and 2) the fMRI signal to near stimuli presented after a far stimulus (Near-after-Far) and after a close one (Near-after-Near, Adaptation Second Part approach). These approaches will be performed separately for HAND, TRUNK and FACE runs to identify hand-, trunk- and face-based PPS underpinnings.

S2. Human's adaptation analyses: stimulation close to the face

After the univariate analyses, we performed adaptation analysis by exploiting both approaches previously described. In the Adaptation Near Repetition approach, the Near-before-Near versus Near-after-Near contrast brings out three significant clusters for H1, two in the right hemisphere and one in the left one. The latter (k=1658, t_{peak}=9.61) report activations in all the ROIs and includes PPS-related areas such as SMG, PMd, IPS and S1. In turn, the two clusters of the right hemisphere also reported activation peaks in SMG, PMd, PMv, IPS, S1 (k=1964, t_{peak}=9.06) and in the putamen (k=334, t_{peak}=6.86).

Also for H2 we find wide activations in this first adaptation approach. Two large clusters emerge one in the left hemisphere (k=3215, t_{peak}=14.19) and one in the right one (k=2927, t_{peak}=12.25). Both clusters included activations in several portions of the IPS, the premotor cortex, the SMG and in S1. Furthermore, two smaller clusters are found at the level of the left (k=290, t_{peak}=12.32) and right (k=319, t_{peak}=11.66) putamen.

However, the pattern of activations observed in the univariate analyses and in the first approach of adaptation analyses does not seem to be repeated in the second approach. Comparing Near-after-Far versus Near-after-Near conditions, a lack of BOLD signal reduction is observed for both participants, with no clusters able to survive the FWE correction. These results are reported in Table S2.

	H1								H2							
	k	Hemisphere	AAL3v1 ROI	Glasser Area	X	Y	Z	t	k	Hemisphere	AAL3v1 ROI	Glasser Area	X	Y	Z	t
Adaptation Near Repetition Face	**1658**	**Left**	**SMG**	**RI**	**-45**	**-39**	**25**	**9.61**	**3215**	**Left**	**SMG**	**PFcm**	**-51**	**-31**	**22**	**14.19**
				PSL								OP4				
				PFcm								PFop				
			Precentral	**6d (PMd)**	**-45**	**-8**	**59**	**8.32**				PSL				
				FEF								PF				
				55b							**Postcentral**	**2 (S1)**	**-23**	**-42**	**53**	**13.14**
				4 (PMC)								3a				
				6a								1 (S1)				
				PEF								Area 43				
				Area 43								3b (S1)				
			IPL	**IP2**	**-51**	**-39**	**50**	**4.94**				4 (PMC)				
				PFm								PFt				
				AIP (IPS)							**SPL**	**POS2**	**-14**	**-73**	**39**	**11.41**
				LIPd (IPS)								IPS1				
				PFt								DVT				
			Postcentral	**3b (S1)**	**-59**	**-11**	**36**	**4.71**				LIPd (IPS)				
				1 (S1)								LIPv (IPS)				
				2 (S1)								7Pl				
				OP1								VIP (IPS)				
				OP4								7Al				
				3a								7PC				
			SPL	**VIP (IPS)**	**-31**	**-59**	**62**	**6.01**				5L				
				7Al							**Precentral**	**PEF**	**-51**	**0**	**42**	**6.84**
				7PC								PMr				
				LIPv (IPS)								6v (PMv)				
				IPS1								6d (PMd)				
	1964	**Right**	**SMG**	**PFop**	**64**	**-25**	**22**	**9.06**				8C				
				PF								IFJp				
				PSL								4 (PMC)				
				RI								FEF				
				STV								55b				
				PFcm								6a				
				PFm							**IPL**	**AIP (IPS)**	**-40**	**-39**	**42**	**6.88**
			Precentral	**6d (PMd)**	**42**	**-8**	**59**	**8.48**				IP2				
				PEF								IP1				
				6v (PMv)								PFm				
				Area 43								LIPd (IPS)				
				8Av								LIPv (IPS)				
				55b								PFt				
				FEF								MIP (IPS)				
				6a								7PC				
			SPL	**LIPv (IPS)**	**30**	**-59**	**59**	**4.45**				PF				
				LIPd (IPS)					**290**	**Left**	**Putamen**	**Putamen**	**-28**	**-17**	**8**	**12.32**
				VIP (IPS)					**2927**	**Right**	**Postcentral**	**2 (S1)**	**25**	**-42**	**53**	**12.25**
				7Al								4 (PMC)				
			IPL	**AIP (IPS)**	**36**	**-48**	**45**	**4.01**				3b (S1)				
				IP2								1 (S1)				
				7PC								OP4				
			Postcentral	**4 (PMC)**	**47**	**-10**	**46**	**5.22**			**SMG**	**PFcm**	**50**	**-28**	**25**	**12.07**
				3a								RI		-36	22	12.01
				1 (S1)								PFop				
				OP4								PF				
				3b (S1)								PSL				
				PFt								STV				
	334	**Right**	**Putamen**	**Putamen**	**36**	**-11**	**-8**	**6.86**				PFm				
											Precentral	**55b**	**56**	**3**	**42**	**7.41**
												6v (PMv)				
												IFJp				
												PEF				
												FEF				
												6r				
												6a				
												6d (PMd)				
											SPL	**VIP (IPS)**	**19**	**-62**	**56**	**5.99**
												MIP (IPS)				
												LIPd (IPS)				
												LIPv (IPS)				
												DVT				
												7Pl				
												7PC				
												7Al				
												7Am				
												5L				
											IPL	**IP2**	**39**	**-48**	**45**	**5.93**
												AIP (IPS)				
												LIPv (IPS)				
												PFm				
									319	**Right**	**Putamen**	**Putamen**	**30**	**-17**	**8**	**11.66**
Adaptation Second Part Face	*No suprathreshold clusters*								*No suprathreshold clusters*							

Table S2. Significant clusters from adaptation analyses for H1 and H2 by comparing stimulations close to or far from the FACE. The significant clusters ($p < 0.05$, cluster-based FWE correction) are reported with the relative activation peaks in MNI coordinates and the relative t-score.

S3. Monkey's adaptation analyses: stimulation close to the face

Also for non-human primates we have conducted adaptation analyses with both approaches described above. However, in this case it seems that the wide network of activations observed in the univariate analyses does not undergo the adaptation of the response, neither following the repetition of the same close-to-the-face stimulus, nor comparing a Near-after-Far versus a Near-after-Near stimulus. Indeed, it is observed that for M1 only one significant cluster emerges (k=46, t_{peak}=15.53) located in the premotor region (F4 and PMdc) for the Adaptation Near Repetition approach, but no cluster survives the FWE correction in the Adaptation Second Part approach. For M2, moreover, neither the first nor the second approach reported significant clusters. These results are reported in Table S3.

	M1					M2				
	k	Hemisphere	CHARM/SARM 4 ROI	CHARM 6 Area	t	k	Hemisphere	CHARM/SARM 4 ROI	CHARM 6 Area	t
Adaptation Near Repetition Macaques	46	Right	Premotor	F4	15.53	*No suprathreshold clusters*				
				PMdc	7.77					
Adaptation Second Part Macaques	*No suprathreshold clusters*					*No suprathreshold clusters*				

Table S3. Significant clusters from adaptation analyses for M1 and M2 by comparing stimulations close to or far from the FACE. The significant clusters ($p < 0.05$, cluster-based FWE correction) are reported with the relative t-score.

S4: Human's adaptation analyses: stimulation close to the hand

We identified brain areas displaying BOLD-adaptation to repeated visual stimulation near the hand. As for the univariate analysis, we performed a first-level analysis by defining a general linear regression model to the data.

In a first approach, we compared the first part and the second part of the near stimulation (condition called "Adaptation Near Repetition"). In H1, brain activations were reported only in the left hemisphere, with three clusters located in the premotor (k=116, t_{peak}=8.83), parietal (k=148, t_{peak}=6.48) and supramarginal region (k=147, t_{peak}=6.01). Also H2 has two activation clusters consistent with what was observed for H1, both in the left hemisphere and with activation peaks in the parietal (k=368, t_{peak}=11.94), postcentral and supramarginal regions (k=355, t_{peak}=9.2).

In a second approach, we compared near stimuli following a far stimulation (Near-after-Far, NaF regressor) with near stimuli following a near stimulation (i.e. near repeated, Near-after-Near, NaN regressor). We called this condition "Adaptation Second Part". We expected a reduction of the BOLD signal in the near repeated condition compared to the near stimulation followed by a far stimulation. This approach reports only one activation cluster in H1, located in the left SMG (k=164, t_{peak}=5.99) and two significant clusters for H2 in the left hemisphere, the first with activation peaks in in the IPS region (k=386, t_{peak}=10.3), the second located in more supramarginal and postcentral regions (k=333, t_{peak}=6.91).

To sum-up, both analysis (univariate and fMRI adaptation) revealed similar patterns of activation in response to stimulations in the space near the hand. The pattern of activations converges with the one described previously by Brozzoli et al. (2011) using a similar approach. In particular, we found a significant reduction of the BOLD signal in premotor and parietal regions involved in PPS representation (i.e. IPS, PMd, PMv, SMG) when the stimulation was repeated near the hand. These results are reported in Table S4.

	H1								H2							
	k	Hemisphere	AAL3v1 ROI	Glasser Atlas	X	Y	Z	t	k	Hemisphere	AAL3v1 ROI	Glasser Atlas	X	Y	Z	t
Adaptation Near Repetition Hand	116	Left	Precentral	4 (PMC)	-40	-11	53	8.83	368	Left	Postcentral	2 (S1)	-23	-39	56	11.94
				FEF							SPL	7Al	-26	-50	59	9.88
				6d (PMd)								7Pl				
				6a								DVT				
			Postcentral	3b (S1)	-44	-18	51	6.01				IPS1				
	148	Left	Postcentral	2 (S1)	-26	-36	59	6.48				VIP (IPS)				
				1 (S1)								7PC				
			SPL	VIP (IPS)	-26	-62	64	4.91				7Am				
				LIPv (IPS)								LIPv (IPS)				
				7PC							IPL	LIPv (IPS)	-28	-49	50	5.92
				7Al								LIPv (IPS)				
	147	Left	SMG	PSL	-54	-42	25	6.01	355	Left	Postcentral	OP1	-51	-20	20	9.2
				PFcm								OP4				
				PF								1 (S1)				
			IPL	PFt	-48	-25	36	5.4				2 (S1)				
				2 (S1)								PFt				
											SMG	PFcm	-48	-31	22	8.14
												PFop				
												PSL				
Adaptation Second Part Hand	164	Left	SMG	PF	-56	-34	34	5.99	386	Left	SPL	7Al	-28	-45	62	10.3
				PSL								7Pl				
				PFcm								VIP (IPS)				
				OP4								5L				
				PFt								7PC				
			IPL	2 (S1)	-47	-27	37	3.25				7Am				
												2 (S1)				
												DVT				
											Postcentral	1 (S1)	-28	-39	67	4.03
									333	Left	Postcentral	OP1	-51	-20	20	6.91
												PFop				
												2 (S1)				
												1 (S1)				
												OP4				
											SMG	PFt	-56	-22	36	5.9
												PFcm				
											IPL	LIPv (IPS)	-26	-57	59	4.52
												AIP (IPS)				

Table S4. Significant clusters from adaptation analyses for H1 and H2 by comparing stimulations close to or far from the HAND. The significant clusters (p <0.05, cluster-based FWE correction) are reported with the relative activation peaks in MNI coordinates and the relative t-score.

S5: Human's MVPA: stimulation close to the hand

The LDA classifier used to investigate the activations associated to stimulations at different distances from the hand allowed to identify specific response patterns to the difference between stimulations close to and far from the hand. In particular, H1 reports a large activation cluster in the left hemisphere (k=2559, z_{peak}=3.09), whose activation peaks are found in almost all PPS-related areas: SMG, IPS, S1, PMv and PMd. These activations are part of a larger pattern that also includes two clusters in the right hemisphere, the first (k=546, z_{peak}=3.09) with response peaks in SMG, IPS and in the postcentral gyrus, the second (k=34, z_{peak}=3.09) in PMd. Secondly, the activation pattern found in H2 covers both hemispheres, with a large cluster in the left one (k=1929, z_{peak}=3.09), including almost all PPS-related areas (SMG, IPS, PMd, S1), and a smaller cluster in the right hemisphere (k=831, z_{peak}=3.09), with activation peaks in the superior and inferior parietal lobule (IPS), in the SMG and in the precentral (PMd) and postcentral gyri (S1, PMC). Complete report of these results and peak of activations in MNI coordinates are reported in Table S5 and displayed in Figure S1.

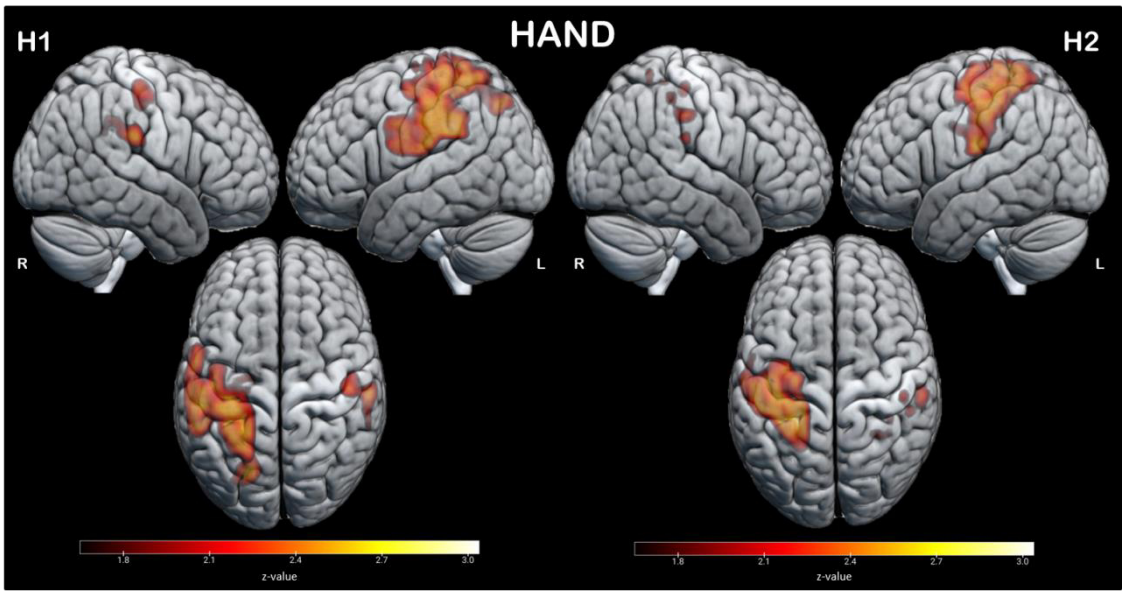


Figure S1. Results from MVPA comparing visual stimuli close to or far from the HAND. z-maps of significant clusters (z<1.65, one-sided t test) for Near vs Far stimulations for participants H1 (left) and H2 (right). For illustrative purposes, z-maps were smoothed after statistics (6 voxels smoothing).

	H1								H2							
	k	Hemisphere	AAL3v1 ROI	Glasser Atlas	X	Y	Z	z-score	k	Hemisphere	AAL3v1 ROI	Glasser Atlas	X	Y	Z	z-score
MVPA Near vs Far Hand	2559	Left	SMG	PFcm	-53	-25	14	3.09	1929	Left	SMG	PFcm	-53	-25	14	3.09
				PFt								PFt				
				PSL								PSL				
				OP1							Postcentral	2 (S1)	-28	-39	61	3.09
			Postcentral	PFop	-59	-19	25	3.09				1 (S1)				
				4 (PMC)								3b (S1)				
				1 (S1)								3a (S1)				
				2 (S1)								5L				
				3b (S1)								PFop				
				OP4								4 (PMC)				
			Precentral	6d (PMd)	-39	-6	56	3.09				OP4				
				6v (PMv)							Precentral	6d (PMd)	-36	-16	67	3.09
				6mp								6a				
				6a								6mp				
				8c								6r				
				FEF								FEF				
				PEF								PEF				
			SPL	7A	-26	-48	67	3.09				55b				
				7Pl								8C				
				7Al								i6-8				
				5L							SPL	7Al	-25	-42	61	3.09
				VIP (IPS)								7Am				
				LIPv (IPS)								VIP (IPS)				
				MIP (IPS)								7PC				
				DTV							IPL	7PC	-39	-42	50	2.75
				IPS1								LIPv (IPS)				
			IPL	7PC	-34	-42	56	3.09				IP2				
				IP1								AIP (IPS)				
				PFm								PFt				
				PF								IPS1				
	546	Right	Postcentral	OP4	66	-16	14	3.09	831	Right	SMG	PF	58	-28	20	3.09
				PFop								PFm				
				1 (S1)								PSL				
				2 (S1)							Postcentral	2 (S1)	38	-36	59	3.09
				4 (PMC)								1 (S1)				
				PFt								5L				
			SMG	AIP (IPS)	35	-33	42	2.95				PFt				
				PF							Precentral	4 (PMC)	44	-11	53	3.09
				PFop								6d (PMd)				
			Precentral	FEF	50	-11	48	2.75				3b (S1)				
				3b (S1)							SPL	7Al	22	-53	67	3.09
				6d (PMd)								IPS1				
	34	Right	Precentral	6d (PMd)	25	-14	64	3.09				7PC				
				6mp							IPL	IP2	52	-36	53	3.09
												PF				
												AIP (IPS)				
												PFm				

Table S5. Significant clusters from MVPA on human participants training and testing the LDA classifier on the difference between near and far stimulations in HAND condition. The significant clusters (z<1.65, one-sided t-test) are reported with the relative activation peaks in MNI coordinates and the relative z-score.

S6: Human's adaptation analyses: stimulation close to the trunk

Also for the trunk, the first (Adaptation Near Repetition) and the second (Adaptation Second Part) adaptation analysis approaches have been performed.

The repetition of the close-to-the-trunk stimulus induces a reduction of the BOLD signal in H1 located in two different clusters, both in the left hemisphere. The first (k=123, t_{peak}=10.43) reports an activation peak in the premotor region, while the second (k=200, t_{peak}=6.93) is

located in the left SMG. H2 shows a modulation of brain activity in a cluster (k=194, t_{peak}=9.46) including the S1 area and the IPS of the left hemisphere.

Comparing the Near-after-Far condition versus the Near-after-Near condition, we observe the same supramarginal cluster (k=220, t_{peak}=6.32) of the first approach for H1, lateralized to the left. Similarly, only one significant cluster is observed for H2, again in the left hemisphere, but with activation peaks in the IPS and S1 (k=168, t_{peak}=6.57). These results are reported in Table S6.

	H1								H2							
	k	Hemisphere	AAL3v1 ROI	Glasser Atlas	X	Y	Z	t	k	Hemisphere	AAL3v1 ROI	Glasser Atlas	X	Y	Z	t
Adaptation Near Repetition Trunk	123	Left	Precentral	4 (PMC)	-42	-11	56	10.43	194	Left	Postcentral	2 (S1)	-23	-39	56	9.46
				6a							SPL	7Al	-20	-53	62	6.48
				FEF								VIP (IPS)				
				6d (PMd)								7PC				
	200	Left	SMG	PFcm	-45	-39	28	6.93				LIPv (IPS)				
				PSL												
				PF												
				STV												
				PFt												
			IPL	2 (S1)	-48	-25	36	5.06								
Adaptation Second Part Trunk	220	Left	SMG	PFcm	-48	-36	31	6.32	168	Left	Postcentral	S1 (area 2)	-23	-39	56	6.57
				PSL							SPL	7Al	-20	-53	62	4.95
				PF								5L				
				STV								7PC				
			IPL	2 (S1)	-48	-28	39	3.78				VIP (IPS)				

Table S6. Significant clusters from adaptation analyses for H1 and H2 by comparing stimulations close to or far from the HAND. The significant clusters (p <0.05, cluster-based FWE correction) are reported with the relative activation peaks in MNI coordinates and the relative t-score.

S7: Human's MVPA: stimulation close to the trunk

The Near versus Far classification conducted through an LDA classifier allowed to highlight a bilateral activation pattern in H1 and H2, which clusters and peak of activations are reported in Table S7 and displayed in Figure S2.

H1 reports a response pattern consisting of a large cluster in the left hemisphere (k=1944, z_{peak}=3.09), including peak of activations in all the ROIs and in PPS-related areas, as SMG, IPS, PMv and S1, and three clusters in the right hemisphere. The first of the latter (k=233, z_{peak}=3.09) is located at the level of the SMG, the second (k=60, z_{peak}=2.41) in IPS and the last (k=56, z_{peak}=2.58) in S1.

Similarly, activation patterns in PPS-related areas were also observed bilaterally for H2, with a cluster in the left hemisphere (k=1063, z_{peak}=3.09) and one lateralized to the right (k=1570,

z_{peak}=3.09) both reporting activations in the supramarginal region, in the IPS and in S1. The cluster on the left, moreover, reported activations in PMv.

	H1								H2							
	k	Hemisphere	AAL3v1 ROI	Glasser Atlas	X	Y	Z	z-score	k	Hemisphere	AAL3v1 ROI	Glasser Atlas	X	Y	Z	z-score
MVPA Near vs Far Trunk	1944	Left	SMG	OP4	-54	-25	14	3.09	1063	Left	SMG	PFcm	-54	-25	14	3.09
				OP1								PFop				
				PFop								PF				
				PFcm							Postcentral	2 (S1)	-28	-42	56	3.09
				PF								3b (S1)				
				PSL								OP4				
			Postcentral	2 (S1)	-23	-34	64	3.09				4 (PMC)				
				1 (S1)								PFt				
				4 (PMC)								3a (S1)				
				3a (S1)							SPL	7Al	-22	-56	61	3.09
				3b (S1)								IPS1				
				PFt								DVT				
			SPL	7Al	-23	-50	62	3.09				7Pl				
				IPS1								7Am				
				DVT								VIP (IPS)				
				7Pl								5L				
				VIP (IPS)							Precentral	6mp	-23	-14	67	2.51
			Precentral	6a	-34	-8	53	3.09				6v (PMv)				
				6v (PMv)								PEF				
				43								6d (PMd)				
				PEF							IPL	7PC	-37	-45	50	2.88
				FEF								AIP (IPS)				
				55b								IP2				
				6mp								LIPv (IPS)				
			IPL	PFm	-48	-53	42	2.37	1570	Right	SMG	PFop	67	-25	20	3.09
				AIP (IPS)								PSL				
				LIPd (IPS)								PFt				
				LIPv (IPS)								PFcm				
				PFt								STV				
				IP2								PF				
	233	Right	Postcentral	OP4	61	-16	16	3.09			Postcentral	2 (S1)	44	-25	45	3.09
			SMG	PFop	64	-22	28	3.09				1 (S1)				
				PF								7PC				
				PFt								3b (S1)				
				PSL								3a (S1)				
				PFm								PFt				
				STV							Precentral	4 (PMC)	44	-11	39	3.09
				PFcm								PEF				
	60	Right	SPL	7Am	16	-59	64	2.41				6a				
				VIP (IPS)								FEF				
	56	Right	Postcentral	1 (S1)	33	-36	67	2.58				8Av				
											SPL	LIPv (IPS)	28	-53	59	3.09
												5L				
												7Al				
												7Pl				
												VIP (IPS)				
												MIP (IPS)				
												DVT				
											IPL	PFm	50	-39	50	3.09
												PF				
												AIP (IPS)				
												LIPv (IPS)				
												IP1				
												IP2				

Table S7. Significant clusters from MVPA on human participants training and testing the LDA classifier on the difference between near and far stimulations in the TRUNK condition. The significant clusters (z<1.65, one-sided t-test) are reported with the relative activation peaks in MNI coordinates and the relative z-score.

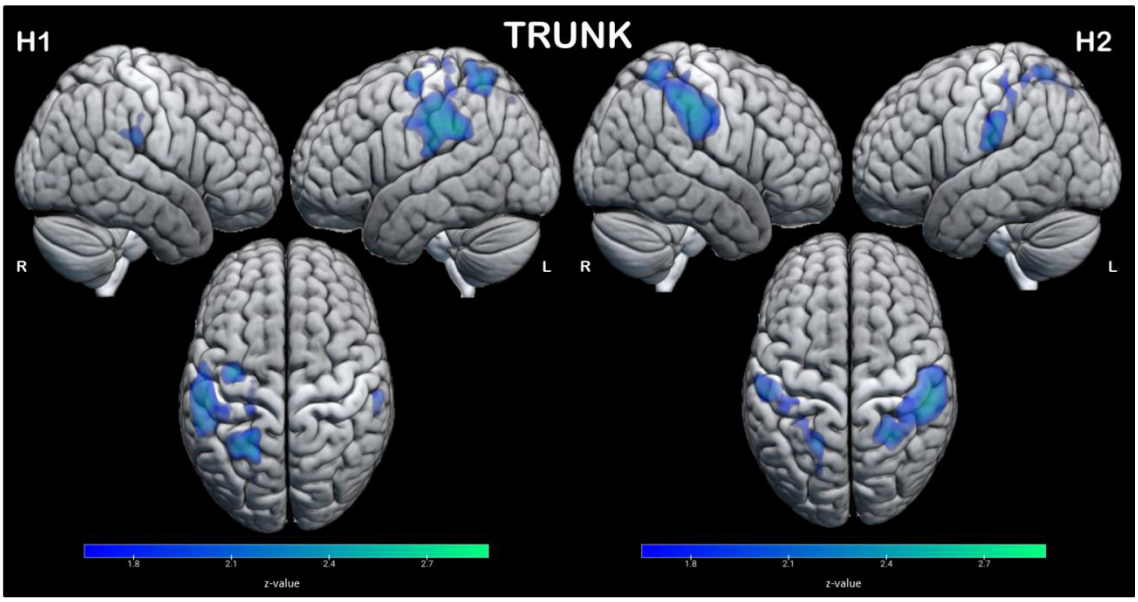


Figure S2. Results from MVPA comparing visual stimuli close to or far from the TRUNK. z-maps of significant clusters (z<1.65, one-sided t test) for Near vs Far stimulations for participants H1 (left) and H2 (right). For illustrative purposes, z-maps were smoothed after statistics (6 voxels smoothing).

Chapter II

The Space Around Us

C'era uno spazio comune tra di loro,
i cui confini non erano ben delineati,
dove sembrava non mancare nulla
e dove l'aria pareva immobile,
imperturbata.

Paolo Giordano

It was with this title, "The space around us", that about twenty-five years ago Rizzolatti and colleagues titled an article in which they tried to describe the possible function of the representation of peripersonal space (Rizzolatti et al., 1997a). This attempt turns out to be very complex, due to the numerous nuances that the PPS can take and the different experimental paradigms that have been used over time to test it. After having investigated its neural basis, therefore, it is now time to go into more detail in what the representation of the peripersonal space of the human being is for. In this chapter, we will first give a brief description of the multiple functions of PPS and the different theoretical models that have been developed to try to describe them. Subsequently, we will analyze in more detail what are the experimental paradigms over time used to study this spatial representation in healthy humans, with particular attention to those that have demonstrated the plasticity of its boundaries. Precisely this plasticity could be one of the factors that led to a theoretical parallelism between the PPS and another representation of the space that surrounds our body: that of the reaching space. We will therefore try to better understand how the latter was defined, what are the experimental paradigms used for its study and what are its neural bases, both specific and in conjunction with those of the PPS.

To conclude this chapter, we will present a study that investigated and provided behavioral evidence for the distinction between the representation of the peripersonal space and that of the reaching space.

2.1 A complex definition

I have so far described the peripersonal space as "the space that surrounds the body", a "bubble" (or a set of bubbles) that surrounds the parts of our body and remaps itself according to their movement. This definition, although relatively simple, already lead to a fundamental question: what is the function of this representation?

The space around us is rich in a myriad of stimuli with different characteristics: static, moving towards the body or away from it, threatening or appetizing. To this, one should add its interactive aspect: we can grab objects, perhaps using them to reach other objects that are more distant. And we must not forget that in our environment there are not only objects, but also people, who can interact with us, move in space and enter our peripersonal space.

A definition that can include these different aspects is that provided by Coello and colleagues: *"the peripersonal space contains the objects with which one can interact in the here and now, specifies our private area during social interactions and encompasses the obstacles or dangers to which the organism must pay attention in order to preserve its integrity"* (Coello et al., 2012).

Several salient elements emerge in this definition. First of all, it emphasizes the versatility of the PPS, which deals with a wide range of stimulations and signals of different nature. Linked to this versatility there are three main functions of this representation: PPS as a defensive region, aimed at preserving the integrity of the body (Bufacchi et al., 2016; de Vignemont & Iannetti, 2015; Graziano & Cooke, 2006), PPS as a sensory-motor interface, allowing the interaction between the body and the object in the close environment (Brozzoli et al., 2009, 2012a; Makin et al., 2012; Patané et al., 2019) and PPS as a space for social interaction (Brozzoli et al., 2013; Iachini et al., 2014; Ishida et al., 2010). Although quite exhaustive, even the definition reported above cannot capture all the complexity and richness of the representation of the PPS. Consider, for example, the fact that PPS contains objects with which we can interact "here and now": more recent studies have shown that the PPS encoding of stimuli also acts in a predictive way, identifying stimuli with which we cannot currently interact, but which will potentially interact or come in contact with our body in the

near future (Belardinelli et al., 2018; Cléry & Ben Hamed, 2018, 2021; Kandula et al., 2017; Lohmann et al., 2019). Finally, a recent line of research has looked at PPS from a different perspective, more linked to embodied cognition: PPS as the space of the Self (Brozzoli et al., 2012a; Grivaz et al., 2017; Makin et al., 2008). According to this perspective, PPS represents a multisensory integration mechanism of the signals coming from the body and the immediately surrounding region, and it is thanks to this mechanism that we can experience the sensation that our Self is integrated with a body that belongs to us (self-identification), which occupies a position in space (self-location) and which looks at the world from a specific perspective (first-person's perspective; see Serino, 2019 for review).

To try to clarify the complex definition of the PPS, we are now going to investigate in more detail how PPS show itself through its various functions.

2.2 A sensorimotor representation of the Self to act and interact

Let's try to make a "small" time jump of a few hundred thousand years and imagine that you are one of the first Homo Sapiens grappling with the problem of feeding. Suddenly, in the middle of the forest, you notice fruit hanging from the branches of a small tree. Shaking it you could easily drop some, and solve the problem of hunger, but since you do not know the consistency of the fruit, it would be preferable not to let it fall to the ground, avoiding the risk of finding yourself with a crushed and inedible fruit. In this situation, there are several factors that make your action effective: you must first of all detect the position of the fruit in space, but at the same time consider the position of your body, your arms and your hands, which will have to grasp it. Furthermore, this information must be constantly updated, because the position of the fruit changes constantly – though predictably, due to the wind blowing through the branches or due to the fall; in the same way, also your hands will have to detach from the trunk of the tree to move towards the fruit. Finally, the timing: if you want to eat, you must consider the speed with which the fruit falls, to avoid arriving late and letting it escape.

In this putative case, it is the representation of the peripersonal space that allows us to carry out this effective action. As we have already had the opportunity to understand, indeed, the

neurons of the brain areas related to the representation of the PPS possess spatially co-registered visual-tactile receptive fields centered on specific parts of the body (see Cléry et al., 2015 for review), and this feature could help us to know at any moment in which position the surrounding objects and our body parts are. Furthermore, the first electrophysiology studies have shown that the depth of the visual RFs of the multisensory neurons present in the F4 area of the macaques varies as a function of the speed of the stimulus directed towards the body. In this way, stimuli that approach faster elicit an anticipated response from these neurons (Fogassi et al., 1996). And it is always the neural network underlying the representation of the PPS that manages and plans this response: the visual-tactile multisensory neurons of the parietal area 7b (Fogassi et al., 2005; Fogassi & Luppino, 2005; Hyvärinen, 1981; Hyvärinen & Poranen, 1974; Hyvärinen & Shelepin, 1979; Leinonen et al., 1979; Leinonen & Nyman, 1979; D. L. Robinson et al., 1978), of premotor area 6 (Gentilucci et al., 1983, 1988; Graziano et al., 1997a; Rizzolatti, 1987; Rizzolatti et al., 1981) and putamen (Crutcher & DeLong, 1984) are activated not only when a visual or tactile stimulation is passively perceived, but also when a motor response is implemented. This sensorimotor activity, moreover, is expressed in a system of common spatial coordinates, which takes into consideration at the same time the position of the body-parts, the target to be reached and the movement necessary to reach it (Caminiti et al., 1991; 1990a; 1990b). This not only applies to the premotor and motor regions, but also to the areas of the posterior parietal cortex involved in the coding of PPS, including area 7b (Fogassi & Luppino, 2005; Rizzolatti et al., 1997b; Ferraina et al., 2009a and see 2009b for review).

These electrophysiological results in the monkey concerning the close link between PPS and action were later confirmed also by studies in humans, although some possible limitations of this investigation must be taken into consideration. As we have already stated, effective action requires continuous monitoring and updating of the representation of the body (which we can define as “body schema”, the sensorimotor representation of the body used for action, de Vignemont, 2007) and of the space that surrounds it (PPS), in which the stimuli to be manipulated are found (N. P. Holmes & Spence, 2004). This is because when the body and / or the objects around it move, all the spatial coordinates change, and must be constantly updated in order to achieve the goal. However, in many cases the stimulation used in human studies is static, as is the observer. Under this condition, considering any

outcome as relative to the PPS-action relationship is often a speculation. Nevertheless, studies that have used stimuli and / or participants in movement are not rare, and have allowed us to confirm also in the human being the basic importance of the representation of the PPS in the carrying out and planning of actions. A further limitation, which concerns most of the studies in the literature, is the use of stimulations located in a narrow portion of the two-dimensional space in front of the subject. Considering that the actions we perform and the stimuli we perceive are localized in a three-dimensional space, this limit can reduce our ability to understand the mechanisms through which the transition from perception to action takes place (for an in-depth review in this regard, see van der Stoep et al., 2016).

Despite these cautions, to be taken into consideration, recent studies have investigated more deeply the relationship between the processing of multisensory information coming from the body and the surrounding space and motor responses. It is thanks to these studies that today it is possible to support that the PPS is an interface between perception and action, between the information coming from the external world and the consequent response.

2.2.1 A peripersonal action space

One of the first evidence of a PPS for action derives from the study by Brozzoli and colleagues (Brozzoli et al., 2009), who investigated the function of the PPS as an interface underlying the execution of voluntary and goal-directed actions. In a series of four experiments, the authors used a modified version of the crossmodal congruency task (Pavani et al., 2000) described in paragraph 1.3, in which the participants had to discriminate as quickly as possible the elevation of a tactile stimulation (up or down) applied to the thumb or the index of the right hand while a synchronous visual stimulation could be presented at a congruent or incongruent elevation. In the first experiment the task was only perceptive, but in experiments 2, 3 and 4 the participants had to perform this task while reaching-to-grasp the cylinder in which visual distractor were embedded, with the right (experiments 2 and 4) or left hand (experiment 3). Performing the action with the left hand allowed to control any hand-centered modulation of the multisensory processing, as the tactile stimulation to be discriminated was always applied to the right hand. Importantly, in experiments 2, 3 and 4 the visual-tactile stimulation could be applied before the movement (in the “static” phase of

motor planning), at the onset of the movement ("start" phase of the movement) or during the movement ("action execution" phase). In the first experiment the authors replicated the cross-modal congruency effect (CCE) that we have already had the opportunity to describe: when the visual and tactile stimulation are congruent, the participants' response is faster. What is observed is a modulation of the CCE by the phase in which the visual-tactile stimulation is applied, with a greater interference of the incongruent condition as the action proceeds. Particularly, it is observed that during the static phase of motor planning the CCE is significantly lower than that reported at the moment in which the action begins. Furthermore, this effect increases even more when the visual-tactile stimulation arrives during the execution of the grasping action. This modulation of the CCE according to the state of the action is present only if the movement is carried out with the stimulated hand, the right, while no effect emerges in case of movement with the left hand. This, therefore, demonstrates a hand-centered online remapping of sensory information processing as a function of movement: the closer the stimulated hand approaches the irrelevant visual stimulation, the more it interferes with the task (Brozzoli et al., 2009). Action and perception are integrated in the representation of the PPS.

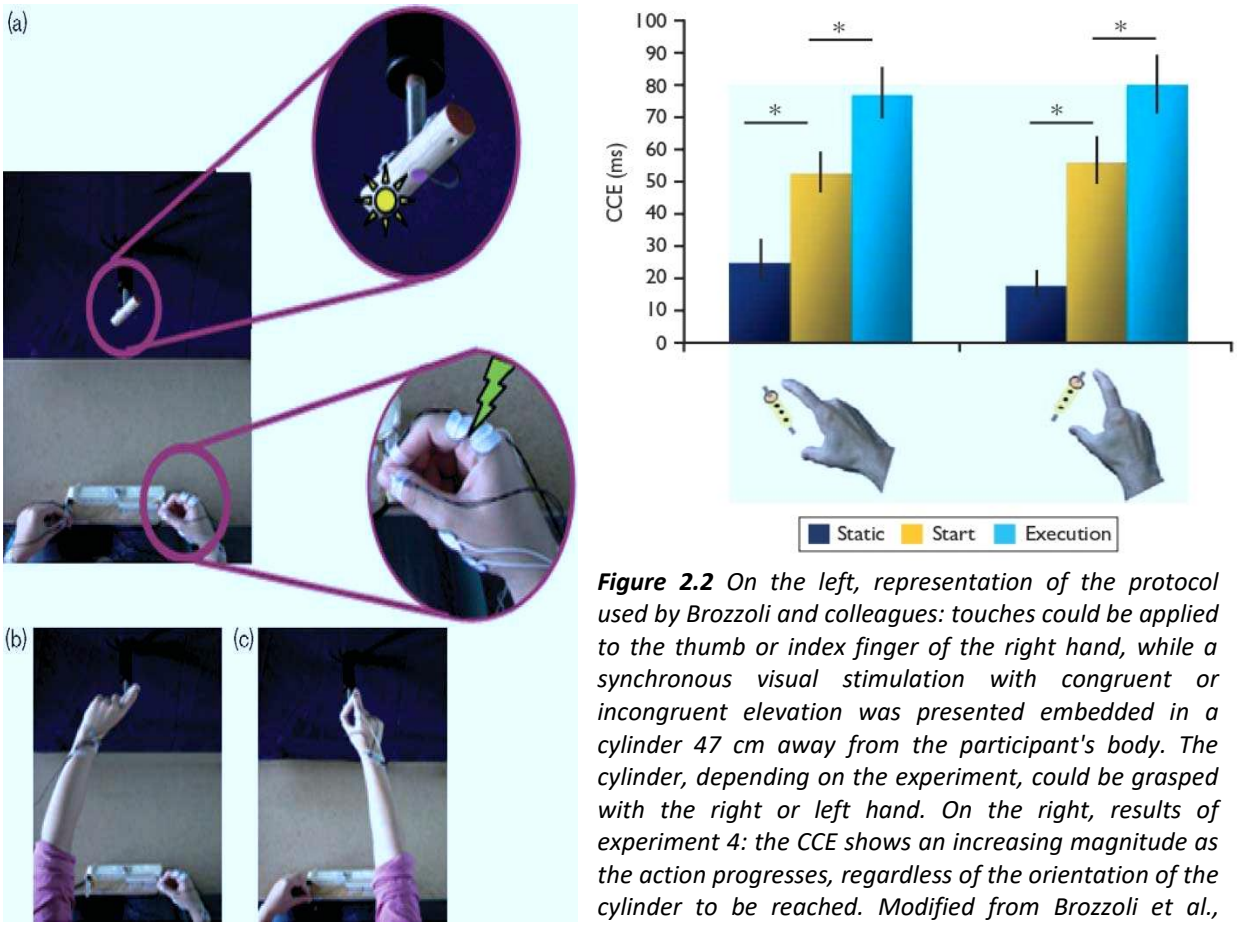


Figure 2.2 *On the left, representation of the protocol used by Brozzoli and colleagues: touches could be applied to the thumb or index finger of the right hand, while a synchronous visual stimulation with congruent or incongruent elevation was presented embedded in a cylinder 47 cm away from the participant's body. The cylinder, depending on the experiment, could be grasped with the right or left hand. On the right, results of experiment 4: the CCE shows an increasing magnitude as the action progresses, regardless of the orientation of the cylinder to be reached. Modified from Brozzoli et al., 2009.*

A second study in this literature used auditory stimuli presented near or far from the participant's hand, from which the authors recorded the motor-evoked potentials (MEPs) induced by transcranial magnetic stimulation (TMS). The magnetic impulses of the TMS, applied at the level of the contralateral motor region corresponding to the representation of the hand, are able to elicit a motor response, and therefore to induce MEPs. These lasts are used as a measure of motor activation: stronger MEPs indicate muscle activation, while weaker MEPs indicate inhibition of the motor response. To test this motor activation at different time intervals, the TMS pulses could be applied to four different delays: 50, 100, 200 and 300 ms. If the processing of sensory information within the peripersonal space were not related to the motor response, the presentation of an auditory stimulus near or far from the hand should not affect the magnitude of the MEPs generated by the TMS pulses. What the authors observed, however, is that the MEPs recorded at 50 ms from the onset of the sound close to the hand are enhanced compared to those recorded for distant auditory stimulations, indicating that the motor representation of the hand is modulated by the spatial position of the irrelevant stimulus. This modulation is reduced at 100 and 200 ms, and it is completely reversed at 300 ms, at which time the magnitude of the MEPs associated with the distant auditory stimulation is greater. Furthermore, this pattern of results is specifically linked to the position of the hand: by moving the hand away from both auditory stimulations, the difference in terms of MEP intensity between near and far stimuli disappears (Serino et al., 2009).

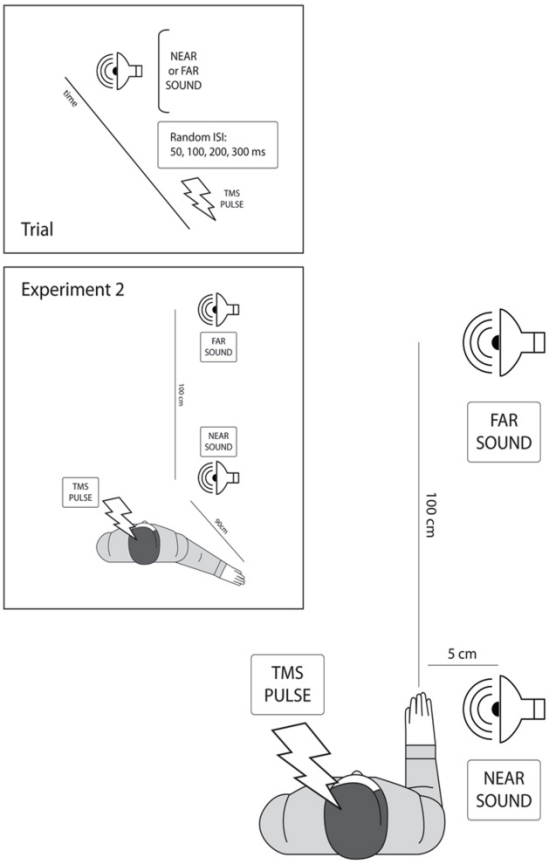


Figure 2.1 *Experimental protocol used by Serino and colleagues: in the main panel the participant places his right hand near the sound source closest to his body. In the small box at the top, the structure of the trial is explained, with the pulse TMS that could be applied to the left motor cortex 50, 100, 200 or 300 ms after auditory stimulation. In the second small box, the protocol used for the second experiment, with the participant's hand positioned away from both sources of sound stimulation. From Serino et al., 2009.*

The study by Serino and colleagues indicates that an auditory stimulus presented within the PPS, even if irrelevant, modulates the excitability of the motor system, unequivocally underlining the relationship between PPS and action. The stronger motor excitability for stimuli close to the hand at a short delay and the reversal of this effect at later time intervals is in line with the motor function of the PPS: stimuli close to the body require a rapid response, while more distant stimuli require a certain delay to reach the body, and therefore the motor response will also be delayed. However, these findings from TMS pulses applied to the motor region corresponding to the representation of the hand, not clarifying the role of the neural network underlying the PPS. Thus, the same research group, a few years later, took advantage of the same experimental protocol associating it with a cathodal transcranial electrical stimulation (tDCS) applied at the level of two regions involved in the representation of the PPS: the premotor cortex (PMc) and the posterior parietal cortex (PPc). Cathodal tDCS is able to modulate the brain activity of the areas to which it is applied, inhibiting it. In this way, the authors replicated the results of the previous study, but also observed an abolition of the effect in case of suppression of PMc activity (Avenanti et al., 2012). This, once again, demonstrates the involvement of PPS representation in the planning and execution of motor responses, and in particular underlines the role of PMc in the mapping of sensory stimuli and hand-centered motor activations.

Although these paradigms have challenged the aspect related to the stillness of the participants, they do not solve the one related to the stillness of the stimulation. A paradigm that has taken advantage of moving stimuli comes from the study of Makin and colleagues (Makin et al., 2009), who investigated the effects of potentially harmful stimuli approaching the hand. Albeit a distinction between "PPS for action" and "PPS for defensive purposes" based solely on the movement of external stimuli is unlikely, this study allows us to begin to dig into what is the defensive role of the PPS. Our little example of a hungry hominin in the forest, struggling with falling fruits, can help us understand why: a small miscalculation can easily transform an appetizing fruit into a painful projectile aimed at the body. It is probably this idea that inspired Makin and colleagues in the development of their paradigm, visible in Figure 2.3.

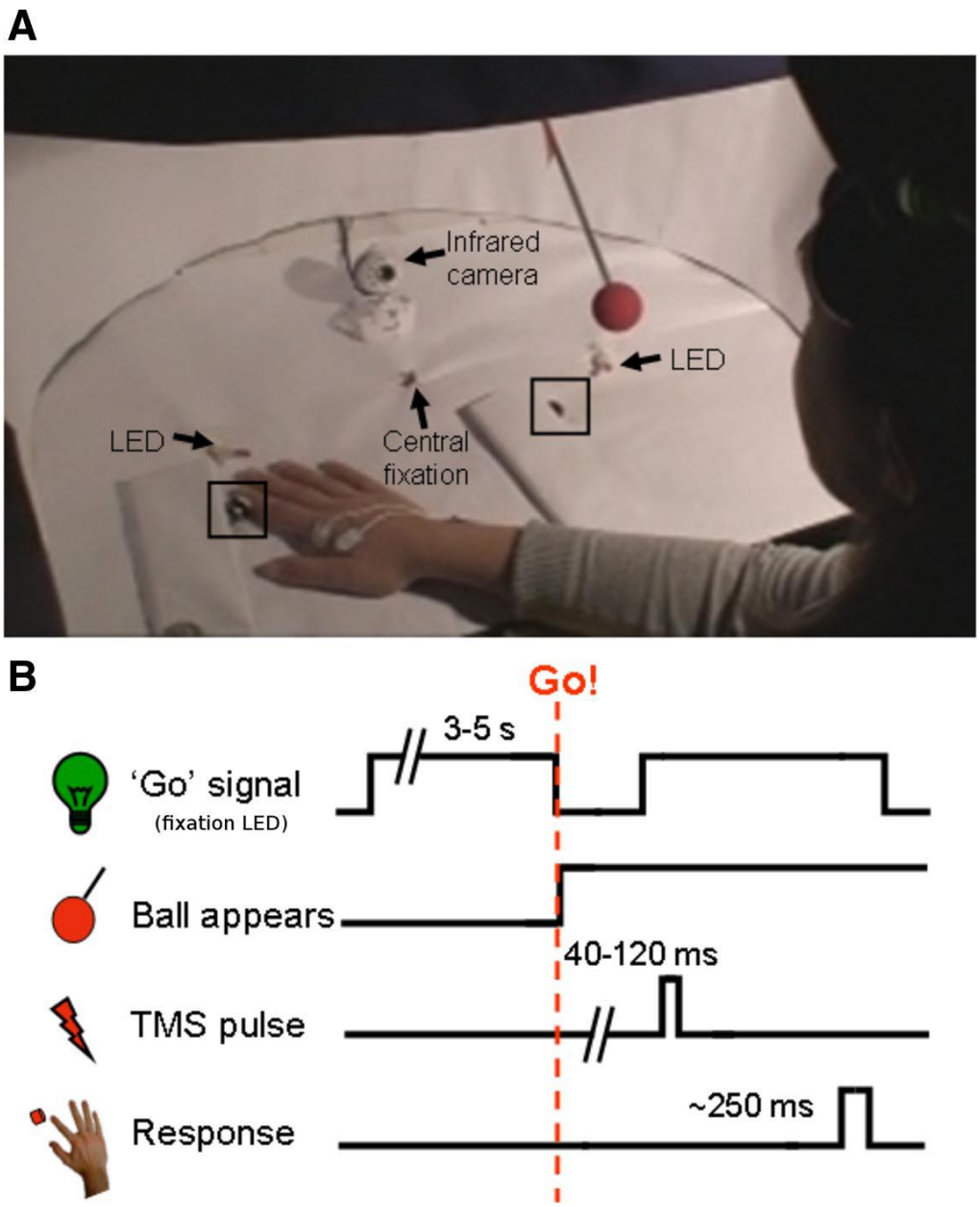


Figure 2.3 *Experimental protocol used by Makin and colleagues. Participants were to fix a central LED and respond by pressing a button to the right or left of the body midline as soon as the LED was turned off. At the same time, a three-dimensional stimulus (a sphere) could quickly and suddenly approach the right or left response position, then near or far from the hand. This appearance was followed by a pulse TMS within a range of 40-120 ms. From Makin et al., 2009.*

In their study, participants had to stare at a LED positioned on the sagittal axis of the body and respond by pressing a lateralized button with their right index finger when the LED turned off. The right hand could be positioned to the right or left of the midline of the body, corresponding to the two positions occupied by the response buttons. The task itself is

necessary to induce the motor planning of the response, evaluated with the MEPs recorded by the right hand in response to TMS pulses applied to the contralateral motor cortex (as in Serino et al., 2009). The authors wanted to investigate the amplitude of the MEPs following the apparition of a three-dimensional stimulus (a sphere) that could fall vertically and suddenly in the position of the hand (close condition) or contralaterally (far condition). Results showed that the sudden appearance of this rapidly approaching stimulus near the hand induces a reduction in the amplitude of the MEPs which appears between 60 and 80 ms from the perception of the threat, indicating an inhibition of the planned motor response (the button press). This seems logical: the participants perceive the potentially threatening stimulus that is falling on their hand, but cannot implement an avoidance response, because the right index finger must be able to press the button at any moment. Threatening away-from-the-hand stimulation, on the other hand, has the reverse effect, inducing an increase in corticospinal excitability. Furthermore, this effect emerges only when the threatening stimulus moves towards the hand, while no modulation of the MEPs is observed if static LEDs are used instead of the spheres. Importantly, finally, this effect is centered on the hand: by changing the position of the fixation LED and shifting the participant's covert spatial attention, the authors still observe a suppression of the MEPs in relation to threatening stimuli approaching the hand, and their enhancement in case of distant stimulus (Makin et al., 2009). The determining factor, in this case, seems to be the distance of the stimulus from the hand, thus the part of the body that is “threatened”.

With this study it therefore seems plausible to suggest that the coding of sensory information in the space around the body subserves not only goal-directed actions, but also defensive responses, aimed at preserving the body (both by avoiding or blocking responses). However, for this last consideration, it is necessary that the sensorimotor system is rapidly updated not only regarding the movement of external stimuli towards the body, but also regarding which part of the body is in danger. Using a very similar experimental protocol, the same research group also investigated this aspect, showing that in a time frame very similar to that reported in the first study (~70 ms) the sensorimotor system supporting PPS representation is already able to establish whether the threatened hand is the right or the left one (Makin et al., 2015).

2.2.2 A peripersonal defensive space

These last interpretations are in line with the results of electrophysiology in monkeys: thanks to the many studies by Graziano and colleagues it was possible to observe that the electrical stimulation of the VIP area in the intraparietal sulcus and of the "polysensory zone" (corresponding to the premotor area) in the frontal cortex it causes a typical pattern of defensive responses (see Graziano & Cooke, 2006 for review). This defensive reaction presents itself in an incontrovertible and stable way after each stimulation, including movements of the eyes, face, shoulders, head and arms (Cooke & Graziano, 2003, 2004a; Stepniewska et al., 2005) aimed at protecting the sensitive parts of the monkey's body from a (non-existent in this case) threat (but see Strick, 2002 regarding the effect of the high intensity used in the electrical stimulations of these studies). This response pattern is also reproduced in the presence of real external threatening stimuli, such as sudden air puffs on the surface of the body (Cooke & Graziano, 2003, 2004a), and the timing with which these movements are implemented is very similar to that of suppression of corticospinal excitability reported by Makin and colleagues (Makin et al., 2009): ~80 ms (Graziano et al., 2005). Furthermore, by chemically modulating the activity of these regions, it is possible to provoke a consequent modulation of the habitual defensive behavior, inhibiting or accentuating it (Cooke & Graziano, 2004b).

A subcortical muscular response quite different from those described above has provided ample evidence in support of the defensive function of the PPS in humans: the so-called hand-blink reflex (HBR), a contraction of the orbicularis oculi muscle that is elicited by the application of a threatening stimulus to the hand. Thanks to electromyography (EMG), it is possible to evaluate the magnitude of this response: a stronger HBR indicates a more pronounced defensive reaction. The research group of Iannetti and collaborators exploited this reflex to delineate, through multiple studies, the extension and form of the representation of the peripersonal space centered on the head (Bufacchi et al., 2016; Sambo, Liang, et al., 2012; Sambo, Forster, et al., 2012; Sambo & Iannetti, 2013). In the typical protocol used in these studies, a short transcutaneous electrical stimulus was applied to the median nerve of the wrist of the participants' right hand, which then had to be positioned at different distances from the face and with different orientations (for a complete review of all positions tested, see Figure 2.4, upper panels). Through this

paradigm, it was possible to highlight that the magnitude of the HBR response increases in a non-linear fashion with the reduction of the distance between the hand and the face, as if there was a "border" (may the authors forgive me for this term) after which the stimulus applied to the hand suddenly becomes more threatening (Sambo & Iannetti, 2013), only if there is no protection between the threatened hand and the face (Sambo, Forster, et al., 2012). But that's not all: Bufacchi and colleagues managed to develop a family of mathematical models capable of evaluating the intensity of the HBR response as a function of the position of the hand in the space around the head. In this way, it was possible to observe that the representation of the head-centred PPS is symmetrical on the horizontal axis, but not on the vertical one, assuming a half-ellipsoidal shape towards the top (see Figure 2.4, lower panel, Bufacchi et al., 2016). This type of asymmetry can, once again, be explained by our simple “hominid” example (and by Sir Isaac Newton): the stimuli around us do not move in a completely random way, but are subject to different laws, including that of gravity. If we throw something, or if something is thrown towards us, its trajectory will tend downwards. The fruit that falls from the tree we have shaken will not follow an unpredictable trajectory, but will fall vertically from top to bottom. It is therefore conceivable that even a mechanism designed to protect the body from external threatening stimuli takes this property into consideration. This hypothesis seems to be corroborated by the fact that by changing the posture of the participants, for example by making them lie down on their backs, the shape of the PPS remains asymmetrical, extending upwards (Bufacchi & Iannetti, 2016).

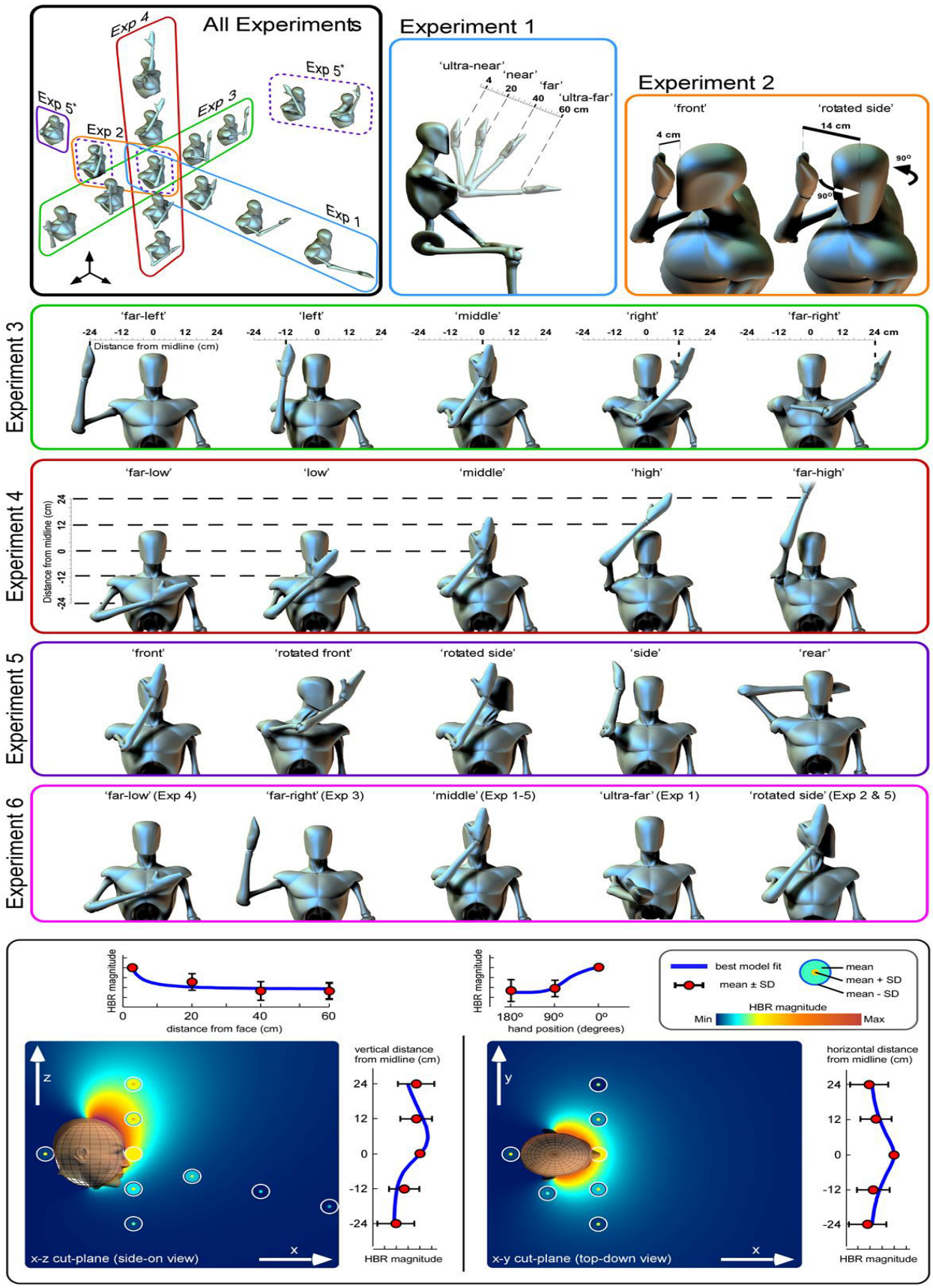


Figure 2.4 *In the upper panels, all the positions of the hand and head tested by Bufacchi and colleagues, measuring the hand-blink reflex (HBR). In the lower panel, it is possible to observe the half-ellipsoidal shape of the PPS centered on the head, as evidenced by the gradual reduction in magnitude of the HBR. Modified from Bufacchi et al., 2016.*

Interestingly, the HBR is not only affected by the approach of one's hand to one's face, but is also susceptible to the presence of another person's hand within the head-centered PPS (Fossataro et al., 2016). Although with a lower absolute magnitude than that reported for one's own hand, a foreign hand approaching the face in association with transcutaneous electrical stimulation on one's own wrist elicits a more marked HBR than when the same foreign hand is away from the face (see Figure 2.5). This opens a glimpse into what is a third widely studied function of the representation of the PPS: the social function.

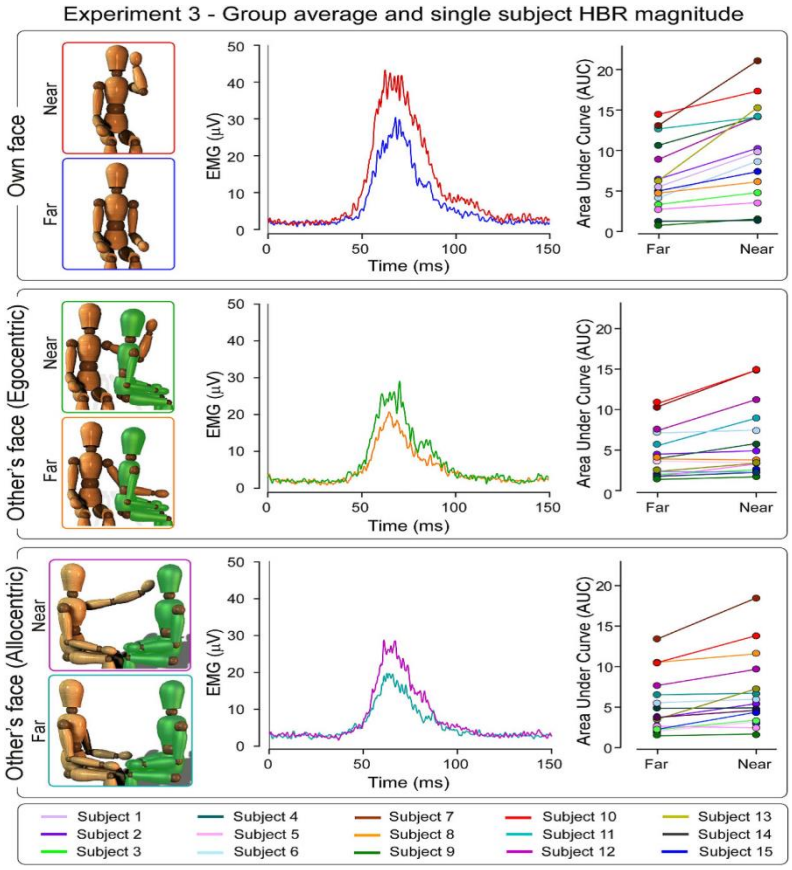


Figure 2.5 *Experimental conditions and results of the study by Fossataro and colleagues (2016). The participant's reflex hand-blink was recorded when his threatened hand is positioned near or away from his face ("own face" panel) or the face of a stranger, both in an egocentric perspective ("egocentric" box) and allocentric ("allocentric" box). The defense response is maximal when one's hand enters one's peri-head space, but HBRs of greater magnitude are also observed when one's hand enters another person's peri-head space. From Fossataro et al., 2016.*

2.2.3 A peripersonal social space

The visual-tactile neurons of the VIP area of the macaque show responses to tactile stimuli on a specific part of the animal's body, to visual stimuli approaching that part of the body but also approaching the body of an experimenter, positioned in front of the monkey (Ishida et al., 2010). Also in the premotor area F5 visuomotor neurons with these properties have been observed, able to respond both to actions performed by the monkey and to observed actions, and thanks to this characteristic they have taken the name of "mirror neurons" (Di

Pellegrino et al., 1992; Gallese et al., 1996; Rizzolatti et al., 1996; Rizzolatti & Matelli, 2003). Furthermore, a subpopulation of these neurons responds preferentially to actions (their own and others) that take place within the PPS, rather than outside of it. The function of these neurons seems to be linked to the understanding of the motor acts of others, and therefore plays a fundamental role in interpersonal interactions.

A first demonstration of the effect of the presence of other people on the representation of human PPS comes from the study by Heed and colleagues (Heed et al., 2010). Using the cross-modal congruency task, that we have already had the opportunity to know, the authors observed a reduction in the extension of the participant's PPS if, in front of him, another person performed the same task. The reduction of the CCE only manifested itself if the partner of the participant was in front of him, invading his PPS, and if he carried out the task himself: no effect emerged if the partner was outside the participant's PPS or passively observed the scene, without carrying out any task (see Figure 2.6). A result of this type seems to suggest that the strength of the visual-tactile integration for the stimuli around our body can vary according to the proximity of other agents. These findings were later confirmed and extended by Teneggi and colleagues with a tactile detection task in the presence of irrelevant auditory stimuli in looming towards the body.

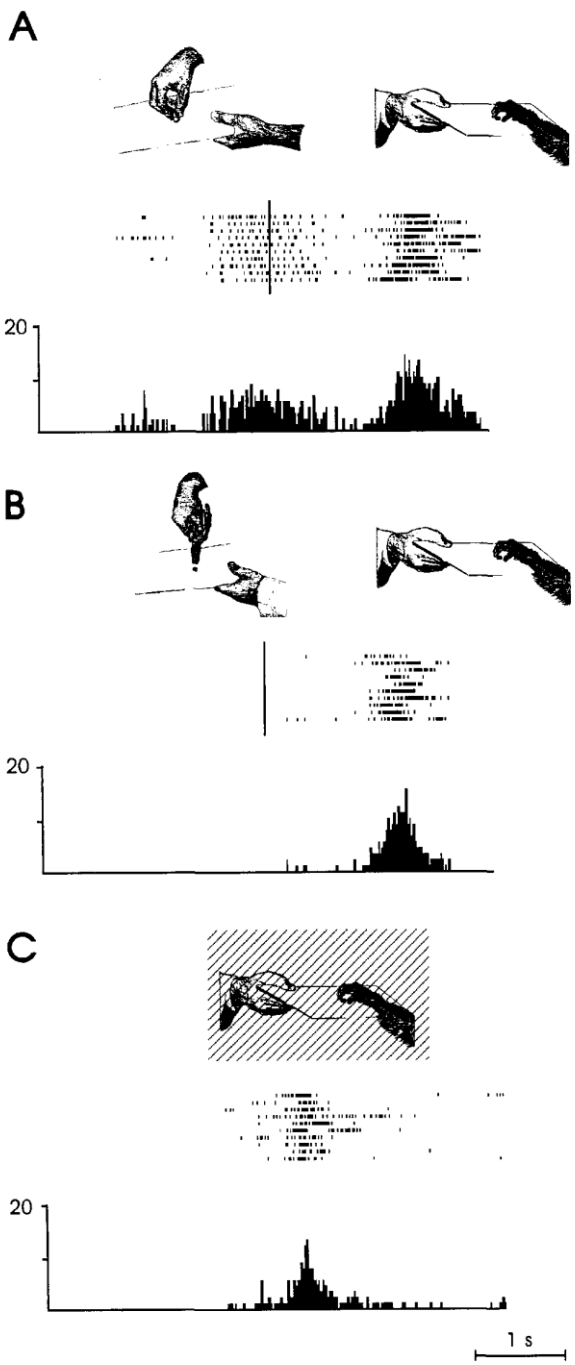


Figure 2.6 *Example of a classic mirror neuron response. A) The neuron responds when the monkey observes the experimenter grasping the food, stops responding when the food is deposited on the ground and responds again when the animal grabs the food. B) Same sequence of actions as in A, but the experimenter uses a tool instead of his hand. The neuron only responds when the monkey's reaching action is performed. C)The monkey grasps food in the dark. While in A the neuron responds from the vision of the experimenter grasping the food, now the neuron begins to respond only when the animal's reaching movement is enacted. From Rizzolatti et al., 1996*

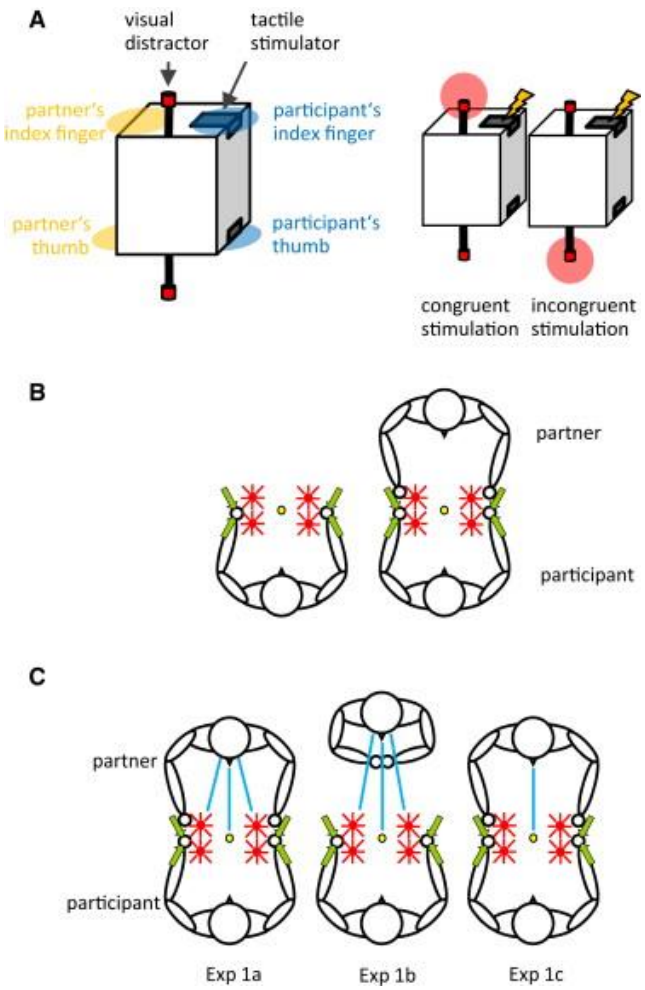


Figure 2.7 *Illustration of the experimental paradigm of the study by Heed and colleagues (2010). A) Representation of the devices used for the administration of tactile and visual stimuli, with indication of the position of the stimulators and the fingers of the participants. B) Illustration of the social manipulation of the experiment. All participants performed the task both alone and with a partner. Green arrows symbolize locations of tactile stimulation; red dots with rays symbolize visual distractors. C) Experimental conditions used in the first three experiments of the study: partner in the participant's PPS responding to visual distractors (Exp 1a), partner outside the participant's PPS responding to visual distractors (Exp 1b) and partner in the participant's PPS, but without performing any task (Exp 1c). From Heed et al., 2010.*

They have shown that the presence of a stranger leads to a reduction in the extension of the PPS, which does not occurs in the presence of an inanimate manikin (Teneggi et al., 2013). However, usually our interactions with others are not limited to mere presence, but involve behaviors that can be cooperative or non-cooperative. In the same study, the authors demonstrated that these different situations also influence multisensory integration in the space around the body: if the other person collaborates with us, our PPS expands towards him/her, while this does not occur if the other person engages in non-cooperative behavior.

This type of plasticity of the PPS clearly refers to the concept of personal space (often called interpersonal space in social psychology) conceived by Hall (Hall, 1966), who describes it as the space around the body within which the presence of a stranger causes discomfort. This region of space could then expand, including a person who helps us. However, caution must be used in superimposing one spatial representation on another. Iachini and colleagues conducted a series of experiments in which, in a virtual reality context, the participants were faced with a human character or non-human stimuli. Their task was twofold: to indicate at what distance they think they can reach the virtual stimulus (reachability judgment task, a task that is often

used for the investigation of PPS) and to indicate at what distance the virtual stimulus causes them discomfort (comfort-distance judgment, a task used for the study of personal space). They observed a similar reduction in the extent of both spatial representations in front of human virtual partners, associated with a similar extension in front of non-human stimuli (Iachini et al., 2014). These findings were then expanded by the same research group, reporting larger reachability and interpersonal distances in the face of virtual partners perceived as immoral (Iachini et al., 2015). This pattern of results would therefore seem to indicate an overlap between the peripersonal and personal space, but a subsequent study seems to demonstrate the dissociation between these two representations. Pellencin and colleagues developed a multisensory interaction task in a virtual reality context (the "social PPS task") in which the participant must respond as quickly as possible to the tactile stimuli received on the hand while ignoring the virtual objects that move towards his body. The authors observe that the region of space where the facilitation of the performance linked to the processing of multisensory stimuli within-PPS takes place expands if a virtual partner perceived as “moral” (rather than “immoral”) is presented in front of the participant. This extension of the PPS is associated with a reduction of the distance at which the presence of the person is judged as uncomfortable (Pellencin et al., 2018). Another clear demonstration of the non-overlap of the peripersonal and interpersonal space comes from the study by Patanè and colleagues, in which a cooperative reaching task performed using a long tool causes an extension of the PPS associated with a reduction in the extension of the interpersonal space, as noted in the study by Pellencin and colleagues (Pellencin et al., 2018). Using a shorter tool, the extension of the PPS did not change, while the reduction in interpersonal space remained (Patané et al., 2017). This pattern of results therefore seems to show a dissociation between the two spatial representations, but the difference found between the latter studies could be related to the type of task used to investigate the PPS (reachability judgment task versus speeded visuo-tactile detection). A little more about this theme will be discussed at the end of this chapter, in a behavioral study that directly compared the two tasks / spaces.

2.2.4 A peripersonal Self space

Last but not least, the representation of the peripersonal space has in recent years elicited strong interest from the literature on embodied cognition. The sensation of owning a body and of its integrity, indeed, has as its fundamental element the continuous integration of coherent multisensory signals coming not only from the external environment, but also from the body itself (Blanke, 2012; Blanke & Metzinger, 2009; Ehrsson, 2012; Gallagher, 2000; Jeannerod, 2003; Makin et al., 2008). The multisensory integration mechanism underlying the PPS, therefore, could be the keystone in the formation of this feeling of body ownership (Ehrsson, 2012; Makin et al., 2008; Tsakiris, 2010) but also of other components of what is defined as "bodily self consciousness": the idea of a Self incorporated into a body that belongs to us (self-identification), which occupies a specific position in space (self-location) and which looks at the world with its own specific perspective (the first-person perspective, see Blanke, 2012; Serino et al., 2013; and Serino, 2019 for in-depth review).

Let's go back, for example, to what was said in paragraph 1.3 regarding the rubber hand illusion (RHI). The synchronous visual-tactile stimulation of a fake hand, positioned next to the real (hidden) hand, induces in the participant an illusion of belonging towards the fake hand (Botvinick & Cohen, 1998). In this context, the illusion of ownership of the fake hand could be due to the association of the tactile stimulation on the real one and the visual stimulation close to it operated by the neurons coding for the peri-hand space. This association, after a few seconds, could lead to a re-tuning of the receptive fields (RFs) of these PPS neurons, making the multisensory integration in the space of the fake hand taking the characteristics of that which occurs in the peri-hand space (see Blanke, 2012; Blanke et al., 2015; Makin et al., 2008; and Serino et al., 2013 for review). This is indicated by several studies in the literature: the establishment of the feeling of ownership and the strength of the illusion correlate with the activity of neurons in the PPS areas of multisensory integration, and in particular at the level of the premotor and posterior parietal cortices (Brozzoli et al., 2012a; Ehrsson et al., 2004, 2005; Makin et al., 2007). Furthermore, as already described, the neurons of these areas are sensitive to the spatial-temporal coherence of within-PPS stimulations (Gentile et al., 2011, 2013), and it is this capability of detecting the synchrony of multimodal stimuli that determine the onset of the RHI (Costantini & Haggard, 2007). Also in monkeys, the RFs of area 5 neurons can be re-tuned to

encode the space occupied by a fake arm (Graziano et al., 2000). At behavioral level, it has been observed that the contact with the dummy hand is not necessary to generate the illusion: by rubbing synchronously the participant's hand and approaching the portion of space near the fake one it is possible to generate the sensation of body-part ownership typical of the RHI, possibly because the visual stimulus induces in any case a re-tuning of the RF of the neurons coding for the peri-hand space (Ferri et al., 2013; Guterstam et al., 2016). In support of this hypothesis, moving the fake hand away from the real one drastically reduces the strength of the illusion (D. M. Lloyd, 2007; Samad et al., 2015).

Another evidence that multisensory integration processes are strongly involved in generating our feeling of body ownership derives from the enfacement illusion (Cardini et al., 2013; Sforza et al., 2010; Tsakiris, 2008; and see Apps & Tsakiris, 2014 for review). As we have already described, in this illusion the participant perceives a touch on the face while seeing a stranger face being touched in a spatially and temporally coherent way. After only a few seconds of synchronous stimulation, the illusion of ownership extends to the stranger face. The onset of this illusion is linked to the activation of neurons in the right intraparietal sulcus (Apps et al., 2015), the area putatively corresponding to the VIP region of the monkey (Bremmer et al., 2001). This area of the network underlying the representation of the PPS is indeed strongly involved in the coding of tactile stimuli on the face and of visual stimuli close to it, both in the monkey and in human, and its activation during the enfacement illusion leads to recoding the space near an unknown face such as PPS of one's own face (Bufalari et al., 2015). As a matter of fact, after the onset of this illusion the presentation of irrelevant auditory stimuli near the unknown face has a more important influence on the detection of tactile stimuli presented on one's own face (Maister et al., 2015).

Finally, by applying a visual-tactile stimulation similar to that used for the rubber hand and the enfacement illusions to the trunk it is possible to elicit the sensation of ownership towards a different body, as in the body swap illusion (Petkova, Khoshnevis, et al., 2011; Petkova & Ehrsson, 2008), or a dislocation of the Self towards a position external to one's body, as in full-body illusion (Lenggenhager et al., 2007; see Serino, 2019; and Serino et al., 2013 for review). Both of these illusions involve the use of a virtual reality setting. In the first, the participants perceive a tactile stimulation on the chest but, looking down, they see through the head-mounted display the body of a mannequin receiving the same stimulation,

temporally and spatially synchronous (see Figure 2.8). The multisensory integration implemented by the intraparietal neurons, involved in the PPS representation, does the rest, leading to identification with the virtual body (Gentile et al., 2015; Petkova, Björnsdotter, et al., 2011).

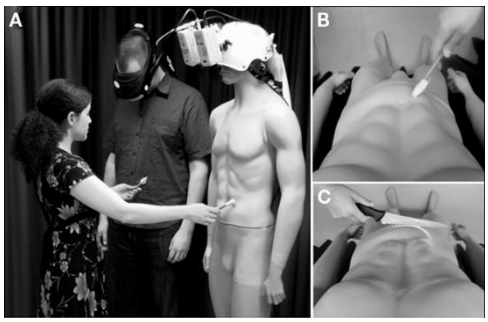


Figure 2.8 *Typical experimental set-up to induce the body-swap illusion: the participant wears a head-mounted display through which he can see a virtual body receiving a tactile stimulation temporally and spatially coherent to the one he perceives on his chest. Modified from Petkova, Khoshnevis & Ehrsson, 2011*

The most interesting aspect is that this illusion can be generated starting from stimulations applied to different parts of the body, such as chest, arms or legs; regardless of the part of the body stimulated, however, there are shared neural activation clusters (Gentile et al., 2015), compatible with the presence of a neural network capable of integrating multisensory signals from the whole body and possibly providing a "whole-body awareness". Although, as we have already seen, different neurons respond to stimulations on different parts of the body, indeed, we do not perceive our body as a "sum of different parts". Our body is one, and it is a totality. Therefore, there would be regions capable of integrating multimodal signals around individual parts of the body, supporting the body-part-centered PPS representations and giving life to rubber hand or enfacement illusions, but also regions that monitor the space around our whole body. This would be the neural basis underlying the whole-body, trunk-centered PPS, the fundamental element that allows us to know where our Self is at all times. This seems to be supported also by full-body illusion (Lenggenhager et al., 2007): by applying the synchronous visual-tactile stimulation on the chest of the participant and on that of a virtual mannequin in a different position, he will experience a strong feeling of dislocation, perceiving his body in a position closer to that of the virtual one. Noel and colleagues exploited this illusion by applying to it a tactile detection task associated with irrelevant auditory stimuli, presented at different distances from the body. They observed that during this illusion the participant's PPS seems to expand in the direction of the "new" body position, facilitating performance in case of auditory stimuli close to it (Noel, Pfeiffer, et al., 2015). This extension into the front-space of the PPS was accompanied

by a reduction of the PPS in the rear-space, as if the participant's body had physically moved in space.

The peripersonal space, therefore, does not necessarily reflect the position of the physical body, but may reflect the position of one's Self. However, it is not yet possible to establish causal links capable of explaining whether it is the remapping of the PPS that causes a shift in self-location or vice versa. A cognitively more parsimonious mechanism would be the bottom-up one, with a multisensory stimulation able to modify the RFs of the PPS neurons, causing a remapping of the whole-body PPS towards the "new body position" and a consequent shifting of the perceived position of one's own Self. Data in this direction seem to come from the study by Salomon and colleagues, who use a continuous flash suppression paradigm with synchronous but imperceptible visual-tactile stimulations for the subject. Despite their unawareness, the participants manifested the classic sensations of full-body illusion (i.e., identification with the virtual body) and the typical performance facilitation associated to multisensory stimuli within PPS. This indicates that the processing of multimodal signals underlying the representation of PPS and bodily self-consciousness does not require awareness (Salomon et al., 2017). Therefore, a bottom-up mechanism seems more likely to be the basis of subjective experience.

Considering the results of the studies cited, an overlap at the neural level of the network underlying the PPS representation and that relating to the sensation of body ownership seems very probable. In this perspective, Grivaz and colleagues carried out an in-depth meta-analysis of the studies in the literature that investigated the neural basis of these two constructs, observing two activation clusters deriving from their conjunction. Both are located in the left parietal cortex, one dorsally, between the superior parietal lobule, the intraparietal sulcus and the area II, the other ventrally, between superior intraparietal sulcus and area II. Furthermore, the disjunction analyzes also showed the specificities of these two networks, with an area preferably linked to the PPS representation in the temporo-parietal junction and a preferential activation of the anterior insula linked to the sensation of body ownership (Grivaz et al., 2017). It therefore seems possible to support the hypothesis that the multisensory integration of stimuli coming from the body and the surrounding space is involved in the formation of the subjective bodily experience, suggesting an intrinsic link between PPS and body consciousness.

Given the complexity and richness of its definition, several theoretical models have been developed in order to try to understand the functioning of the representation of the PPS. Is there a single or several PPSs? If there is only one, how can it deal with the immense variety of signals from the surrounding environment? Is it correct to speak of "the" PPS and its boundaries or should we instead think of a more gradual and nuanced representation of space? To try to answer these questions, let me now describe the different theoretical models of the representation of the peripersonal space.

2.3 One space or many spaces?

The provocative question is the basis of the first theoretical model developed to try to understand the functioning of the human PPS, theorized by de Vignemont and Iannetti (de Vignemont & Iannetti, 2015).

In this model, the fundamental element of this spatial representation is action: the PPS is a fundamental mechanism for integrating the perception of external signals to the implementation of effective motor responses. However, the type of action implemented strictly depends on the evaluation or the goal concerning the stimulus: an apple on the table elicits a reach-to-grasp movement (goal-directed action), whereas a spider close to the hand suggests moving the arm away from it (avoidance response). The model therefore proposes a dual vision of PPS, with a functional distinction between PPS for the protection of the body and PPS for the implementation of goal-directed actions. However, in this case it is not possible to make a clear distinction between perception and action, as already described in the literature between body schema (representation of the body aimed at performing actions) and body image (representation including perceptual and structural judgments of the body, de Vignemont, 2010; Dijkerman & de Haan, 2007), as the PPS is sensorimotor both to defend the body and to grasp an object. Thus, a problem arises: is there a single representation of the peripersonal space, which, depending on the type of stimulus, generates a different response, or two different representations, specialized in the coding of different stimuli and capable of generating goal-directed or defensive behavior?

The first model is called the "swiss army knife" PPS: there is only one generalized cerebral map of the space surrounding the body, which codes all external stimuli. Depending on the coding carried out, a goal-directed (grasping or reaching) or defensive (fight or flight) response will be implemented. The second model is the "specialist" PPS, in which at the cerebral level there are two different representations of the space around the body, one specialized in motor function and goal-directed actions (the so-called working space, Rizzolatti et al., 1997a), the other in the defensive function (the defensive PPS, Sambo & Iannetti, 2013). In this second model, the two representations are in close communication with each other: the threatening characteristics of an object can influence its reachability (Coello et al., 2012), just as sometimes to defend oneself it is necessary to carry out goal-directed actions (remove the spider walking on our arm, for example). However, these maps could be centered on different parts of the body (thus also explaining the body-part-centered modularity of the PPS): the working space is probably centered on the hands, with which we carry out most of the actions, and could coincide with the representation of the space of reaching; the defensive space, on the other hand, is probably centered on the trunk and head, two very vulnerable parts (and for this reason we find a defensive “ultra near space” around the face, Sambo & Iannetti, 2013). As we will see in this chapter and in the next one, the use of a tool can modify the extent of the working space without affecting the defensive space, while high levels of anxiety seem to reduce the working space and extend the protective space. This dissociation therefore seems to support the specialist model.

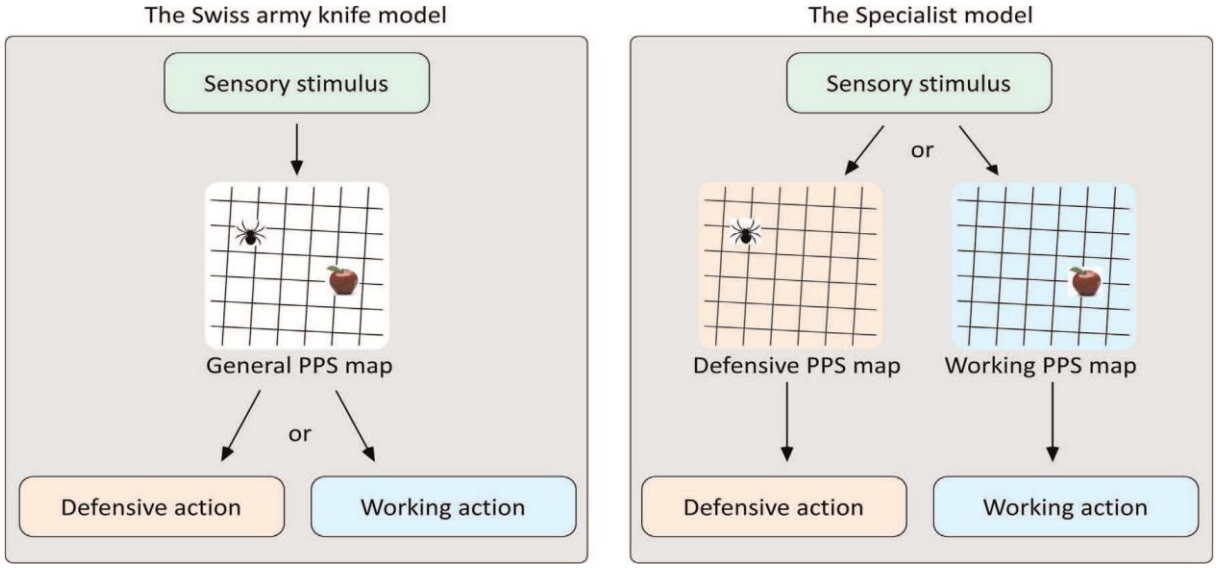


Figure 2.9 *The two models proposed by de Vignemont and Iannetti, regarding the existence of a single, generalized PPS map versus the presence of two specialized and separated PPS representations for goal-directed and defensive actions. From de Vignemont & Iannetti, 2015.*

Action is also a fundamental element underlying the second model (Bufacchi & Iannetti, 2018) which sought to shed light on the functioning of the PPS, defining it "a set of graded response fields". According to the authors, the representation of PPS as a “bubble” with precise spatial limits is improper, deriving from the fact that already the first electrophysiology studies used representations of this type to indicate the RFs of PPS neurons (as in Figure 2.10, Panel A). Subsequent studies built on the “near versus far” dichotomy have validated this perspective, using stimuli located in only two positions, one near and one far from the body, in bisection tasks (McCourt & Garlinghouse, 2000), visuotactile extinction (Làdavas, Di Pellegrino, et al., 1998), audiotactile extinction (Farnè & Làdavas, 2002), visuotactile interaction (Sambo & Forster, 2009), hand-blink reflex (Sambo, Forster, et al., 2012; Sambo, Liang, et al., 2012) and temporal-order judgments of nociceptive stimuli (De Paepe et al., 2014). This involved in-or-out interpretations of the PPS, in which behavioral facilitation was present only within the "boundaries" of the "PPS. However, using only two spatial positions does not mean negating the continuum that can exist between such points, just as having a greater number of positions of stimulation does not mean not providing interpretations of PPS as having "boundaries" (e.g., Canzoneri et al., 2012).

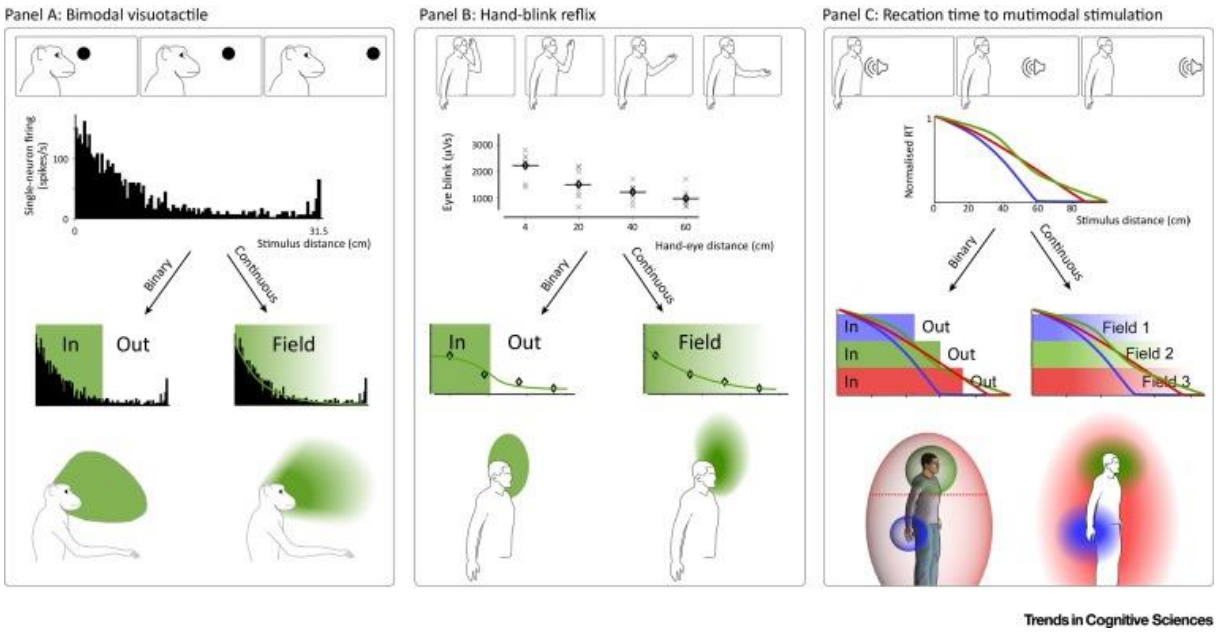


Figure 2.10 *In the past few years, several behavioral and neuronal responses have been considered as measures of PPS, as they increase in magnitude in the presence of stimuli close to the body. In this representation we find, for example, the responses of single neurons (panel A), the hand-blink reflex (panel B) and the reduction of reaction times in the presence of audiotactile stimuli within PPS (panel C). However, these measures have often been evaluated by considering and interpreting the PPS as an in-or-out zone (left side of each panel). The authors of the action field theory of PPS instead argue the need to consider these responses as gradual and continuous, rather than in-or-out (right side of each panel), as the magnitude of these responses does not zeroed by stimuli "outside" PPS, but it descends gradually. From Bufacchi & Iannetti, 2018.*

To contradict this in-or-out view, the authors highlight that already in electrophysiological studies it is well described that the response of PPS neurons is "preferential" for close-to-the-body stimuli: this means that there is a weaker response even for more distant stimuli (Colby et al., 1993; Duhamel et al., 1997). Furthermore, they argue that since aspects such as walking (Amemiya et al., 2019; Berger et al., 2019; Noel et al., 2015) or the use of a tool (Canzoneri et al., 2013; Farnè, Iriki, et al., 2005) can modify the extent of the PPS, there cannot be "one" PPS and there are no rigid limits, but rather a set of fields in which the response of neurons gradually decreases *also* with distance. However, other factors can influence this response, such as the force of gravity (Bufacchi & Iannetti, 2016), vestibular signals (Pfeiffer et al., 2018), movements of parts of the body (Berger et al., 2019; Bisio et al., 2017; Brozzoli et al., 2009, 2010; Wallwork et al., 2016), direction of the stimulus (Serino, Noel, et al., 2015), stimulus trajectory (Cléry, Guipponi, Odouard, et al., 2015) or higher-level factors such as its valence (A. M. de Haan et al., 2016; Ferri et al., 2015; Taffou & Viaud-Delmon, 2014) or its semantics (Heed et al., 2010).

On these bases, the authors suggested that it would be preferable to use for the PPS the concept of "field", a term coming from physics which refers to a quantity that, in every point of space and in every time interval, has a specific magnitude (McMullin, 2002), which can vary continuously according to multiple factors. These factors, in different moments and contexts, could increase the salience of a certain spatial sector around our body, and this mechanism clearly shows the bond between action and representation of the PPS: in a given context, a part of the field may become more salient because a stimulus evokes potential approach or flight actions. The displacement of the stimulus may thus cause the weights of the field to vary, modifying the representation of the close space (see Figure 2.11). This mechanism is closely related to the theory of the interactive behavior, according to which the passage from perception to action is not composed of a series of sequential "steps", but rather of a set of parallel processes that evaluate, among the different potential actions , the most effective to implement (Cisek & Kalaska, 2010). Particularly, this selection seems to take place in brain areas that represent important nodes of the PPS network: the premotor and parietal cortices (R. A. Andersen & Buneo, 2002; Cisek & Kalaska, 2010; Whitlock et al., 2008). This would also explain the effect of stimuli in looming towards the body and the prediction of possible impacts with them (Cléry et al., 2017; Cléry, Guipponi, Odouard, et al.,

2015; Kandula et al., 2017): the greater the probability that a stimulus impacts our body, the greater the tendency to avoid it (Bufacchi et al., 2016).

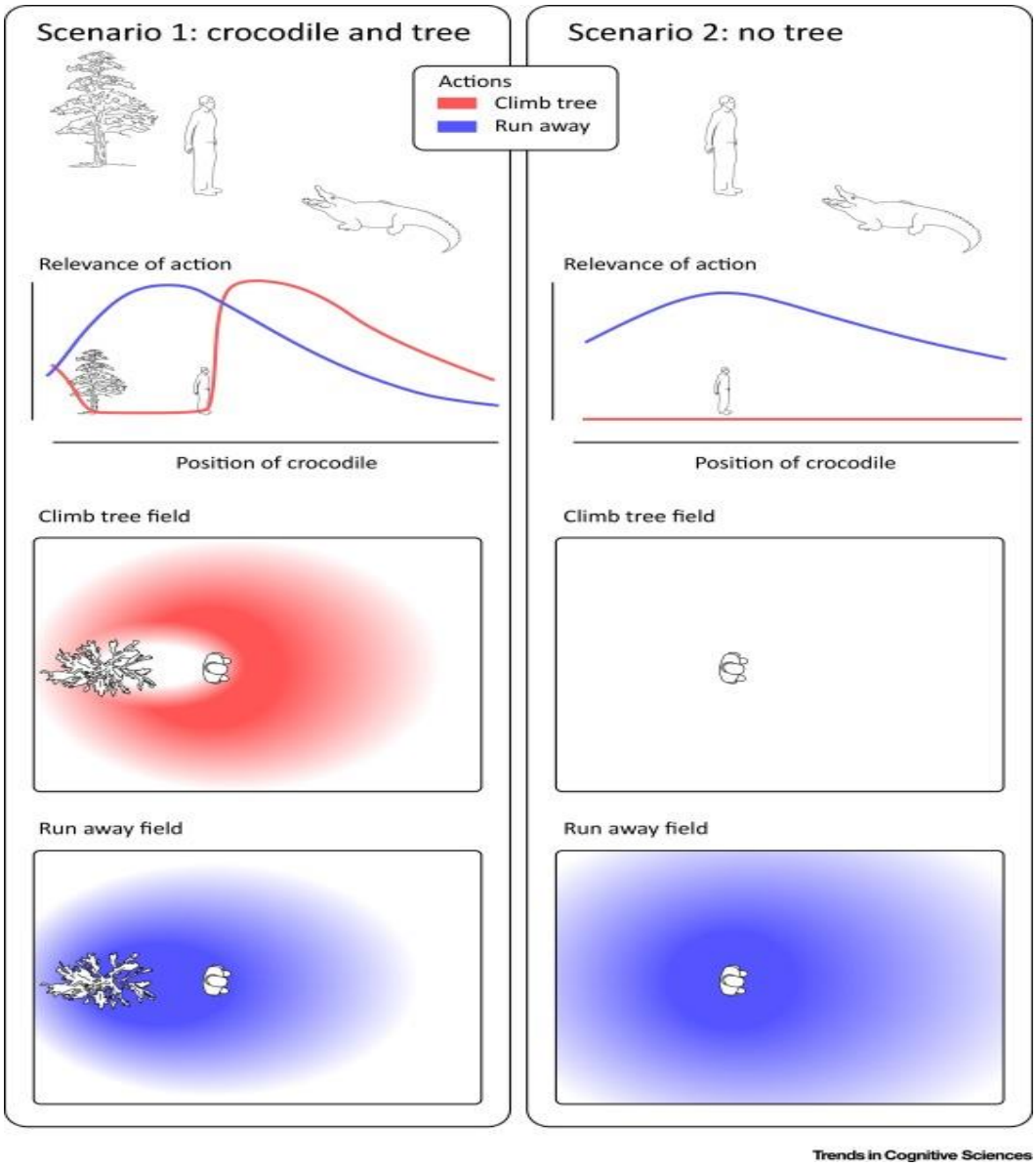


Figure 2.11 *Explanatory example of the action field theory. In the left column, we imagine a scenario in which a threatening stimulus (crocodile) and a neutral stimulus (tree) are present. In the face of the threat, the actions that carry the most weight are climbing the tree (red line in the graph in the second row) or running away (blue line). Except when the crocodile is between us and the tree, the climbing action is the most likely, and the PPS fields are distributed as in the graph in the third row. If, on the other hand, the crocodile is between us and the tree, the most effective action is to run away. In the right column, the tree is absent. As can be seen from the graphs in the second and third lines, the climbing action now has no probability of being performed, and the fields are distributed according to the action of running away. From Bufacchi & Iannetti, 2018.*

Within this model, the social function of the PPS also finds its place: when we find ourselves in the midst of other people, the decision about which actions to carry out depends not only on us and the context, but also on the potential actions of others individuals present. By coding the other person as moral or immoral, cooperative or non-cooperative, we give weight to different sets of actions, which affect PPS fields differently.

The last model I want to introduce has used simulation models of neural activity capable of replicating the characteristics response of PPS neurons, such as the preferential discharge for stimuli close to the hand rather than far away or the superadditive response in the case of multisensory stimulations (Magosso, Ursino, et al., 2010; Magosso, Zavaglia, et al., 2010). In this model, a series of unisensory layers represented the visual, somatosensory and auditory areas are connected to each other and to a multisensory layer through feedforward and feedback connections. The network reproduces the strength of the synaptic connections between these layers in case of stimulations located within or outside the PPS: the unisensory neurons with tactile, visual or auditory RFs located on the body or around it will project to the multisensory layer with stronger synapses than those of the neurons with RFs centered on far space (Magosso, Zavaglia, et al., 2010). With these characteristics, the model ensures that a tactile, visual or auditory stimulation near the body is able to activate multisensory neurons, while stimuli in far space cannot. Thanks to this network, the authors were able to reproduce the performance facilitation effects (more accurate and faster responses) observed in behavioral studies through the association of tactile and visual (Magosso, 2010; Magosso, Serino, et al., 2010) or auditory (Serino, Canzoneri, et al., 2015) presented close to the body. Furthermore, by simulating the activity of the two hemispheres and implementing horizontal (between the unisensory layers of the two hemispheres) and feedback inhibitory connections (between the multisensory and unisensory layers), this model was also able to replicate data from patients with crossmodal extinction following brain lesions (Magosso, Zavaglia, et al., 2010). Critically, the model was also able to replicate the extent of the RFs of these neurons following the use of a tool ... without using a tool. A tactile stimulation was applied to the hand, simulating contact with a tool, and a synchronous auditory stimulation was presented away from the body, as if it were the result of a tool-mediated action. After this simulation, PPS neurons showed preferential responses to distant stimuli, just as happens after the use of a tool (and we will see this in more detail

shortly). This result was later confirmed also by behavioral experiments using the same type of synchronous audio-tactile stimulation (Serino, Canzoneri, et al., 2015). In this case, therefore, it seems that the effects usually produced by an action are reproducible even based on perception alone. According to the model developed by the authors, this is due to the fact that in our daily experience, a tactile stimulus is usually associated with a visual or auditory stimulus in near space. Consequently, the coding regions for the tactile body part (e.g. the hand) and the coding regions for visual or auditory stimuli around that body part are most often activated simultaneously. According to a Hebbian principle of synaptic communication ("neurons wire together if they fire together", Lowel & Singer, 1992), the synapses between these areas are therefore reinforced, which does not happen for the synapses of the regions coding for the far space, less often associated to tactile stimulations. If we use a tool, the rules change, associating tactile stimulations with visual or auditory stimulations in far space, and this affects the strength of those synapses. The same thing happens by *simulating* the use of the tool: since the stimulation on the hand and the auditory stimulation far from it arrive synchronously, they will activate the corresponding brain regions in a synchronous way, enhancing mutual synaptic communication. If, indeed, the two stimuli are separated by an asynchrony of 500 ms, the effect vanishes, probably due to the fact that the causal link between the two stimulations is lost. This could be a possible explanation of the extension effects of PPS also observed in case of movement (Berger et al., 2019; Brozzoli et al., 2009, 2010): the tactile stimulation received on the hand, during the experiments, is almost always associated with a visual or auditory stimulation distant and synchronous. The model is also able to explain the inverse effect: the shrinking of the PPS. Bassolino and colleagues observed that by immobilizing the participants' arm for about ten hours, the extension of the peri-hand space is reduced (Bassolino et al., 2015). In the model of Magosso, Serino and colleagues, this is due to the fact that for a prolonged period of time the tactile and auditory or visual stimulations in the near space were disconnected, and their decoupling induced a weakening of the usually stimulated synapses (see Serino, 2019 for review about the model).

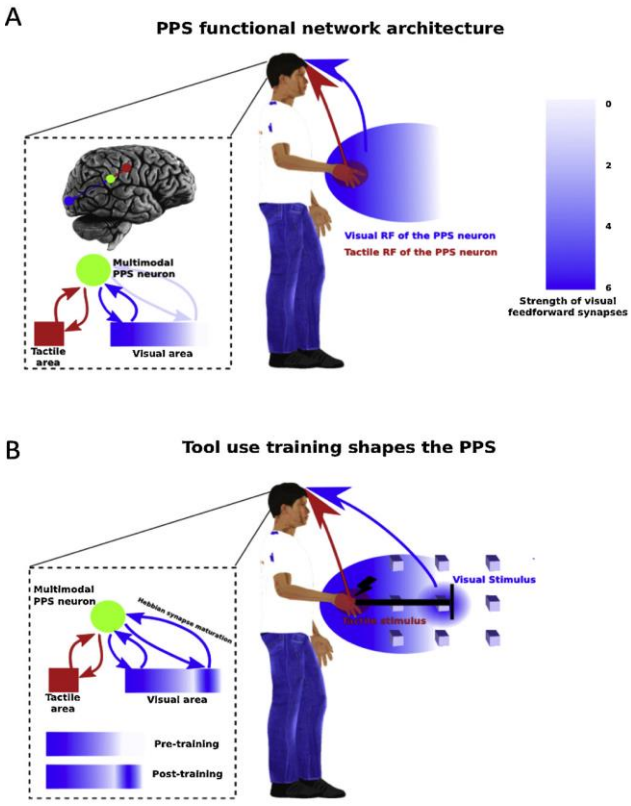


Figure 2.12 *In panel A, the structure of the simulation model of the PPS neural network (Magosso, Ursino, et al., 2010; Magosso, Zavaglia, et al., 2010). The representation of the visual-tactile peri-hand space is reconstructed through the communication of tactile (red) and visual (blue) unisensory areas, which have receptive fields centered on the hand (touch) or on the space surrounding it (vision), and areas of multisensory integration through feedforward and feedback synapses. In order to reproduce the main characteristic of PPS representation, i.e. stronger interaction for multisensory stimuli close to the body, the strength of the synapses from the unisensory to the multisensory neurons are set so to be stronger from visual neurons with receptive fields close to the hand and weaker from neurons with far receptive fields. In panel B, the use of a tool leads to coupling tactile stimulations with visual stimulations far from the hand, reinforcing the synapses between the multisensory regions and the visual regions with receptive fields centered on distant space via a hebbian-type mechanism. This causes an extension of the PPS. Modified from Serino et al., 2019.*

In summary, we can state that behavioral effects, neuroimaging data and data from electrophysiology give rise to several possible interpretations. Although lacking the gift of synthesis, the review described here does not want to take on the role of unraveling the theoretical tangle of definition by giving greater weight to a specific model or a specific perspective. However, a brief summary of these theories was necessary to indicate the complexity of the definition of the representation of the peripersonal space, its richness and the possible confusion in the literature linked to different experimental paradigms, different variables of interest and different theoretical perspectives. Given that different experimental paradigms could influence the results and interpretations related to PPS, let's now quickly review more in detail the main experimental paradigms used for the study of PPS in healthy humans.

2.4 PPS investigation in healthy humans

The existence of a different processing of multisensory stimuli as a function of their spatial position has been investigated over time through the study of the influence that auditory or visual stimulations in different portions of space can have on tactile perception.

One of the first experimental paradigms developed for this purpose is undoubtedly the cross-modal congruency task (Pavani et al., 2000; Shore et al., 2006; Spence et al., 1998; Spence, Pavani, & Driver, 2004; and see Spence et al., 2004; Maravita et al., 2003; and Macaluso & Maravita, 2010 for review), which we have already had the opportunity to describe. In this task, participants place the index finger and thumb of both hands on four vibrotactile stimulators, embedded in two foam cubes (see Figure 2.13A). Through the use of a pedal, they must discriminate the elevation of the tactile stimulus, which can be on the thumb (down) or on the index (up), while ignoring the visual distractor that is presented close to the four tactile stimulators. The association between touch and visual distractor occurs in a pseudo-randomized way, generating two different situations: the visual and tactile stimuli are presented at the same elevation ("congruent" condition) or at different elevations ("incongruent" condition). Crucially, incongruent visual distractors, even if irrelevant, interfere with the tactile discrimination: the response is slower and less accurate than when the tactile stimulus and the visual distractor are presented at the same elevation, regardless of the hand being stimulated. This type of effect is called the cross-modal congruency effect (CCE), calculated as the difference between the participant's reaction time in the incongruent and in the congruent condition: the greater the magnitude of this difference, the greater the interference of the visual distractor on the performance (Spence et al., 1998; Spence, Pavani, & Driver, 2004; Spence, Pavani, Maravita, et al., 2004). Interestingly, a visuo-tactile investigation around the lower limbs (Pozeg et al., 2015; Schicke et al., 2009) and an audio-tactile version of this paradigm reported the same kind of effect (Aspell et al., 2010). The research group of Spence and colleagues developed this paradigm and observed that the CCE was greater for stimuli presented on the same foam cube, as if the proximity between tactile and visual stimulation played a role in that interference. Or, using a more PPS-jargon, as if the distractor's proximity to the stimulated body part was relevant. For this reason, the same protocol was used by systematically varying the proximity of the hand and the visual distractor (see Figure 2.13B): in this way, the discrimination of the elevation of the vibrotactile stimulus could take place in the presence of a congruent or incongruent distractor, positioned close to the hand itself (in the peri-hand space) or away from it (outside the peri-hand space). Interestingly, visual distractor interference depended on its distance from the hand, hindering tactile discrimination when presented within the peri-hand space (Spence, Pavani, & Driver, 2004).

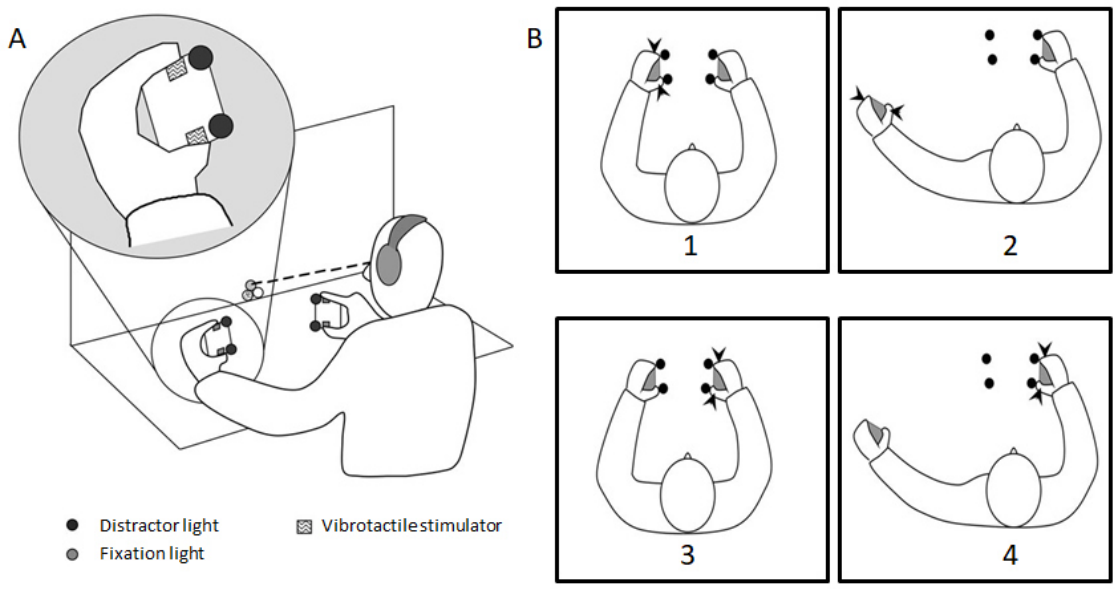


Figure 2.13 *A) representation of a classic cross-modal congruency task set-up. The participant holds a foam cube in each hand, placing index and thumb on the vibrotactile stimulators, located next to the visual stimulators (detailed view in the bird's eye). B) Experimental conditions that allowed evaluating the different interference of the visual distractors presented inside or outside the peri-hand space. Tactile stimulation and visual distractor could be presented on the right or left hand, at the thumb or index finger. When the elevation of the visual stimulus differs from that of the tactile stimulus, the performance is less accurate and less rapid. The effect is reduced with the distance between the hand and the visual distractor: in box 2, the distractor is outside the peri-hand space of the subject's left hand. An incongruent tactile stimulation on the left hand, in this case, will suffer less from the interference caused by the visual distractor. Modified from Spence, Pavani & Driver, 2004*

Therefore, the CCE can be considered a measure related to the representation of the PPS (but see N. P. Holmes et al., 2004), as the magnitude of the cross-modal interference varies as a function of the distance of the stimuli from the body. Moreover, the CCE is also body-part-centered, revealing another fundamental characteristic of the PPS. Crossing the hands, and placing the right hand on a sponge cube positioned in the left hemispace (see Figure 2.14), a stronger CCE is observed when the tactile stimulus on that hand is associated with an incongruent visual distractor presented in the left hemispace (Macaluso & Maravita, 2010; Spence et al., 2001; Spence, Pavani, & Driver, 2004).

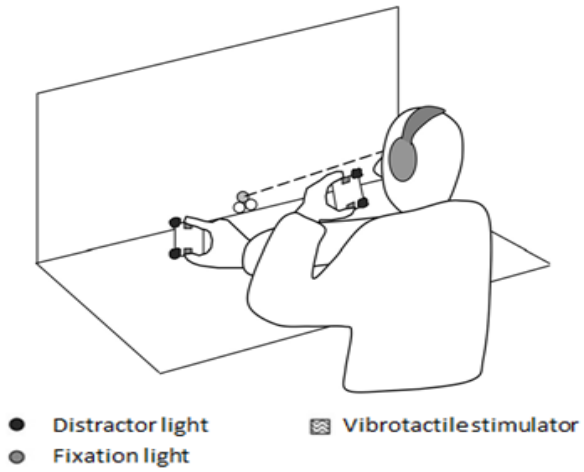


Figure 2.14 *Schematic representation of a cross-modal congruency task set-up with crossed arms. From Spence, Pavani & Driver, 2004*

Another experimental paradigm, developed a few years later than the cross-modal congruency task and equally widely used in this literature has exploited the peculiar preferential response of PPS neurons to moving stimuli (Graziano et al., 1997a; see Cléry et al., 2015 for review). A stimulus moving close to our body is more informative than a static stimulus, as it is necessary to consider its trajectory, its speed and the possibility of it coming into contact with a part of our body. Canzoneri and colleagues have therefore developed a paradigm that we have already recalled several times in the previous paragraphs, consisting in the use of auditory stimulations moving towards the body (looming movement) or in the opposite direction (receding movement, Canzoneri et al., 2012). Through the use of some speakers positioned at different distances from the body, indeed, it is possible to produce sound sequences that give the subject the impression of a sound approaching or moving away, increasing or decreasing the intensity of the acoustic stimulus as a function of the distance (see Figure 2.15A). During its displacement, an electrocutaneous stimulus is applied to the participant's hand (but also to the face or trunk, see Serino et al., 2015) with different SOAs (stimulus onset asynchronies, the temporal difference between the onset of the auditory stimulus and the onset of the tactile one). In this way, later SOAs give the participant the impression that the tactile stimulus arrives when the sound is closer (looming) or further away (receding) from the body (see Figure 2.15B). In addition, some tactile stimulations are applied before the sound onset and after its offset: these stimulations are considered unisensory, as their detection occurs in the absence of an auditory stimulus, and for this reason they are considered as a performance baseline. The task to be performed is in fact a simple tactile detection, responding through the voice

(Canzoneri et al., 2012), a button (Ferri et al., 2015; Serino et al., 2015) or a pedal (A. M. de Haan et al., 2016) as soon as the tactile stimulus is perceived. By calculating the difference (or delta reaction time, ΔRT) between the average reaction time to unisensory trials (touch before or after sound) and that to multisensory trials (touch during sound) it is possible to obtain a measure of the multisensory facilitation for each "position" in which the sound stimulus was accompanied by touch.

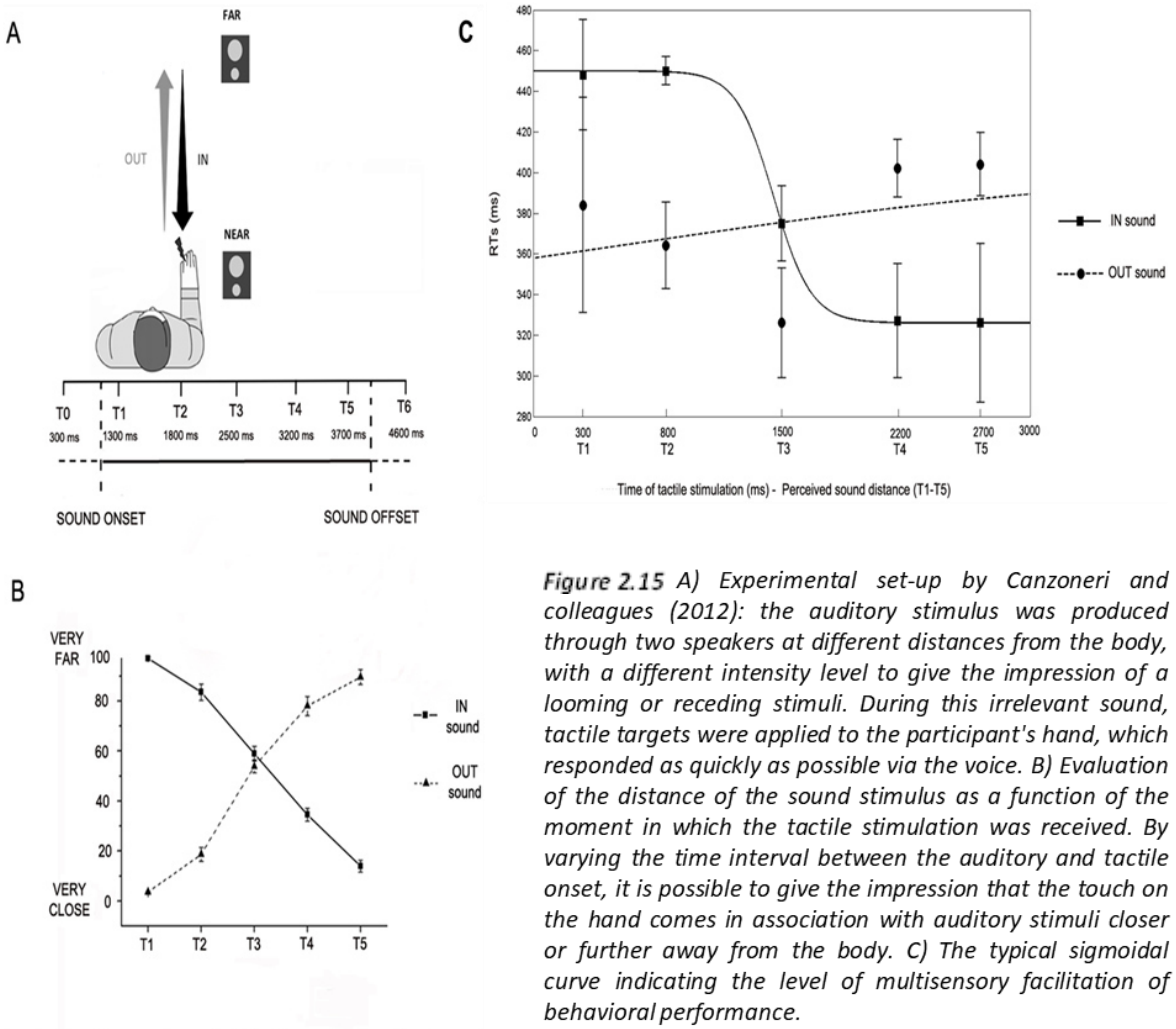


Figure 2.15 A) Experimental set-up by Canzoneri and colleagues (2012): the auditory stimulus was produced through two speakers at different distances from the body, with a different intensity level to give the impression of a looming or receding stimuli. During this irrelevant sound, tactile targets were applied to the participant's hand, which responded as quickly as possible via the voice. B) Evaluation of the distance of the sound stimulus as a function of the moment in which the tactile stimulation was received. By varying the time interval between the auditory and tactile onset, it is possible to give the impression that the touch on the hand comes in association with auditory stimuli closer or further away from the body. C) The typical sigmoidal curve indicating the level of multisensory facilitation of behavioral performance. The inflection point of this sigmoid, indicating the moment in which auditory stimuli become capable of improving the performance, is considered as a proxy of the boundary of the individual PPS. Modified from Canzoneri et al., 2012.

Through a measurement of this type, it was possible to map the multisensory facilitation for stimuli moving around the body, observing that an irrelevant stimulus in looming is able to influence the performance in a non-linear way, but according to a sigmoidal curve (see

Figure 2.15C). Particularly, starting from a certain distance from the hand (~40-50 cm), the irrelevant stimulus in looming is able to improve performance, drastically reducing the reaction time. The inflection point of this sigmoidal curve, therefore, has been considered an indicator of the limit of the peripersonal space, beyond which multisensory stimuli are no longer able to generate a behavioral facilitation. Receding stimuli, on the other hand, generate a linear response pattern, in which facilitation gradually decreases with distance but with a much lower magnitude than that of looming stimuli. This is predictable: considering what we know about PPS functionality, a looming stimulus can more easily come into contact with our body, causing an expectation of impact (Cléry et al., 2017; Cléry et al., 2015; Hobeika et al., 2020; Kandula et al., 2017) and increasing the probability of escape or avoidance actions (Bufacchi & Iannetti, 2018).

Over time, this paradigm has been widely used in the study of PPS, both by exploiting audio-tactile (Canzoneri et al., 2012; Finisguerra et al., 2015; Noel et al., 2015; Serino et al., 2015; Teneggi et al., 2013), visual-tactile (Noel et al., 2020; Serino et al., 2015; see Serino, 2019 for review) and also audio-visuo-tactile integration processes (Serino et al., 2018), investigating multisensory facilitation around the hand, face or trunk (Serino, Noel, et al., 2015) and testing multiple characteristics of the stimuli used, such as speed (Kandula, 2020) or its emotional value (A. M. de Haan et al., 2016; Ferri et al., 2015; Taffou & Viaud-Delmon, 2014).

A third paradigm frequently used for the study of peripersonal space, and of particular interest for the research questions of my doctoral dissertation, is the reachability judgment task. In this type of task, participants have to judge whether they can reach a stimulus (real, 2D or virtual) in front of them by only stretching their arm, without moving the feet or leaning forward with the body (Coello et al., 2008; Coello & Iwanow, 2006). In this way it is possible to evaluate the so-called arm reaching space (ARS), the space that we can cover by fully stretching our arm. If from a "physical" point of view ARS is easily defined, measuring the length of the arm for example, from a cognitive point of view the question seems to be more complex, as its extension is influenced by contextual aspects (Coello & Iwanow, 2006), characteristics of the stimulus (Coello et al., 2012) and aspects of motor planning (Carello et al., 1989; Rochat & Wraga, 1997). The link between the representation of the peripersonal space and that of the reaching space may seem obvious: the PPS interfaces perception and

action, and we can only act and interact with the objects and stimuli that are within our reaching space. To evaluate its real extension, the maximum distance that the subject can reach with the fully stretched arm is measured before the experiment. Subsequently, to investigate its flexibility as a function of the different experimental factors, it is possible to exploit different approaches to the task of reachability judgment. First of all, the nature of the stimulus to be judged , which can be represented by an inanimate object in 2D (Bourgeois & Coello, 2012; Coello & Iwanow, 2006; Spaccasassi et al., 2021) or in 3D (Carello et al., 1989; Rochat & Wraga, 1997), by a virtual avatar (Iachini et al., 2014; Iachini, Pagliaro, et al., 2015; Iachini, Ruggiero, et al., 2015) or from real confederates (Patané et al., 2017). Secondly, the stimulus may be static (Bourgeois & Coello, 2012; Iachini et al., 2014; Iachini, Ruggiero, et al., 2015; Iachini, Pagliaro, et al., 2015; Spaccasassi et al., 2021; Wamain et al., 2016) or in motion (Iachini et al., 2014; Iachini, Pagliaro, et al., 2015; Iachini, Ruggiero, et al., 2015). But also the participants, in turn, may have to make their judgments in a passive condition (maintaining the same position, while the stimulus moves) or active (moving towards the target stimulus, Iachini et al., 2014; Iachini, Pagliaro, et al., 2015; Iachini, Ruggiero, et al., 2015). In the case in which both the stimulus and the participant are static, the task is to discriminate between reachable and unreachable stimuli, with or without time pressure. If, on the other hand, the stimuli and / or the subject are in motion, participants have to respond by stopping (active condition) or stopping the stimulus (passive condition) when they thinks that, by stretching their arm, they can touch the stimulation (Iachini et al., 2014; Iachini, Pagliaro, et al., 2015; Iachini, Ruggiero, et al., 2015).

Using a reachability judgment task it is therefore possible to evaluate whether the subjective perception regarding the region of space around one's own body on which one can act varies according to the experimental factors manipulated. A change in the ARS limit is interpreted as an extension or reduction of the PPS. Thanks to this paradigm it was possible to observe that the representation of the PPS is not static and with well-defined boundaries, but rather plastic and continuously influenced by the characteristics of the stimulus (Coello et al., 2012; Iachini, Pagliaro, et al., 2015), of the context (Coello & Iwanow, 2006), of the task (Patané et al., 2017) and also by individual characteristics, such as the level of anxiety (Iachini, Ruggiero, et al., 2015).

The most widely investigated case of PPS plasticity, however, is certainly the one related to the use of tools (see Cléry, Guipponi, Wardak, et al., 2015; Coello & Cartaud, 2021; and Serino, 2019 for review). Already in the first pioneering electrophysiological studies, Iriki and colleagues observed that after prolonged use of a tool to reach food, otherwise unreachable, the receptive fields of the PPS neurons were remapped, starting to respond to stimulations close to the tip of the tool (Iriki et al., 1996; Maravita & Iriki, 2004). In particular, the visual-tactile bimodal neurons were shown to be able to respond to tactile stimulations on monkey's hand and to visual stimulations in the far space (see Figure 2.16), where the tip of the tool allowed reaching the food (for a deeper insight into cerebral plasticity and use of tools in monkeys, Iriki & Sakura, 2008). This finding was interpreted as indicating that the instrument used is no longer considered as a separate object, but has become part of the body schema, the motor representation of our body (Cardinali et al., 2009, 2011, 2012). Being PPS the representation of the space around our body, the prolonged use of a tool may thus cause a modification of how stimuli are processed in far space.

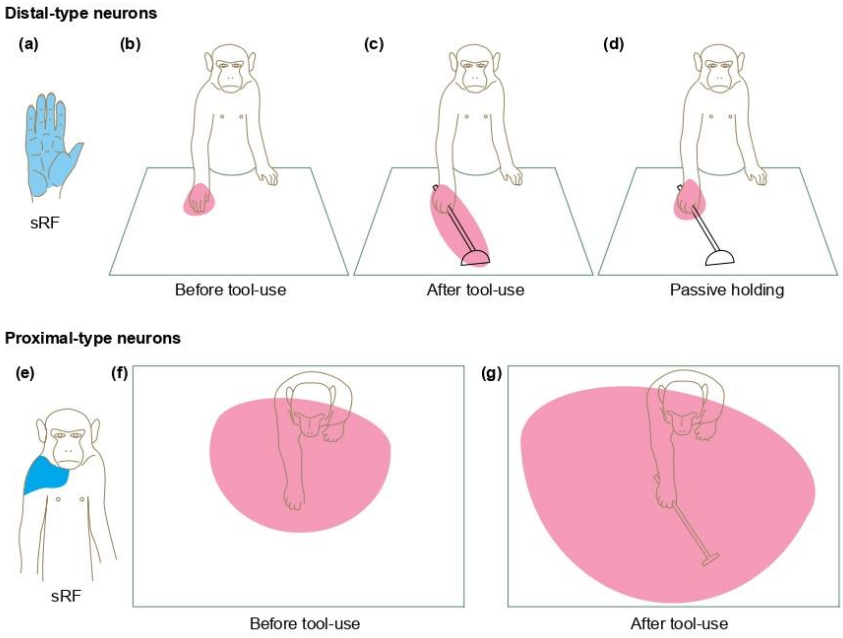


Figure 2.16 *Modifications of the receptive field (RF) of bimodal neurons following a tool use. The visual RF of a neuron is defined as the area in which most responses are obtained from the presentation of visual stimuli. For distal neurons, with tactile RF on the hand (a), an extension of the visual RF is observed following the use of the tool (from b to c), but only if the tool is actively used (d: no extension). For neurons with more proximal tactile RF (e) the visual RF is represented before (f) and after (g) the use of the tool. From Maravita & Iriki, 2004.*

Even in humans, the active use of a tool is able to remap the PPS (see Brozzoli et al., 2014 for review), making "far becomes near" (Berti & Frassinetti, 2000): patients who show neglect in near but not far space, can perform a line bisection task without problems if this is done with a laser pointer on lines outside the PPS. If the same task is performed with a long stick, the deficit shown in the near space also reappears in the extrapersonal one. This is because the use of the tool has not only made the space previously unreachable attainable, but has also modified the patient's body representation, something that does not happen with a "distal" tool such as the laser pointer (Berti & Frassinetti, 2000). A similar effect was also found in patients with extinction: the deficit, normally less severe in the case of visual stimulations in the extrapersonal space associated with tactile stimulations on the hand, became more severe following the active use of a tool and presenting the same visual stimulus around its tip (Farnè & Làdavas, 2000). However, the use of a tool can also reduce the extent of this deficit (Maravita et al., 2002). A re-sizing and remapping of the PPS is also observable through the cross-modal congruency task already described: Holmes and colleagues have shown that the hand-centered effect of cross-modal interference can be replicated, after an active use of a tool, presenting visual distractors around the tips of these prolongation of the arms (N. P. Holmes et al., 2004).

However, to achieve a plastic modification of the PPS, some principles must be respected. First of all, it is necessary to have experience in the active use of the tool to reach or grab objects outside one's own reachable space, as to hold it passively in hand (Farnè & Làdavas, 2000; Iriki et al., 1996; Maravita et al., 2001; Serino et al., 2007), pointing in the direction of stimuli without a tool (Canzoneri et al., 2013; Serino et al., 2015) or using a short tool within PPS (Bourgeois et al., 2014) do not cause extension. However, considering Magosso and colleagues' model described above, this "experience" in using the tool may not be necessary (Serino, Canzoneri, et al., 2015). What would count, indeed, would be the synchronous association of a stimulus on the body (i.e., the tactile sensation we have holding a tool) and a visual or auditory stimulus far from it (i.e., the result of an action in far space operated thanks to the tool). Secondly, and consistent with the motor function of the PPS, the multisensory processing of information will be altered only around the functional region of the tool, regardless of its structure or length (Farnè et al., 2005; Bonifazi et al., 2007; but see N. P. Holmes et al., 2004). Third principle: the observed changes occur rapidly, sometimes even after a few seconds of tool use (N. P. Holmes et al., 2007), and are reversible in the

short term, as they disappear after a few minutes of inactivity (Farnè et al., 2007; Farnè & Làdavas, 2000). Also in this case, PPS therefore seems to expand according to experience, incorporating the part of the tool that must interact with objects and reducing itself again when this context is no longer current. However, it seems that a prolonged use of the tool can generate less temporary effects (Serino et al., 2007).

This plasticity of the representation of the PPS following the use of tools, however, could add complexity at the definitional level. As we saw in the previous section, the different functions and the plasticity of the PPS have indeed made the validation of a univocal definition of this representation / mechanism / set of graded fields problematic. Similarly, over time there has been an overlap between the definition of peripersonal and arm reaching space, due to which a large number of studies have defined PPS as ARS (or vice versa) or have tested PPS using reachability tasks. However, the link between the two spatial representations does not necessarily imply their total overlap, or identity: in electrophysiology and neuroimaging studies, stimuli close to the hand and inside the ARS generated activations that other stimuli, always within-ARS but far from the hand, did not generate (Brozzoli et al., 2012a; Graziano et al., 1994). It is well-established that PPS has a motor function, supporting goal-directed actions such as reaching or grasping, and it is true that, by definition, these actions can only be carried out within the ARS (not considering the use of tools). But early electrophysiology studies on monkeys defined PPS based on a preferential neural response to stimuli near the body, which gradually decays with distance (Graziano et al., 1994, 1997a; Rizzolatti et al., 1981a, 1981b). This response was not necessarily linked to the reachability of the stimulus. Considering these aspects, is it correct to conflate the two representations? Can a judgment regarding the reachability of a stimulus be informative about the extent of the PPS? And is it possible that the ARS actually possesses the same fundamental characteristics as the PPS, such as the enhanced multisensory processing and the body-part centered reference frame?

First evidence that could help to understand the possible identity or difference between the representations of PPS and ARS concerns their neural basis. As previously described, the neural underpinnings of the PPS include a network of fronto-parietal regions whose pivotal areas are the anterior intraparietal sulcus, the supramarginal gyrus, the premotor cortex and the putamen (Bremmer et al., 2001; Brozzoli et al., 2011, 2012a; Gentile et al., 2011, 2013;

Makin et al., 2007; Sereno & Huang, 2006; and see Grivaz et al., 2017 for a meta-analysis). As a first step, therefore, I will now try to briefly describe the neural areas specifically related to the reaching space.

2.5 Neural correlates of the reaching space in humans and non-human primates

As for the PPS, the first studies on the neural underpinnings of reaching space and movements also come from electrophysiology. Before going into the literature, however, a clarification is necessary. While the studies on PPS, given its role as intermediary between perception and action, have investigated and related both perceptual and motor aspects, the essentially motor nature of the reaching space has been tested above all through the implementation of reaching or grasping movements. Thus, few studies have investigated the neural perceptual differences between stimuli presented inside or outside the reaching space. In these tasks, therefore, aspects of motor intention, motor imagery or motor performance are certainly present, with greater or lesser weight, which are not necessarily evident in the study of the PPS.

For this obvious reason, one of the main areas underlying the reaching movements is certainly the primary motor cortex, or M1 (Caminiti et al., 1990; Georgopoulos et al., 1982; Rizzolatti et al., 1998). However, its activity seems mainly linked to the execution of the movement, rather than to its spatial planning, and this first difference with respect to the PPS network of monkeys could therefore be linked more to intrinsic aspects of the experimental set-up.

A brain region, closely interconnected to M1, which appears to be linked to movement planning is the posterior parietal cortex, or PPC (see Filimon, 2010; Fogassi & Luppino, 2005; and Vesia & Crawford, 2012 for review). Here it is possible to find different areas related to the execution of movements of different body districts, such as the arms, hands or eyes (R. A. Andersen & Cui, 2009; Graziano & Gross, 1998b), especially at the level of the medial bank of the IPS, called medial intraparietal area (MIP, Colby, 1998; Eskandar & Assad, 1999; Johnson et al., 1996; Marconi et al., 2001; Rizzolatti et al., 1997b) or, according to some authors, parietal reach region (PRR, R. A. Andersen & Cui, 2009; Batista et al., 1999;

Bhattacharyya et al., 2009; Buneo et al., 2002; Chang et al., 2008; Scherberger & Andersen, 2007). The localization of the PRR is not precisely defined, as well as its exact extension, but the coiners of the term identify it between the MIP and another area often reported in the literature on the neural basis of reaching: the visual-motor area V6A, at the boundary between the parietal and occipital lobe, capable of processing aspects such as the shape, movement and localization of external stimuli, supporting actions of reaching and grasping (Fattori et al., 2009; Galletti et al., 2003; Luppino et al., 2005; Marconi et al., 2001; Pitzalis et al., 2006). For the purposes of the present doctoral dissertation, we will consider the PRR as overlapping areas MIP and V6A. According to the results of the studies in the literature, it is precisely at the level of the PPC, and in particular of the PRR, that the visual information coming from the retina is transformed from an eye-centered reference frame to a hand-centered one (R. A. Andersen & Buneo, 2002; Batista et al., 1999). This is a fundamental aspect to implement effective reaching and grasping movements: PPC is the fundamental node that coordinates the position of external stimuli and the position of our body parts, bridging the difference between the two coordinate systems (see R. A. Andersen & Cui, 2009 for review). Furthermore, the activations found in the PRR seem to support its role in the selection of actions, as well as in the transformation of the two coordinate systems (R. A. Andersen & Buneo, 2002; Scherberger & Andersen, 2007).

As with PPS, the neural network underlying the reaching space is not limited to the parietal region, but includes important connections with more frontal areas, such as the premotor cortex (Caminiti et al., 2017; Graziano & Gross, 1998b; Johnson et al., 1996; Rizzolatti et al., 1997b, 1998). Indeed, it would be at the level of the PMd (or area 6) that the aspects of motor planning and spatial representation would meet with aspects more related to the execution of movement in space (Caminiti et al., 1991; Colby, 1998; Rizzolatti et al., 1998). The connections between the parietal lobe and the frontal one would be found above all between the V6A area and the F2 and F7 sectors of the premotor cortex (Marconi et al., 2001). According to some studies, at least part of the transformation from an eye-centered to a hand-centered coordinate system would occur here, at the level of PMd cortex (Pesaran et al., 2006).

Observing these findings, it therefore appears that the neural underpinnings of the reaching space in non-human primates are distributed, as for the PPS, along a fronto-parietal network of areas. However, although some overlap is present for some regions and others are

anatomically contiguous, it is not possible to state that the two spatial representations rely on the same neural bases (Matelli & Luppino, 2001).

Similarly in humans, the studies that have dealt with investigating the neural basis of the reaching space have often involved aspects of movement or motor imagery. One of the first results confirming what was observed in monkeys is that also in humans, the primary motor cortex seems to be involved in the judgment of which stimuli are reachable and which are not (Coello et al., 2008; Lara et al., 2018). A disruption of its activity through TMS, indeed, is able to influence the opinion expressed by the participants.

Also thanks to a TMS study it was possible to observe a further correspondence between the results on humans and non-human primates. Desmurget and colleagues have indeed observed that disrupting the activity of PPC is possible to induce alterations in the ability to correct reaching movements online (Desmurget et al., 1999). This result was later confirmed and deepened (for review, see Filimon, 2010; Medendorp et al., 2008; Vesia & Crawford, 2012), reporting the involvement of this area both in the planning of ocular saccades and reaching movements (Hinkley et al., 2009). This feature would make the posterior parietal cortex the perfect candidate for integrating eye-centered spatial coordinates with hand and arm position, and it is for this reason that human PPC is considered as the homolog region of the simian PRR (Connolly et al., 2003; Hagler et al., 2007). And the similarity between the two species is confirmed with the identification of two brain activation clusters significantly involved in the planning of reaching movements: the first located at the level of the medial bank of the intraparietal sulcus (corresponding to the MIP area of the macaque) and involved in the preparation of reaching and pointing movements (Beurze et al., 2007, 2009; DeSouza et al., 2000; Grefkes et al., 2004; Hagler et al., 2007; Medendorp et al., 2003; Prado et al., 2005; Tosoni et al., 2008). A study on a patient with optic ataxia following an injury to the medial bench of the IPS showed a selective deficit for the execution of reaching actions (Trillenberg et al., 2007). The second cluster is more displaced towards the parieto-occipital junction and corresponds to the superior parieto-occipital cortex (SPOC), which instead seems more involved in the implementation of actions of reaching towards peripheral spatial sectors (Beurze et al., 2009; Connolly et al., 2003; Culham et al., 2008; Monaco et al., 2011; Pitzalis et al., 2013; Prado et al., 2005; Tosoni et al., 2008; Zettel et al., 2007). This second activation cluster would therefore correspond to the V6A area of the monkey, and

indeed also shows purely visual responses: Goodale & Milner have reported specific responses following visual perception of 3D reachable stimuli, even when no action is required (Goodale & Milner, 1992; Milner & Goodale, 2008).

Finally, connections of these posterior parietal areas with more frontal ones, such as the supplementary motor area (SMA) or the PMd, have also been identified in humans (Kertzman et al., 1997; Lara et al., 2018; Picard & Strick, 2001; Prado et al., 2005; see Filimon, 2010 for review). At the PMd level it is still possible to observe a caudal portion that subserves reaching movements and a rostral portion that subserves saccades, leading to hypothesize its possible role in hand-eye coordination for goal-directed actions.

Therefore, also with regard to the neural underpinnings of the human reaching space, it is possible to observe some overlap with the network underlying the PPS. However, the overlap is not complete, and the two networks actually include different areas, albeit close to each other.

Considering the differences existing both at the definitional and neuronal levels, we posited the hypothesis that PPS and ARS are not the same concept. In particular, the use of a reaching or reachability judgment task, supported by a specific neural network distinct from that of the PPS, could provide non-interpretable results in terms of extension or reduction of the latter. Conversely, it is possible that the fundamental characteristics of the PPS, i.e. the body-part centered reference frame and the enhanced multisensory processing are not shared by the representation of the reaching space.

To this aim, we conducted a behavioral experiment on healthy humans to directly compare the two experimental protocols: a speeded tactile detection task to assess PPS and a reachability judgment task to assess ARS. Notably, the same stimulations were used in both protocols: electrocutaneous stimuli applied to the right hand and static visual stimuli presented in ten different positions, spanning from near to far from the body. By placing the participant's hand in two different positions, we observed a hand-centred facilitation of the performance in the tactile detection task, as expected. The observed facilitation pattern, in particular, reflects a hand-centered isomorphic Gaussian distribution, and in no way corresponds to the ARS extent. Conversely, in the reachability judgment task we did not observe any multisensory facilitation of performance, neither hand- nor ARS-centred. These results led us to support the hypothesis of a functional and spatial distinction between PPS and ARS.

Peripersonal and reaching space differ
evidence from their spatial extent and multisensory facilitation pattern

(Psychonomic Bulletin & Review, 2021)

Psychonomic Bulletin & Review
https://doi.org/10.3758/s13423-021-01942-9

BRIEF REPORT

Peripersonal and reaching space differ: Evidence from their spatial extent and multisensory facilitation pattern

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Accepted: 1 May 2021

Abstract

Peripersonal space (PPS) is a multisensory representation of the space near body parts facilitating interactions with the close environment. Studies on non-human and human primates agree in showing that PPS is a body part-centered representation that guides actions. Because of these characteristics, growing confusion surrounds peripersonal and arm-reaching space (ARS), that is the space one's arm can reach. Despite neuroanatomical evidence favoring their distinction, no study has contrasted directly their respective extent and behavioral features. Here, in five experiments ($N = 140$) we found that PPS differs from ARS, as evidenced both by participants' spatial and temporal performance and by its modeling. We mapped PPS and ARS using both their respective gold standard tasks and a novel multisensory facilitation paradigm. Results show that: (1) PPS is smaller than ARS; (2) multivariate analyses of spatial patterns of multisensory facilitation predict participants' hand locations within ARS; and (3) the multisensory facilitation map shifts isomorphically following hand positions, revealing hand-centered coding of PPS, therefore pointing to a functional similarity to the receptive fields of monkeys' multisensory neurons. A control experiment further corroborated these results and additionally ruled out the orienting of attention as the driving mechanism for the increased multisensory facilitation near the hand. In sharp contrast, ARS mapping results in a larger spatial extent, with undistinguishable patterns across hand positions, cross-validating the conclusion that PPS and ARS are distinct spatial representations. These findings show a need for refinement of theoretical models of PPS, which is relevant to constructs as diverse as self-representation, social interpersonal distance, and motor control.

Keywords Peripersonal space · Hand-centered space · Reaching space · Multisensory · Perception

Introduction

Seminal studies described multisensory neurons in primates' fronto-parietal regions coding for the space surrounding the body, termed *peripersonal space* (PPS) (Colby et al., 1993;Graziano & Gross, 1993 ; Rizzolatti et al., 1981a, 1981b). These neurons display visual receptive fields anchored to tactile ones and protruding over a limited area (~5 to 30 cm) from specific body parts (e.g., the hand) (Graziano & Gross, 1993; Rizzolatti et al., 1981a, 1981b). Neuroimaging results in humans are in line with these findings: ventral and anterior intraparietal sulcus, ventral and dorsal premotor cortices and putamen integrate visual, tactile and proprioceptive signals, allowing for a body part-centered representation of space (Brozzoli et al., 2011, 2012). Behaviorally, visual stimuli modulate responses to touches of the hand more strongly when presented near compared to far from it (Farnè et al., 2005; Làdavas & Farnè, 2004; Serino et al., 2015; Spence et al., 2004), a mechanism proposed to subserve both

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Published online: 22 June 2021

defensive (de Haan et al., 2016; Graziano & Cooke, 2006) and acquisitive aims (Brozzoli et al., 2009, 2010; Brozzoli et al., 2014; De Vignemont & Iannetti, 2014; Patané et al., 2019).

As a multisensory interface guiding interactions with the environment, PPS shares some characteristics with the arm-reaching space (ARS), the space reachable by extending the arm without moving the trunk (Coello et al., 2008). In humans, ARS tasks typically require judging the reachability of a stimulus (Carello et al., 1989; Coello & Iwanow, 2006). Despite their anatomo-functional differences (Desmurget et al., 1999; Filimon, 2010; Lara et al., 2018; Pitzalis et al., 2013), some research on human PPS diverged from the original electrophysiological findings and combined ARS and PPS (Coello et al., 2008; Iachini et al., 2014; Vieira et al., 2020). However, multisensory stimuli within ARS and close to the hand activate neural areas typically associated with PPS, whereas the same stimuli within ARS, but far from the hand, do not (Brozzoli et al., 2012; Graziano et al., 1994). To date, no empirical evidence exists to distinguish these spatial representations. The consequences of this conflation on spatial models of multisensory facilitation have to date been neglected, despite the crucial role it plays in sensorimotor control (Makin et al., 2017; Suminski et al., 2009, 2010) and the study of the bodily self (Blanke et al., 2015; Makin et al., 2008).

Here we leveraged empirical outcomes to disentangle two alternative theoretical models, hypothesizing that PPS and ARS are either identical or distinct spatial representations. To ensure fair comparative bases for this purpose, and to allow making clear alternative predictions, we set two pre-requisites: (1) not to oppose PPS and ARS in the context of different functions, and (2) to test both spaces with reference to the same body part. Thus, in Experiment 1 we used a tactile detection task and computed multisensory (visuo-tactile) facilitation, a typical proxy of PPS extent. In Experiment 2 we used a reachability judgment task and computed the point of subjective equality (PSE), a typical estimate of the ARS extent (Bourgeois & Coello, 2012). As visual and tactile stimuli were harmless and semantically neutral, our tasks were devoid of any defensive or social function. In addition, both PPS and ARS tasks were applied in reference to the hand, as PPS has been shown to be hand-centered (di Pellegrino et al., 1997) and what we can reach (ARS) is defined by how far our hand can reach (Coello & Iwanow, 2006), thus fulfilling the criteria for a fair comparison. Two additional experiments manipulated hand vision (visible or not) and position (close or distant), to progressively equate the reachability task to the multisensory conditions of Experiment 1.

Following this rationale, if PPS and ARS are equal, we should observe similar spatial extents from multisensory facilitation and reachability estimates. In addition, we should observe facilitation from all visual stimuli falling within ARS independently of hand position. Conversely, we should measure different spatial extents and observe multisensory facilitation only for stimuli near the hand, as a function of its position, resulting in specific and distinguishable spatial patterns of multisensory facilitation.

Experiment 1

Methods

Participants We calculated our sample size with G*Power 3.1.9.2, setting the 10*2 (V-Position*Hand Position) within-interaction for a RM ANOVA hypothesizing a power of 0.85, an $\alpha = 0.05$ and a correlation of 0.5 between the measures. We assumed that the visuo-tactile effect size might be greater than the audio-tactile one (small, corresponding to Cohen's d=0.2 so to f = 0.1) reported by Holmes and colleagues (Holmes et al., 2020). We thus considered a medium-low effect size (f = 0.20) and we needed to recruit at least 23 participants per study. All participants were right-handed, as evaluated via the Edinburgh Handedness Test (mean score 82%). Twenty-seven subjects (13 females; mean age = 26.12 years, range = 20–34; mean arm length = 79.41 ± 5.83 cm, measured from the acromion to the tip of the right middle finger) participated in Experiment 1.

All participants reported normal or corrected-to-normal vision, normal tactile sensitivity, and no history of psychiatric disorders. They gave their informed consent before taking part in the study, which was approved by the local ethics committee (Comité d'Evaluation de l'Ethique de l'Inserm, n° 17-425, IRB00003888, IORG0003254, FWA00005831) and was carried out in accordance with the Declaration of Helsinki. Participants were paid 15 € each.

Stimuli and apparatus *Visual stimuli* were identical for both the experiments. We used a projector (Panasonic PT-LM1E_C) to present a two-dimensional (2D) gray circle (RGB = 32, 32, 32) in one of ten positions, ranging from near to far from the body. The diameter of the gray circle was corrected for retinal size using the formula:

$$\frac{3cm^{*}(57cm + x)}{57cm}$$

where 3 cm is the diameter of the circle, 57 cm is the distance from the eye at which 1° of the visual field roughly corresponds to 1 cm, and x is the distance of the center of the stimulus from the point at 57 cm. Visual stimulus duration was 500 ms. The fixation cross (2.5 cm) was projected along the body's sagittal axis (see Fig. 1). The ten positions were calibrated such that the sixth one corresponded to the objective limit of reachability for each participant. We ensured this before the experiment: participants stayed with eyes closed,

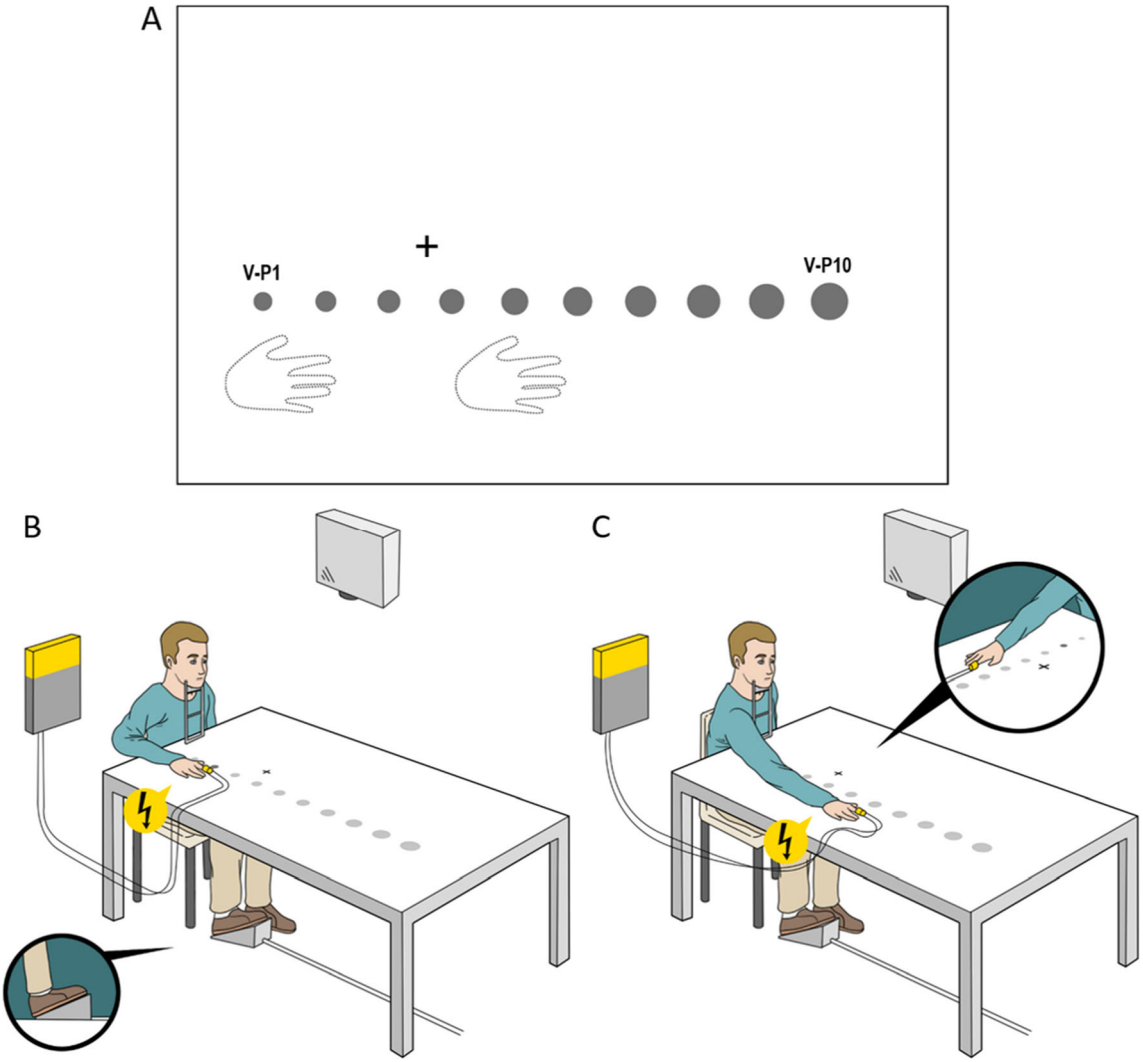

Fig. 1 Experimental setup across experiments. **a** Positions of right hand, fixation cross, and visual stimuli. **b** and **c** The close hand (**b**) and the distant hand condition (**c**). In both experiments, the visual stimuli (here displayed as gray circles) were projected one at a time, in one of the ten possible positions (from V-P1 to V-P10), corrected for retinal size (**a**–**c**). Tactile and visual stimuli were presented alone (unisensory) or coupled synchronously with each other (multisensory). Globally, we adopted two conditions of unisensory stimulation (only tactile or visual stimulation) and a multisensory condition (visuo-tactile stimulation). To these, we added catch trials (nor visual nor tactile stimuli presented) to monitor participant's compliance

their head on a chinrest (30 cm high), and placed their right hand as far as possible on the table. Starting from the sixth position, four positions were computed beyond the reachable limit and five closer to the participant's body, 8 cm rightward with respect to the body's sagittal axis. Positions, uniformly separated by 9 cm, spanned along 90 cm of space and were labelled V-*P1* to V-*P10,* from the closest to the farthest (see Fig. 1).

Tactile stimuli were brief electrocutaneous stimulations (100 μs, 400 mV) delivered to the right index finger via a constant current stimulator (DS7A, DigiTimer, UK) through a pair of disposable electrodes (1.5*1.9 cm, Neuroline, Ambu, Denmark). Their intensity was determined through an ascending and a descending staircase procedure, incrementing and decrementing, respectively, the intensity of the stimulation to find the minimum intensity at which the participant could detect 100% of the touches over ten consecutive stimulations. Intensity was further increased by 10% before the first and third experimental block.

Design and procedure Participants performed a speeded tactile detection task. Tactile stimulation of their right index finger could be delivered alone or synchronous to a visual one, in one of the ten positions (see Fig. 1). Participants rested with their head on the chinrest and eyes on the fixation cross. Their right hand was placed on the table 16 cm rightward from the body's sagittal axis, with the tip of the middle finger corresponding to V-P2 (hereafter close hand) or V-P6 (hereafter distant hand), in different blocks counterbalanced across

participants (116 randomized trials per block): two blocks with the close hand and two with the distant hand. Considering the distance between the positions of visual stimulation, the hand in the distant position covers positions V-4 (wrist), V-5, and V-P6 (tip of the middle finger), and the hand in the close position is flanked by the positions V-P1 and V-P2 (see Fig. 1). Each hand condition included 16 visuo-tactile (VT) stimulations per position and 16 unimodal tactile trials (T trials). To ensure compliance with task instructions, there were also four unimodal visual trials per position (V trials) and 16 trials with no stimulation (N trials). Participants had to respond to the tactile stimulus as fast as possible by pressing a pedal with their right foot. The total duration of the experiment was about 45 min.

Analyses Both the experiments adopted a within-subject design. When necessary, Greenhouse-Geisser sphericity correction was applied. The first analyses focused on the accuracy of the performance. Four participants performed poorly (>2 SD from mean) and were excluded from further analyses.

To have a direct index of the proportion of multisensory facilitation over the unimodal tactile condition, we calculated the Multisensory Gain (MG):

$$MG = \frac{T_M - VT}{T_M}$$

T_M was the average reaction time (RT) for unimodal tactile stimuli, and VT was the raw RT for a multisensory visuo-tactile stimulus. Larger MG values correspond to greater facilitation (namely, larger benefits for VT compared to T conditions). This measure is more rigorous than an absolute delta, as it allows correction of the RTs considering the subject-specific speed for each visual position and for each position of the hand (analyses on the delta RT are also reported in the Appendix – Experiment 1). Computing MG values per hand and stimulus position, we obtained two vectors of 10 MG values (from V-P1 to V-P10) for each participant: one for the close hand and one for the distant hand. We applied a multivariate SVM approach (Vapnick, 1995) to test whether a data-driven classifier could reliably predict the position of the hand from the spatial pattern of MG. The SVM was trained on (N – 1) participants (leave-one-out strategy) and tested on the two vectors excluded from training, using a linear kernel. Overall accuracy was calculated as the sum of the correct predictions for both hand positions divided by the total number of predictions.

To map multisensory facilitation more locally, we compared Bonferroni-corrected MG values for each position against zero and performed a *Hand* (close vs. distant)**Position* (V-P1 to V-P10) within-subject ANOVA.

To compare the shape of these multisensory facilitation maps, we first tested which function better fit the spatial pattern and, second, we cross-correlated them to test their shapes for isomorphism. MG values were fitted to sigmoidal and normal curves, limited to two parameters. Table 1 reports formulas for curve fitting (Curve Fitting toolbox) with MATLAB (version R2016b, MathWorks, Natick, MA, USA). Similar to previous work (Canzoneri et al., 2012; Serino et al., 2015), we considered a good sigmoidal fit when data fitted a descending slope, indicating a facilitation close to the body that fades away with increasing distances.

Next, we performed a cross-correlation analysis on MG values to evaluate the isomorphism of the facilitation curve for both hand positions. Our prediction was that shifting the close hand pattern of facilitation distally (i.e., towards the distant-hand position), should bring higher correlations due to the overlap of the curves. We correlated the pattern of averaged MG values for all reachable stimuli (V-P1 to V-P6) in the close hand condition, with that of six averaged MG values observed in the distant hand condition. The correlation was then tested for four incremental position shifts (distally, one per position), up to the last shift, where we correlated the V-P1 to V-P6 pattern for the close hand with the V-P5 to V-P10 pattern of the distant hand.

Results

We tested the effect of VT stimulation over ten uniformly spaced positions, to obtain a fine-grained map of patterns of multisensory facilitation (validated in a pilot study). Participants performed accurately (90% hits, < 2% false alarms). First, the multivariate classifier was able to predict the two positions of the hand with an accuracy of 0.72 (33/46 correct classifications), with no bias for one hand position over the other (17/23 and 16/23 for the close and distant hands, respectively). This accuracy was significantly higher than chance (one-tailed binomial test $p = 0.002$). Hence, different patterns of multisensory facilitation were associated with different hand positions within the ARS.

A *V-Position*Hand* repeated-measures ANOVA (Fig. 2a) revealed a significant main effect of *V-Position* ($F_{(5.85,128.71)} = 3.52$, $p = 0.003$, $\eta^2_p = 0.14$), further modulated by hand position, as indicated by the significant interaction ($F_{(6.45,141.85)} = 3.47$, $p = 0.002$, $\eta^2_p = 0.14$). Tukey-corrected multiple t-test comparisons revealed faster responses in V-P2 than in V-P4 and in all the positions from V-P6 to V-P10 when the hand was close (all $p_s < 0.05$ except V-P2 vs. V-P8, $p = 0.054$); responses were faster in V-P4 than in V-P1, V-P2, V-P3, V-P8, V-P9, and V-P10 when the hand was distant (all $p_s < 0.05$). Critically, the MG was larger in V-P2 when the hand was close than when it was distant ($p = 0.041$). This pattern was reversed in V-P4, where the MG was larger when the hand was distant than when it was close ($p = 0.022$). No other differences were significant.

Table 1 Formulas adopted to fit the curves for the multisensory gain values in Experiment 1. X represents one of the ten experimental positions (from V-P1 to V-P10). We used the same formulas to fit the sigmoidal and normal curves to reachability judgments in Experiment 2

Sigmoidal	Normal
$\frac{100}{1+e^{-a(X-b)}}$	$100*e^{\left(\frac{X-a}{b}\right)^2}$

To identify where multisensory facilitation was significant at the single position level, we ran a series of Bonferroni-corrected t-tests on the MG values versus 0 (i.e., no facilitation). When the hand was close, the MG significantly differed from 0 in V-P2 and V-P3 (all ps < 0.05). In contrast, when the hand was distant, the MG was larger in V-P4, V-P5 (all ps < 0.05) and marginally in V-P6 ($p = 0.055$). Figure 2 shows the number of trials reporting MG values greater than 0 with the hand close (2b) and distant (2c). The density peak shifted

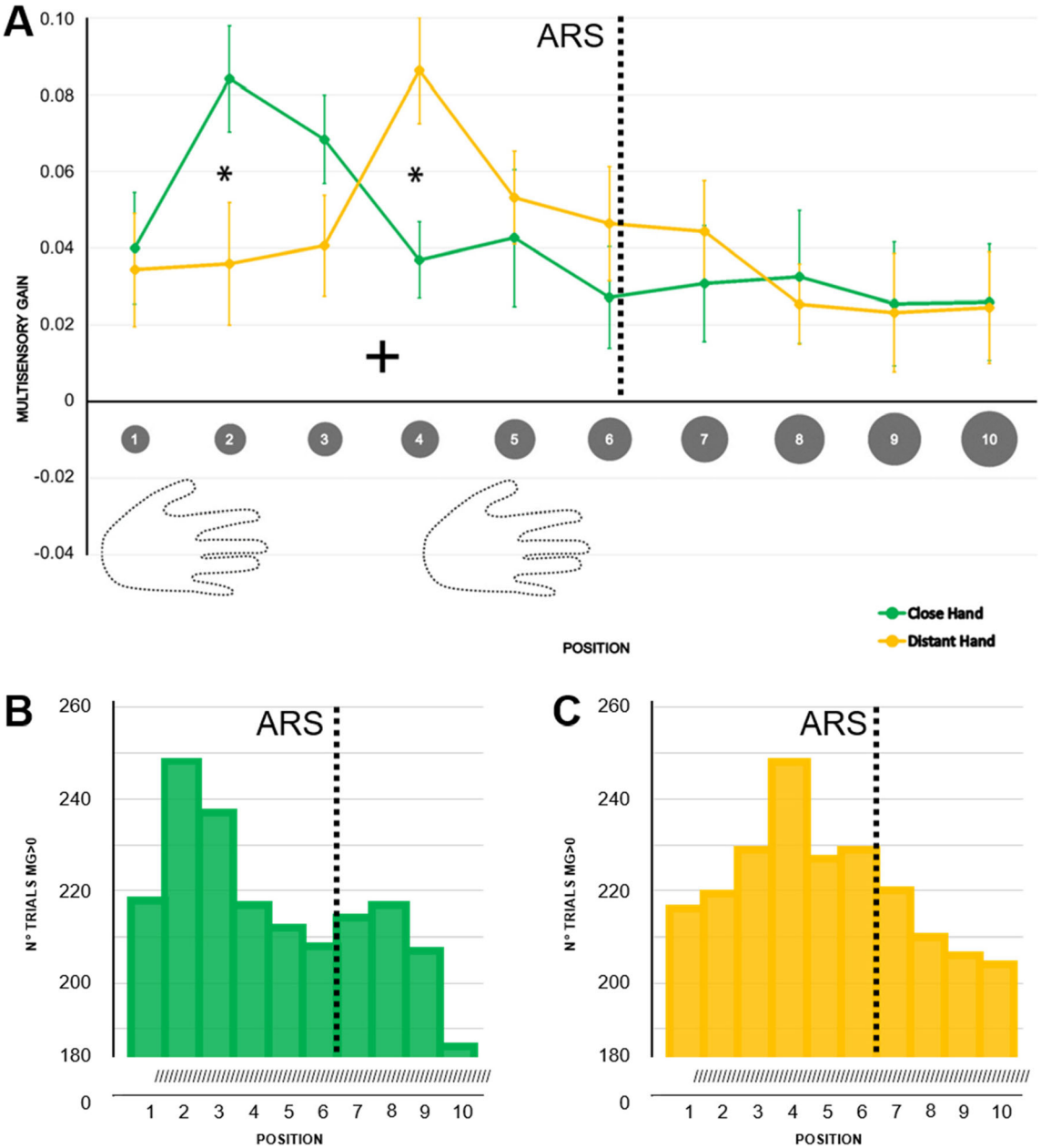

Fig. 2 Different patterns of hand-centered multisensory facilitation within ARS. **a** Multisensory gain (MG) values along the ten visual positions, ranging from near to far space, for the distant (yellow) and the close (green) hand conditions. Higher values of MG represent stronger facilitation in terms of RT in the multisensory condition than in the unisensory tactile baseline (by definition, MG = 0). Error bars represent the standard error of the mean. Asterisks represent a significant difference ($p < 0.05$, corrected). **b** and **c** Number of trials reporting MG values greater than zero (unisensory tactile baseline) along the ten visual positions, ranging from near to far space, for the close (**b**) and the distant (**c**) hand conditions

coherently with the position of the hand within ARS. Similar results were obtained by analyzing the delta RT for both the ANOVA and the t-tests (see Appendix – Experiment A1). Furthermore, the results of Experiment S1 show that this multisensory facilitation does not depend on sheer attentional factors.

These findings highlight the hand-centered nature of the multisensory facilitation, occurring in different locations, depending on hand position. From this, one would expect (1) the facilitation to be maximal in correspondence with hand location and to decay with distance from it and (2) the bell-shaped pattern of facilitation to follow the hand when it changes position. To test the first prediction, we modelled our data to a Gaussian curve. To test the alternative hypothesis, namely that facilitation spreads all over the ARS to decay when approaching the reachable limit, we compared the Gaussian to a sigmoid function fitting (Canzoneri et al., 2012; Serino et al., 2015). The sigmoidal curve could fit the data for a limited number of participants (distant hand: 5/23 subjects, 21.7%; close hand: 9/23 subjects, 39.1%). Instead, fitting the Gaussian curve to the same data accommodated convergence problems for a higher number of participants (distant hand: 14/23 subjects, 59.9%; close hand: 15/23 subjects, 65.2%).

The second prediction, that the bell-shaped facilitation should shift following the hand, was confirmed by the estimation of the position of the peak of the Gaussian curve in each hand position: with the hand close, the peak fell between V-P2 and V-P3 (2.34 ± 1.51); with the hand distant, it fell between V-P4 and V-P5 (4.15 ± 1.28). We then performed a cross-correlation analysis testing whether the curves reported for the two hand positions overlapped when considered in absolute terms. We reasoned that shifting the position of the hand – within the ARS – should bring to an isomorphic facilitation around the new hand position. This would imply the maximum correlation between MG values emerge when the close-hand curve shifts distally, towards the distant-hand position curve. We considered the first six values of MG with the close hand (from V-P1 to V-P6, i.e., the reachable positions) and correlated this distribution with six values of the MG for the distant hand (Fig. 3). We found the maximum correlation ($r = 0.94$ $p = 0.005$) when shifting the close hand distally by two positions. No other correlations were significant (all $p_s > 0.20$).

Discussion

The results of Experiment 1 clearly indicate that PPS and ARS are not superimposable. Yet we cannot exclude that a reachability judgment task might still capture some of the PPS features. To investigate this possibility, we performed three experiments adopting this task and the same settings of Experiment 1. The results of Experiments S2 and S3 (Appendix) replicated well-established findings about the ARS, including the overestimation of its limit (Bourgeois & Coello, 2012; Carello et al., 1989). However, they failed to show any similarity with PPS, either in terms of absolute extent (ARS is larger than PPS) or in position-dependent modulation (PPS is hand-centered, whereas ARS is not, see Appendix, S2 and S3). To allow a full comparison, in Experiment 2 we made the reachability judgment task as similar as possible to the tactile detection task, using the same hand positions and multisensory stimulations.

Experiment 2

Methods

Participants Twenty-five (16 females; mean age = 24.44 years, range = 18–41; mean arm length = 78.46 ± 7.26 cm) participants matching the same criteria as Experiment 1 participated in Experiment 2.

Stimuli and apparatus *Visual* and *tactile* stimuli were identical to those used in Experiment 1.

Design and procedure We took advantage of an ARS multisensory task by asking participants to perform reachability judgments while tactile stimuli were concurrently presented with the visual stimulus. Experiment 2 was meant to assess whether the multisensory stimulation (in addition to having the hand visible and in the same positions as Experiment 1) could either induce hand-centered facilitation in the reachability task performance and/or change the extent of the reachability limit. We employed the same settings as in Experiment 1 and applied the same tactile stimulation to the right index finger, placed in either the close or the distant position. However, in this case the tactile stimulus was task-irrelevant. Overall, 160 randomized V and 160 randomized VT trials were presented for each hand position, administered in two blocks in a randomized order. The order of hand positions was counterbalanced across participants.

Analyses Similar to Experiment 1, we tested the classifier on the MG patterns and performed the same procedures already described on delta RTs and MG. The percentage of "reachable" responses per position was calculated and then fitted to sigmoidal and normal curves, as in Experiment 1. We fitted the curves separating hand positions and type of stimulation (unimodal visual vs. multisensory visuo-tactile). *Hand* (close vs. distant)**Stimulation* (visual vs. visuo-tactile)**Model* (Gaussian vs. Sigmoid) ANOVA on RMSE (root mean square error) values assessed which model best fitted the data, both at the individual and at the group level. Either way, the best-fitting model for these data was the sigmoidal curve. Thus, we investigated the PSE and slope values by subjecting them

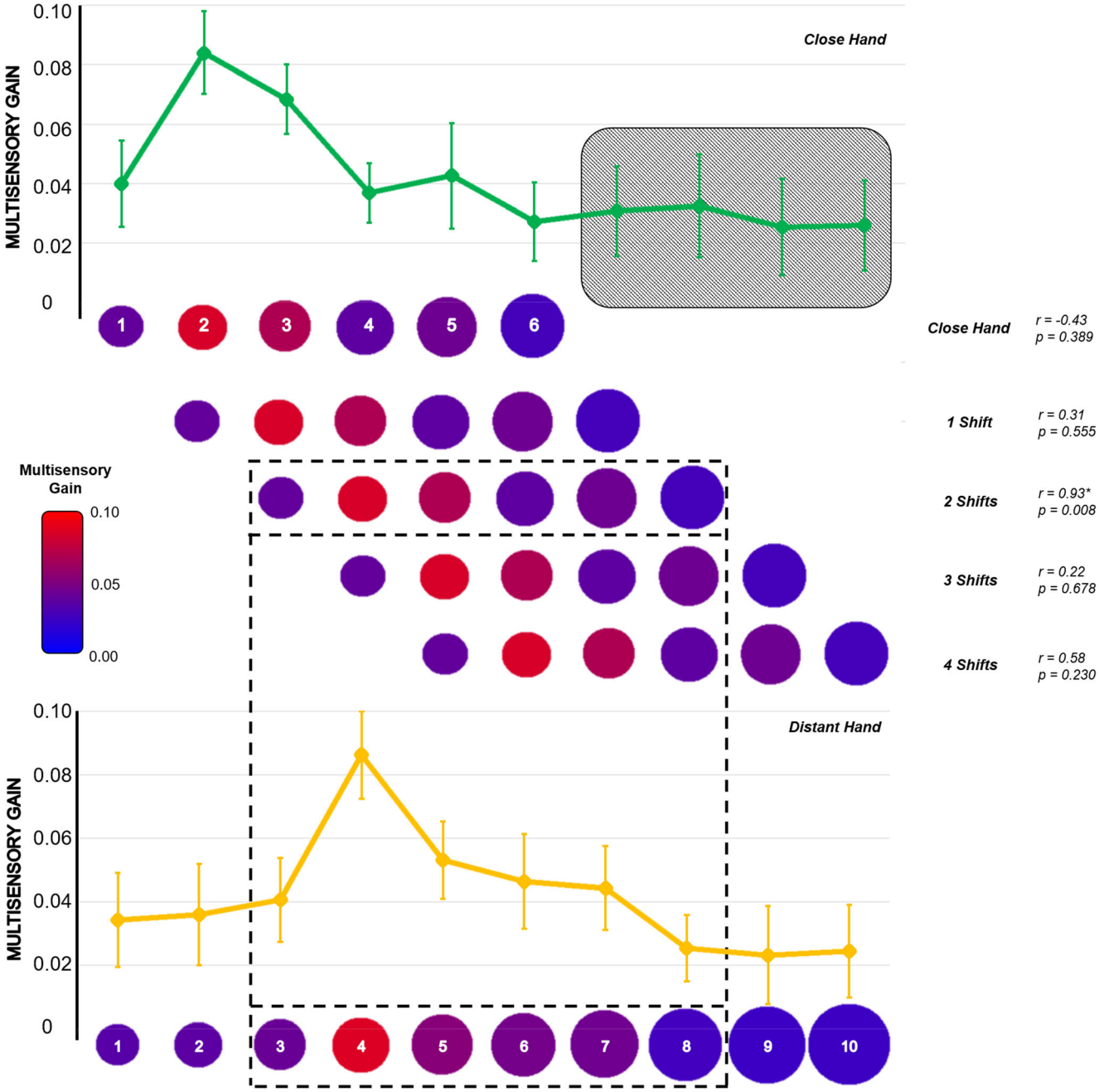

Fig. 3 The spatial pattern of MG shifts and follows the hand within reaching space. Cross-correlation analysis of distally shifting the pattern of MG values for all reachable positions with the hand close. Red colors represent higher MG values. Values of Pearson's r and p values are reported for all the correlations performed. The black grid highlights the only significant correlation ($p < 0.05$)

to two separate repeated-measure ANOVAs with *Hand* (close vs. distant) and *Stimulation* (visual vs. visuo-tactile) as within-subject factors.

Results

Participants were accurate (>90% hits, <2% false alarms). We computed for each subject two vectors of MG values, as in Experiment 1, and we could leverage a similar data-driven classifier to discriminate the close from the distant hand. Prediction accuracy was lower than in Experiment 1 (0.36, 18/50 correct classifications) and not significantly higher than chance level (one-tailed binomial test $p = 0.98$), indicating that the classifier failed to distinguish between hand positions within ARS.

Moreover, the V-*Position***Hand* within-subject ANOVA on the MG did not reveal any significant effect (Hand: $F_{(1,24)} = 0.83$, $p = 0.37$; V-Position: $F_{(6.31,151.56)} = 1.20$, $p =$

0.31; Hand*V-Position: $F_{(5.35,128.5)} = 1.82$, $p = 0.11$). However, the significant intercept ($F_{(1,24)} = 9.80$, $p = 0.005$) confirmed the general facilitation produced by multisensory stimulation, with respect to the unisensory one. Multiple Bonferroni-corrected comparisons revealed that none of the positions presented an MG significantly different from 0 (all $p_s > 0.05$) when the hand was close. V-P5 and V-P6 differed from 0 (all $p_s < 0.05$) when the hand was distant. Similar results were obtained by analyzing the delta RT, both with ANOVA and with t-test (see Appendix – Experiment 2).

Reachability judgments were then fitted to sigmoidal and Gaussian curves. Within-subject ANOVA on the RMSE of these models was performed with a *Model* (sigmoidal vs. Gaussian)**Stimulation* (visual vs. visuo-tactile)**Hand* (close vs. distant) design. The sigmoidal curve reported the best fit, irrespective of stimulation type and hand position (Model*:* ($F_{(1,24)} = 220.11$, $p < 0.001$, $\eta^2_p = 0.90$)). For each variable, we estimated the coefficients of the sigmoid, obtaining the PSE and the curve slope. Through a *Hand* (close vs. distant*)*Stimulation* (visual vs. visuo-tactile) within-subject ANOVA on PSE values, we observed a main effect of stimulation type ($F_{(1,24)} = 4.38$, $p = 0.05$, $\eta^2_p = 0.15$): the mean PSE was closer to the body in the unimodal visual (mean ± SE = 6.67 ± 0.17) than in the multisensory visuo-tactile condition (6.76 ± 0.18). The main effect of *Hand* ($F_{(1,24)} = 0.07$, $p = 0.79$) and its interaction with *Stimulation* ($F_{(1,24)} = 3.49$, $p = 0.07$) were not significant. Last, we performed a *Hand* (close vs. distant*)*Stimulation* (visual vs. visuo-tactile) within-subject ANOVA on slope values. Neither main effects (*Hand*: $F_{(1,24)} = 1.75$, $p = 0.20$; *Stimulation*: $F_{(1,24)} = 0.35$, $p = 0.56$) nor the interaction (*Hand*Stimulation*: $F_{(1,24)} = 0.27$, $p = 0.61$) were significant (Fig. 4).

Discussion

We contrasted two theoretical views about PPS and ARS: one proposing they are different, the other opposing they are the same. Our findings clearly point against the latter, whether contrasted in terms of their spatial extent, by using their respective gold-standard paradigms and measures, or in terms of pattern of multisensory facilitation.

Due to obvious differences between paradigms, we did not compare the multisensory facilitation directly. We rather reasoned that, would PPS and ARS be the same spatial representation, using their typical paradigms applied to the same body part we should obtain similar results. Our visuo-tactile version of the reachability judgment task confirms previous findings on the extent and overestimation of ARS (Bootsma et al., 1992; Bourgeois & Coello, 2012; Carello et al., 1989; Coello & Iwanow, 2006), but its comparison with the PPS multisensory task resulted in two main advances arguing against the PPS-ARS identity.

First, we observed that multisensory facilitation depends on hand position, peaking in correspondence with its location and deteriorating with distance from it. Notably, this near-hand facilitation effect is independent of attention orienting (see Appendix, S1 results). Thus, PPS is smaller than the ARS, either objectively (from V-P1 to V-P6) or subjectively (PSE) measured. Were they superimposable, we should have observed faster RTs for all the reachable positions of visual stimulation. Both the classifier and the location-specific differences indicate instead that different spatial patterns of multisensory facilitation emerge for the close- and distant-hand positions, despite being both within the ARS limits. Interestingly, we add that overestimation is not modulated by hand vision (see Appendix, Experiments S2 and S3), and is independent of the position of the hand (Experiments 2 and Appendix, S3).

Second, our findings indicate that ARS is not hand-centered, whereas PPS is. In Experiment 2, adapting the reachability judgment task to a multisensory setting, the only significant effect was a general multisensory facilitation, spread over the ten positions tested: there was no modulation as a function of stimulus reachability or hand proximity, which, on the contrary, define PPS (Experiment 1). Therefore, ARS is not encoded in a hand-centered reference frame. Indeed, hand position was robustly classified from the distribution of MG in Experiment 1 (PPS), but not in Experiment 2 (ARS). Thus, the proximity of visual stimuli to the hand – not their reachability – predicts the increase in multisensory facilitation. Cross-correlation and univariate analyses further demonstrated that visual boosting of touch is hand-centered, following changes in hand position. In sum, here we show that (1) PPS does not cover the entire ARS, (2) ARS is not hand-centered, and (3) ARS is not susceptible to multisensory stimulation. Taken together, these results combine to show that PPS and ARS are not superimposable. Previous neuroimaging (Brozzoli et al., 2011, 2012) and behavioral studies (di Pellegrino et al., 1997; Farnè et al., 2005; Serino et al., 2015) reported body part-centered multisensory facilitation within PPS. Here we disclose that the facilitation is isomorphically "anchored" to the hand: present in close positions when the hand is close, it shifts to farther positions when the hand is distant, without changing its "shape." Notably, the facilitation pattern fits well a Gaussian curve, similar to what is observed in non-human primate studies (Graziano et al., 1997) and in line with the idea of PPS as a « field », gradually deteriorating around the hand (Bufacchi & Iannetti, 2018).

The amount of multisensory facilitation observed in Experiment 1 for the position closest to the trunk (V-P1, thus clearly within ARS) is also remarkable. First, it is lower than that observed in correspondence of the close-hand PPS peak (between V-P2 and V-P3) and, second, it is comparable to that obtained for all the out-of-reach positions (V-P7 to V-P10), irrespective of hand distance.

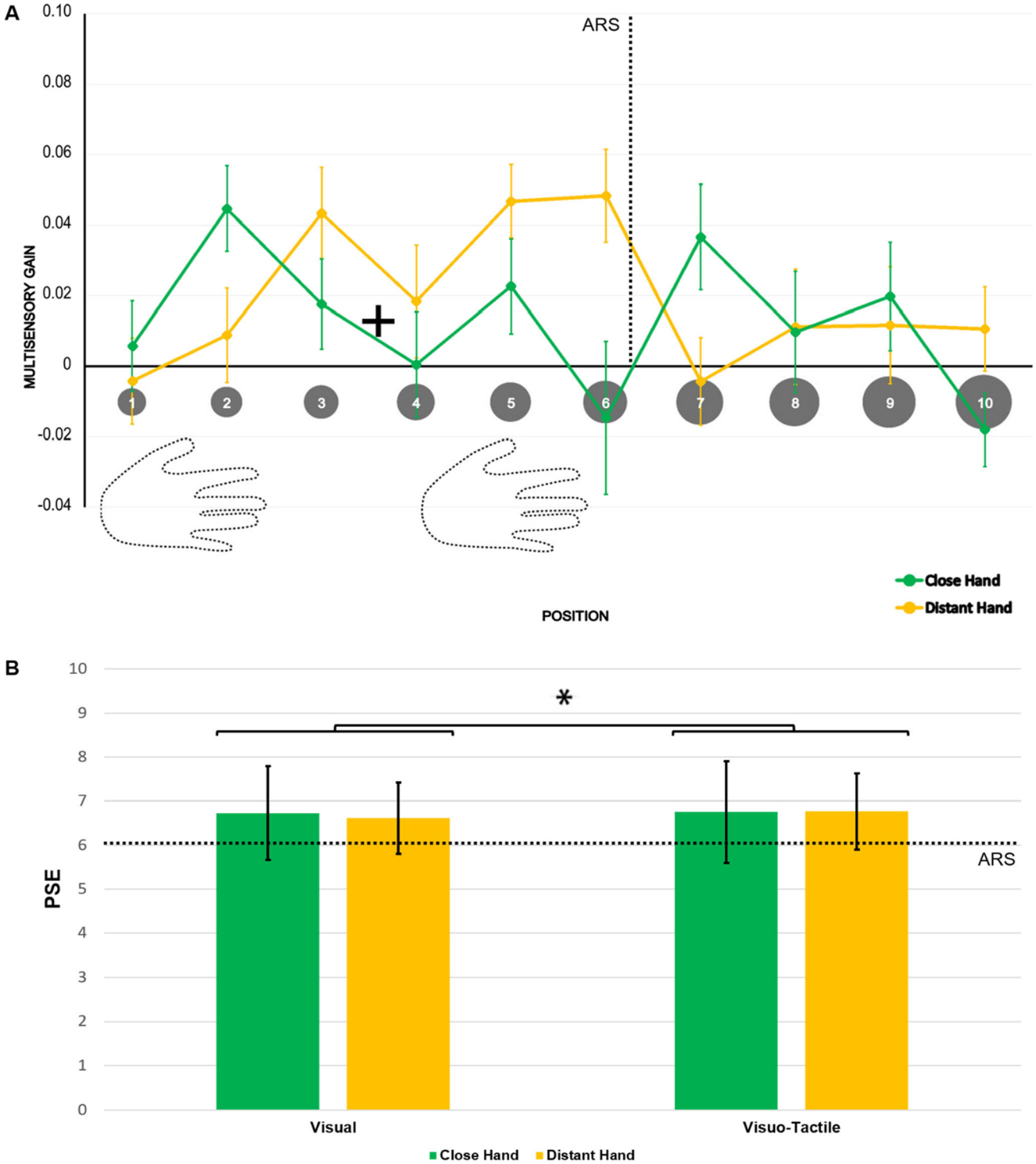

Fig. 4 No hand-centered MG spatial patterns in a reachability judgment task. **a** Multisensory gain (MG) values along the ten positions, ranging from near to far space, for the close (green) and distant (yellow) hand conditions. Higher values of MG represent a stronger facilitation in terms of RT with respect to the unimodal visual baseline (by definition, MG = 0). Error bars represent the standard error of the mean. No significant differences between hand postures emerged. **b** PSE values calculated for both unimodal visual and multisensory visuo-tactile conditions for both hands. Error bars represent the standard error of the mean. Asterisks indicate a significant difference between unisensory and multisensory conditions ($p < 0.05$)

These findings are consistent with what one would predict from neurophysiological data. Studies on non-human primates requiring reaching movements performed with the upper limb found activations involving M1, PMv and PMd,

parietal areas V6A and 5, and the parietal reach region (Buneo et al., 2016; Caminiti et al., 1990; Georgopoulos et al., 1982; Kalaska et al., 1983; Mushiake et al., 1997; Pesaran et al., 2006). In humans, ARS tasks require judging stimulus reachability (Carello et al., 1989; Coello et al., 2008; Coello & Iwanow, 2006; Rochat & Wraga, 1997) or performing reaching movements (Battaglia-Mayer et al., 2000; Caminiti et al., 1990, 1991; Gallivan et al., 2009). Brain activations underlying these tasks encompass M1, PMd, supplementary motor area, posterior parietal cortex, and V6A, as well as the anterior and medial IPS (Lara et al., 2018; Monaco et al., 2011; Pitzalis et al., 2013; see Filimon, 2010, for review). Therefore, despite some overlap in their respective fronto-parietal circuitry, PPS and ARS networks do involve specific and distinct neuroanatomical regions, in keeping with the behavioral differences reported here.

At odds with previous studies employing looming stimuli (Canzoneri et al., 2012; Finisguerra et al., 2015; Noel et al., 2015, b; Serino et al., 2015; but see Noel et al., 2020), we used "static" stimuli flashed with tactile ones to avoid inflating the estimates of multisensory facilitation. Looming stimuli with predictable arrival times induce foreperiod effects that, though not solely responsible for the boosting of touch, may lead to overestimations of the magnitude of the facilitation (Hobeika et al., 2020; Kandula et al., 2017). Most noteworthy, the findings of the attentional control experiment provide the first behavioral evidence that multisensory near-hand effects may be appropriately interpreted within the theoretical framework of peripersonal space coding. This study therefore offers a bias-free (Holmes et al., 2020) protocol for fine-grained mapping of PPS.

In conclusion, this study provides an empirical and theoretical distinction between PPS and ARS. Discrepancies concern both their spatial extent and their behavioral features, and warn against the fallacy of conflating them. A precise assessment of PPS is crucial because several researchers exploit its body part-centered nature as an empirical entrance to the study of the bodily self (Blanke et al., 2015; Makin et al., 2008; Noel et al., 2015, b). Moreover, our results have direct implications for the study of interpersonal space, defined as the space that people maintain with others during social interactions. Several studies drew conclusions about interpersonal space using reachability tasks (Bogdanova et al., n.d.; Cartaud et al., 2018; Iachini et al., 2014). The present findings make clear that using these tasks does not warrant any conclusion extending to PPS, or informing about its relationship with the interpersonal space. Instead, they highlight the need to investigate the potential interactions between PPS and ARS, as to better tune rehabilitative protocols or brain machine interface algorithms for the sensorimotor control of prosthetic arms, for which multisensory integration appears crucial (Makin et al., 2007; Suminski et al., 2009, 2010).

Supplementary Information The online version contains supplementary material available at https://doi.org/10.3758/s13423-021-01942-9.

Acknowledgements This work was supported by the Labex/Idex (ANR-11-LABX-0042) and by grants from the James S. McDonnell Foundation, the ANR-16-CE28-0015-01 and ANR-10-IBHU-0003 to A.F. E.B. was supported by the European Union's Horizon 2020 research and innovation program (Marie Curie Actions) under grant agreement MSCA-IF-2016-746154; a grant from MIUR (Departments of Excellence DM 11/05/2017 n. 262) to the Department of General Psychology, University of Padova. C.B. was supported by a grant from the Swedish Research Council (2015-01717) and ANR-JC (ANR-16-CE28-0008-01). We thank S. Alouche, J.L. Borach, S. Chinel, A. Fargeot, and S. Terrones for administrative and informatics support, and F. Volland for customizing the setup.

Declarations

Conflict of Interest The authors declare no competing financial interests.

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Chapter III

A Space for Values

Ma non sì che paura non mi desse
la vista che m'apparve d'un leone.
Questi parea che contra me venisse
con la test'alta e con rabbiosa fame,
sì che parea che l'aere ne tremesse.
Ed una lupa, che di tutte brame
sembiava carca ne la sua magrezza,
e molte genti fé già viver grame,
questa mi porse tanto di gravezza
con la paura ch'uscia di sua vista,
ch'io perdei la speranza de l'altezza.

Dante Alighieri

After having delighted us with the aspects most linked to the definition of the peripersonal space, this doctoral dissertation moves towards its conclusion by focusing on a specific function of this representation: the defensive one. Briefly summarizing what has already been described, the defensive peripersonal space, or dPPS, is that region of space around our body parts that allows us to preserve our bodily integrity, informing us of the potential threats that surround us. We can consider it as a kind of “radar” that keeps track of the position of our body parts and the surrounding threatening stimuli, avoiding having us put a bare foot on a Lego building brick, for example.

The different theoretical models we have described have had to face the dichotomy between a "PPS for goal-directed actions" and a "PPS for defensive actions", but the difference between the two PPS functions cannot lie only in the type of action to be put in place. The action is indeed the observable result of the performance of its functions, but to allow us to grab an apple on the table or to chase away the spider that is approaching our leg, the PPS must be informed by something else. In this last chapter, a brief review of the studies that investigated the effects of stimuli with positive and negative valence inside and outside the PPS will be initially presented, trying to understand how the meaning attributed to a stimulus can influence the processing of sensory information within the PPS. Next, we will delve into the more social-defensive nuance of PPS, describing the results of some studies that investigated the effect of emotions on PPS encoding. In particular, we will focus on a specific emotion, which plays an important adaptive role: fear. The neural basis of this emotion will be described and then the concept of "conditioning" will be introduced, a procedure through which it is possible to establish associative links between different stimuli.

Finally, a behavioral study will be presented that used a fear learning protocol through conditioning, in order to test the possibility of learning associative links between stimuli in a hand-centered reference frame.

3.1 Snakes, spiders and dogs

Not all the stimuli that surround our body have the same meaning for us (and for our survival). Depending on their characteristics and context, it is possible to discriminate appetitive, endowed with a positive value, and aversive stimuli, endowed with a negative one. The former can be considered as an impulse or a reinforcement to implement and / or maintain an approach behavior, while the latter reinforce or give impetus to avoidance or flight behaviors (American Psychological Association, 2021). To improve our chances of survival, it is therefore important to quickly recognize the stimuli that can benefit or harm us and react accordingly. Given its role as an interface between perception and action, therefore, it is not surprising that numerous studies have been concerned with understanding the effect that aversive or appetitive stimuli have on the PPS representation.

A first and important contribution in this sense is that of Lloyd and colleagues (Lloyd et al., 2006). Using a rubber hand illusion paradigm within an fMRI scanner (see figure 3.1), the authors first induced a sense of ownership towards a fake hand and then approached it with a neutral (a cotton swab) or threatening stimulus (a fake syringe). What is observed is a greater activation of the posterior parietal cortex (as we have seen, also involved in the coding of PPS stimuli) in response to the threatening stimulus, but not to the neutral one. According to the authors, this would address the involvement of this region of cortex in the processing of aversive stimuli, and this view would be compatible with the defensive function that the PPS performs. Interestingly, this response disappeared if the fake hand was placed in a way that was incompatible with the subject's hand, nullifying the illusory feeling of body ownership.

Figure 3.1 *Lloyd and colleagues' experimental set-up: the participants' hand was covered by a rigid plastic tube on which the fake hand was placed. Following synchronous rubbing of the real hand and the rubber hand, the participants experienced the feeling of ownership towards the latter. From Lloyd et al., 2006*

A similar effect, but on a behavioral level, as described in the first chapter, was also observed by Pavani and colleagues: the magnitude of the CCE interference increased in case of visual stimuli positioned near two fake hands in a position compatible with that of the hands of the participant and decreased if the fake hands were in a spatially incompatible one (Pavani et al., 2000). However, the visual stimuli used in this study were neutral (simple and harmless LEDs), and therefore cannot provide insight into the behavioral effect of aversive or appetitive stimuli in a context of crossmodal congruency task. It will take a few years to observe that the valence of a visual stimulus, even if irrelevant, can influence the processing of sensory information within the peri-hand space. Poliakoff and colleagues (Poliakoff et al., 2007) used a modified version of the crossmodal congruency task in which participants had to discriminate the frequency (high or low) of tactile stimulations applied to the right or left hand while ignoring a visual stimulus that could be presented just before the touch in a congruent (visual stimulus in the same position as touch) or incongruent way (visual stimulus on the opposite hand, see Figure 3.2). These distractors could be threatening (spiders or snakes) or neutral (flowers or mushrooms). What the authors observed is a faster response when the tactile stimulus is associated with a snake in a congruent position. However, the same effect is not observed for the other threatening stimulus, the spider, and is not observed for neutral stimuli. Furthermore, this difference is found only when the temporal distance between the visual stimulus and the tactile target is reduced, fading away with longer time intervals. The interpretation of these results is therefore complex, as it seems that the defensive reaction is not present in the face of all threatening stimuli. However, Poliakoff and colleagues report a direct correlation between the fear of snakes and spiders and the facilitation observed: the greater the fear reported for the animal, the greater the facilitation when it is presented in a spatially congruent configuration with the touch. This therefore seems consistent with the defensive function of the PPS: the more the stimulus induces a feeling of fear, the greater the threat it will represent, and this could therefore lead to faster responses.

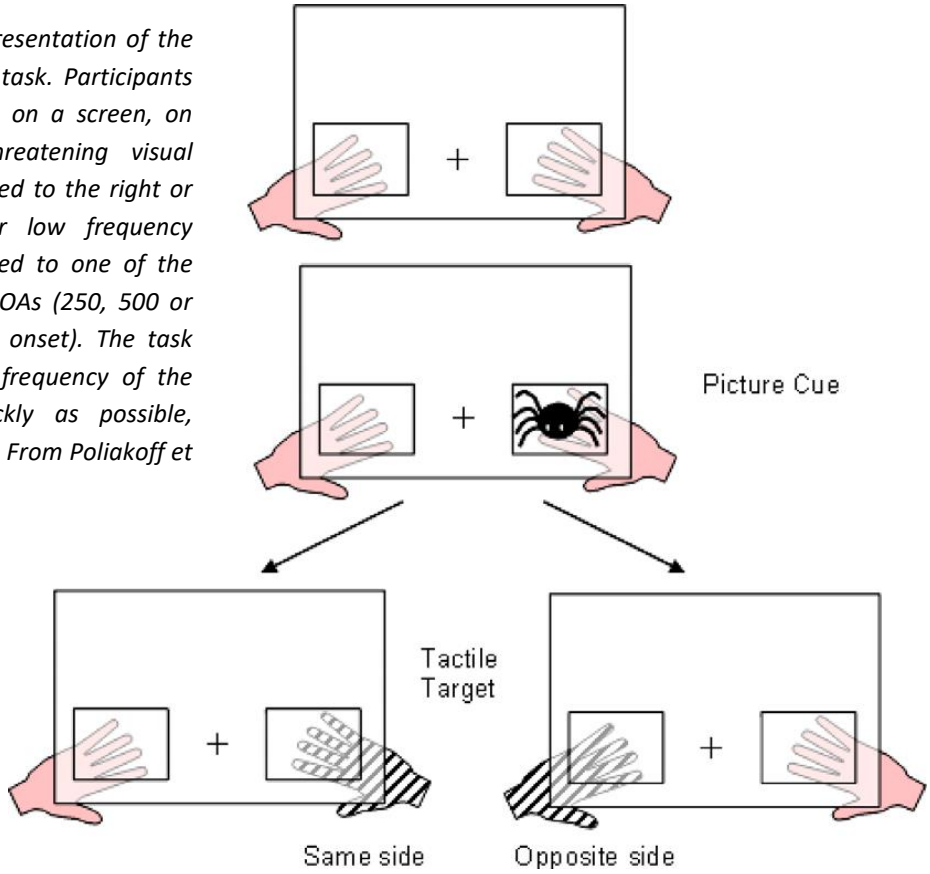

Figure 3.2 *Schematic representation of the Poliakoff and colleagues' task. Participants had to place their hands on a screen, on which a neutral or threatening visual stimulus could be presented to the right or left hemispace. High or low frequency tactile stimuli were applied to one of the two hands, at different SOAs (250, 500 or 1000 ms from the visual onset). The task was to discriminate the frequency of the tactile stimulus as quickly as possible, ignoring the visual stimuli. From Poliakoff et al., 2007.*

Another study that used spiders (very fashionable in the threat domain) to investigate the influence of aversive visual stimuli on tactile sensing comes from de Haan and colleagues (A. M. de Haan et al., 2016). As already described, the neurons of the PPS areas are particularly sensitive to moving stimuli (Graziano et al., 1997a; see Cléry et al., 2015 for review); in their study, they used a horizontal screen on which participants had to place their right hand, while an aversive (spider) or neutral (butterfly) visual stimulus moved towards or away from it (see Figure 3.4). The task was to ignore this stimulus and respond as quickly as possible to tactile stimuli that could be applied to the hand in 25 different timepoints, thus giving the impression that the touch arrived in correspondence with visual stimuli at different distances from the body (a "visual" version of the audio-tactile protocol of Canzoneri et al., 2012). What is observed is a boost of the behavioral response that depends on the distance at which the visual stimulus is located: the closer the visual stimulus is to the hand, the faster the response will be. However, this occurs only for stimuli looming towards the hand, and not for stimuli moving away (as already described in the audio-tactile version of this protocol). The distribution of this facilitation is not compatible with a sigmoidal curve, often

used to represent a boundary of the PPS, but rather with a linear progression, which instead seems in line with the idea of a representation whose magnitude gradually decreases with distance (Bufacchi & Iannetti, 2018). Moreover, the effect is observed specifically for the threatening stimulus, but only in the group of participants who previously reported increased fear of spiders. These results clearly support the defensive aspect of PPS, and demonstrate that an approaching aversive stimulus can modulate the behavioral response. The authors suggest that the enhanced visuo-tactile interaction within PPS may be mediated by a process of visuo-tactile prediction of the contact: when a threatening stimulus approaches us, we can predict the negative consequences deriving from its contact with our body, and this leads to enhanced tactile processing.

Figure 3.3 *Neutral (butterfly) and threatening (spider) visual stimuli moving towards the participant's hand in de Haan and colleagues' experiment. From de Haan et al., 2016.*

By abandoning spiders and moving on to somewhat larger animals, Taffou & Viaud-Delmon reported results similar to those just described using a dog's growl as a threatening stimulus (Taffou & Viaud-Delmon, 2014). Their participants, divided into a dog-fearful and a non-fearful groups, had to respond as quickly as possible to the tactile stimuli applied to the hand while ignoring the sounds that seemed to approach them from the rear space, coming from the right or left (see Figure 3.5). Such sounds could be threatening (dog growl) or neutral (sheep bleating). Converging with the results obtained through the visuo-tactile protocol of

de Haan and colleagues (A. M. de Haan et al., 2016), the response to the tactile stimulus was faster with the approach of the threatening auditory stimulus, but only in the cynophobic group. In particular, in this case the results seem to fit a sigmoidal curve (perhaps due to a lower number of timepoints to which tactile stimulation could be applied), whose inflection point, considered as a proxy of the PPS boundary, is more distant from the body in case of threatening rather than harmless auditory stimuli, but only in the dog-fearful group. This is considered as an expansion of the PPS in case of a threatening stimulus, consistent with the idea that, in the presence of a danger, it is appropriate and adaptive to react more quickly, for example by anticipating the approach of the threat.

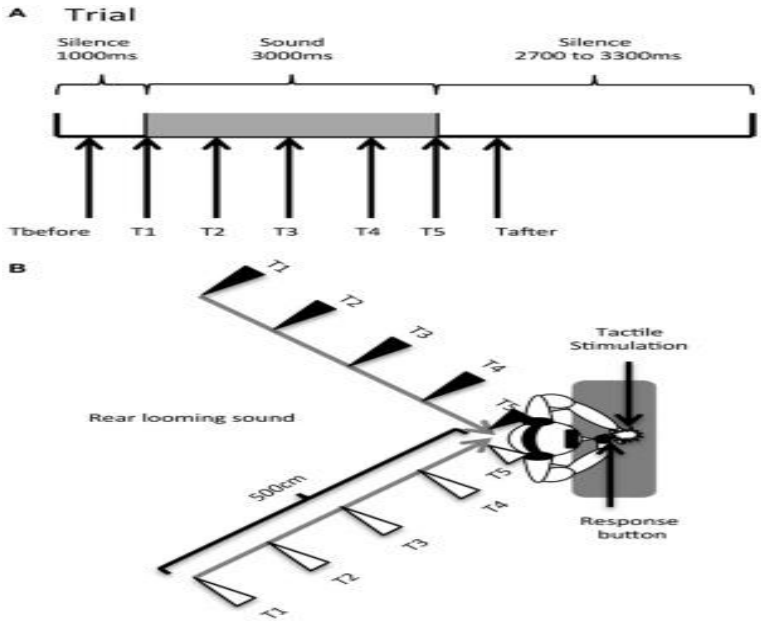

Figure 3.4 *Trial description (A) and experimental set-up (B) of the experiment by Taffou & Viaud-Delmon, 2014. Threatening or non-threatening auditory stimuli were perceived as moving towards the back of the subject, who received a tactile stimulation at different SOA. From Taffou & Viaud-Delmon, 2014.*

A similar result, again using a tactile detection protocol with acoustic stimuli moving towards the body, was also obtained by Ferri and colleagues (Ferri et al., 2015). Their two experiments allowed to confirm the extension of the limits of the PPS just described, both in the presence of artificial (whose physical properties aroused negative sensations) and ecological sounds (a woman screaming) with a negative value. However, these two results are in contrast with those concerning the reachability of threatening stimuli: in this second case, aversive stimuli are perceived as non-reachable at a shorter distance from the body than non-aversive stimuli (Coello et al., 2012; Valdés-Conroy et al., 2012). With reference to what has been discussed at the end of the previous chapter, this again seems to support the idea of a distinction between PPS and ARS.

Leaving the past chapters behind us, not all the studies in this literature adopted only stimuli with negative valence. Spaccasassi and colleagues, for example, have developed a tactile detection paradigm by associating touches with irrelevant visual stimuli with both positive and negative valence (see Figure 3.5). In particular, the authors demonstrated that the facilitation of the response observed when the visual distractor enters the peri-hand space is not only associated with threatening stimuli, but also with appetitive and neutral ones (Spaccasassi et al., 2019). On the contrary, positive and negative visual stimuli in the far space boosted the performance, whereas neutral stimuli did not. According to the authors, this is consistent with a vision of PPS as a space "of interaction", covering both the function of working and defensive space. According to this perspective, therefore, all the stimuli within the PPS would undergo enhanced visuo-tactile interaction, as both trigger a function of the PPS.

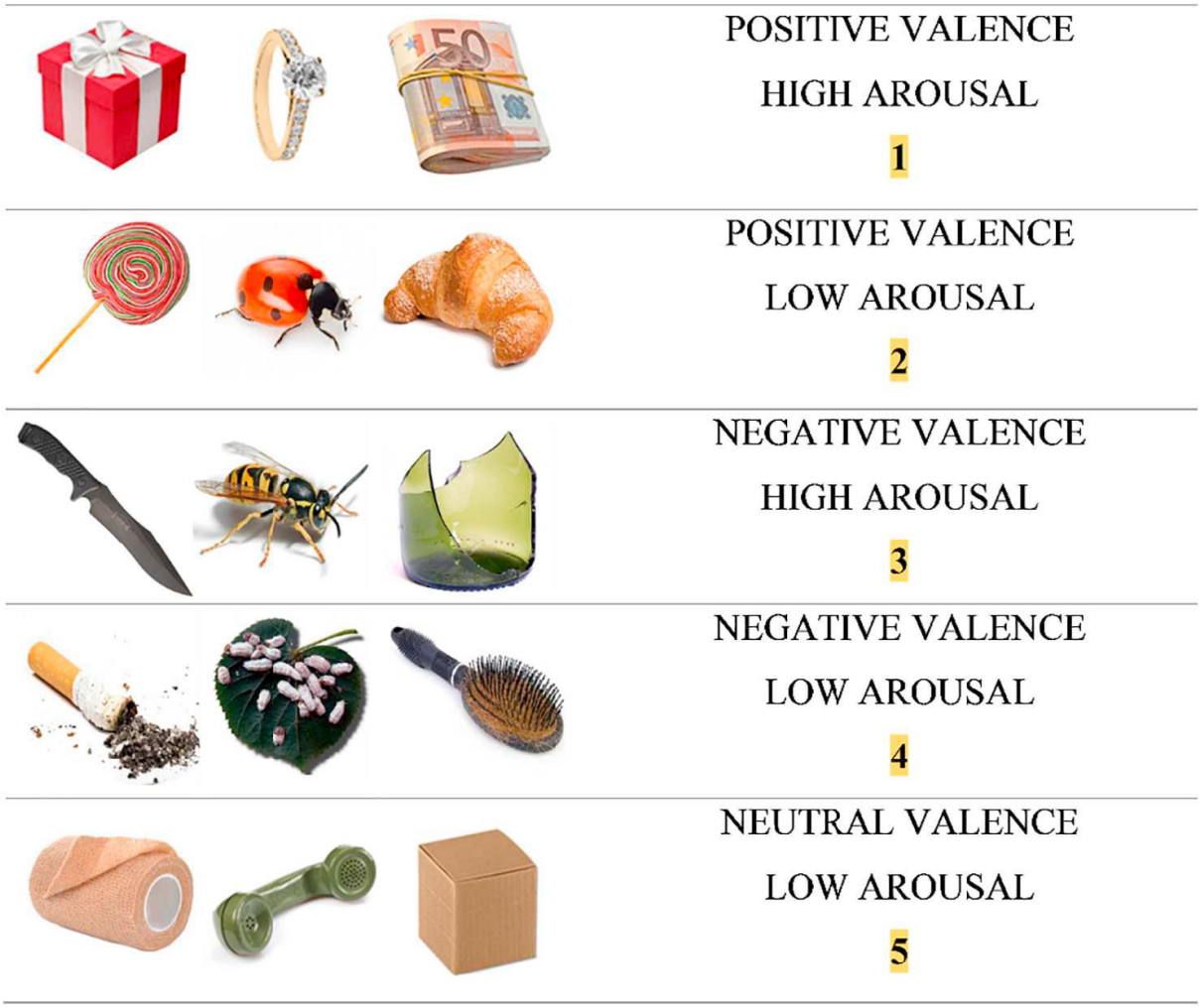

Figure 3.5 *Appetitive and aversive stimuli adopted in Spaccasassi et al., 2019. From Spaccasassi et al., 2019.*

More recently, the same research group has completed a study to demonstrate that stimuli of different valence affect working and defensive space in different ways (Spaccasassi et al., 2021). Using tactile stimuli applied to the hand associated with visual stimuli of positive or negative valence in looming towards it, the authors report a reduced extension of the PPS for positive stimuli compared to stimuli with negative valence. This result is associated with increased sensorimotor cortical activity, as measured by electroencephalogram (EEG), during the processing of tactile information coupled to visual stimuli with negative valence. On the other hand, the working space is investigated through a task of reachability judgment of stimuli with a positive or negative value, but no modulation emerges either at the behavioral or at the EEG level. However, for both these representations of space an effect of the distance of the visual stimulus from the hand emerges: closer visual stimuli elicited a weaker synchronization of μ power. These results are considered by the authors as possible evidence in support of the swiss-army knife model (de Vignemont & Iannetti, 2015): there is only one cortical representation of the space around the body, which is early influenced by the distance of the stimuli with respect to it. Defensive and working space, therefore, would be only two sides of the same coin, and the valence of a stimulus would affect only the later steps of the processing of sensory information within-PPS.

Approaching the more social nuance of PPS, in view of the next paragraph, Åhs and colleagues conducted a study to test a fear conditioning effect associated with 3D humanoid avatars (Åhs et al., 2016). In a first experiment, the authors used a virtual reality context to show that the presence of 3D avatars is able to influence the eye-blink startle response, considered a defensive reaction following the intrusion of stimuli and other people inside one's own PPS. In particular, the shorter the distance at which the avatar was presented, the stronger the defensive reaction was, in accordance with what has been observed and hypothesized by other studies of this line of research (Iachini et al., 2014, 2015). Of interest for this dissertation, the authors continued the study with a second experiment in which the presentation of an avatar (which we will define conditioned stimulus, or CS+) was linked to a transcutaneous electrical stimulus (the stimulus with innate aversive characteristics, or unconditioned stimulus, US). By measuring the skin conductance response (SCR, a typical measure used for the study of fear reactions), the authors observed the success of the conditioning process, as greater anticipatory fear responses were associated only with CS+,

but not with the avatar not coupled to electrical stimuli (CS-). Critically, in the subsequent test phase, the participants tended to halt the advance of the CS+ at a greater distance with respect to what happened for the CS-. This is interpreted by the authors as a demonstration of the fact that the acquired negative valence of a social stimulus influences the extension of the PPS, increasing it.

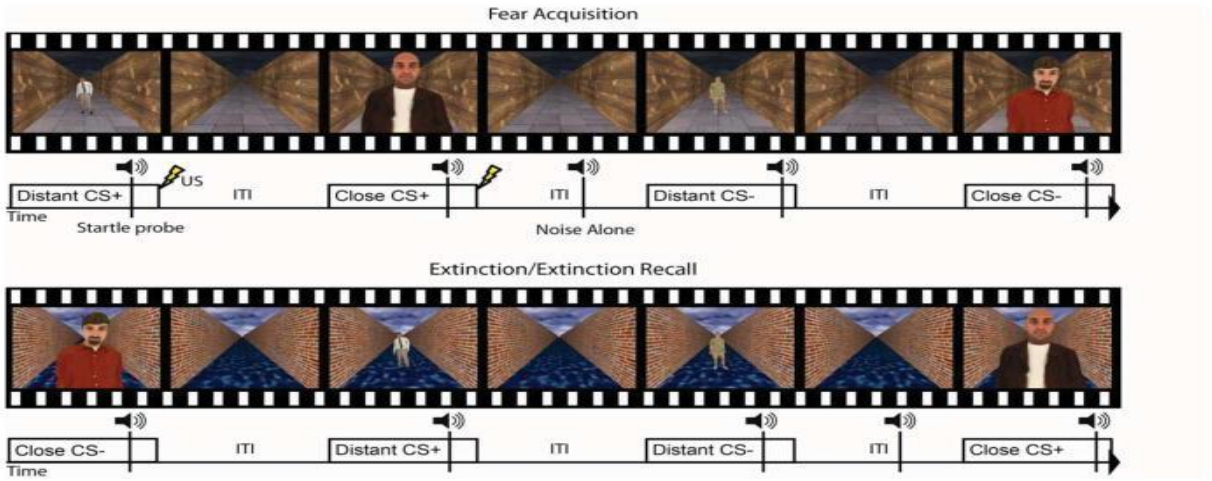

Figure 3.6 *Virtual context used by Åhs and colleagues. A virtual avatar could be presented in the space near the participant or away from it. One of these avatars (CS +) was associated with unpleasant transcutaneous electrical stimulation, while the other (CS-) was not associated with tactile stimulation. From Åhs et al., 2016*

These results clearly demonstrate that the processing of sensory information in the space around the body is not insensitive to higher-level characteristics of the stimulus, such as its positive or negative valence. In our daily experience we come into contact with numerous stimuli associated with specific values, which can be innate or acquired. A particularly important source of information for our social interactions is emotional expressions, which have an innate positive or negative value.

3.2 A space for emotions

Precisely because of their innate positive or negative value and their importance in our social interactions, the study of human emotions has elicited enormous interest over time. According to Ekman, primary emotions are a communicative tool with a cognitive and a physiological components, which developed by natural selection as an adaptive mechanism (Ekman, 2004). These emotions are defined as primary because of their universality: their manifestation involves expressive and physiological reactions that are undoubtedly

recognized by different peoples and cultures, even if they developed in total isolation (see Figure 3.7, Ekman & Friesen, 1971). Such primary emotions, according to Ekman's original model, include happiness, anger, fear, surprise, disgust and sadness (to which contempt has been added later), and it is on this range of emotions that, until today, the study of the relationship between emotional expressions and peripersonal space has focused its interest (see Bogdanova et al., 2021 for review).

Figure 3.7 *The six primary emotions of Ekman's original model, with some of the facial reactions typically related to them and universally recognizable.*

One of the first studies on the subject used a virtual reality context in which participants were asked to provide judgments of reachability and judgments of comfort referred to male and female virtual avatars with neutral, angry or joyful facial expressions (Ruggiero et al., 2016). In the passive approach condition, participants saw the avatar advancing towards them and had to stop its motion when they thought they could touch it (reachability judgment task) or when its distance became uncomfortable (stop-distance task, to evaluate the level of discomfort generated by the intrusion of the avatar in the participant's PPS). In

the active approach condition, the task was the same, but it was the participants who moved towards the avatar, stopping when they felt most appropriate. Results show that virtual avatars approaching with angry facial expressions prompted participants to maintain a greater distance than neutral or joyful expressions, both in terms of reaching and comfort judgments; in the active condition, however, this result was found only for the stop-distance task. This result seems to be consistent with what has been observed in studies investigating the influence of threatening stimuli on the representation of the PPS (Ferri et al., 2015; Taffou & Viaud-Delmon, 2014), in which an approaching threat induced an extension of the PPS. Probably this is due to the fact that anger is coded as a threatening stimulus, towards which it is necessary to take a wider margin of safety. Similar results were obtained by Cartaud and colleagues, who used the same tasks to investigate the effects of a human-like point-light avatar on electro-dermal activity (EDA), a physiological skin response often used as an index of emotional arousal (Cartaud et al., 2018). The avatars in this case did not have a real human body, but they were able to reproduce its biological movement; the face, however, was visible and could express anger, joy or have a neutral expression (see Figure 3.8). In addition to replicating the behavioral results of Ruggiero and colleagues (Ruggiero et al., 2016), the authors observed that the physiological response is influenced by the perceived emotional expression: the approach of an avatar with an expression of anger induces a 45% increase in the EDA response, while this increase is not observable in the case of neutral or happy expressions. Furthermore, the expression of anger perceived in the near space was associated with an EDA response 40% greater than that observed for neutral expressions, at the same distance. Thanks to this study it is possible to observe that the greater the arousal generated by the perceived emotional stimulus, the greater the distance of comfort maintained towards it, as if to indicate that more threatening stimuli induce the need to maintain a wider defensive space. And this effect is present also in the case of barely visible emotional facial expressions, such as those we can perceive in our daily experience walking on the street, in the corridors or in crowded places (Cartaud et al., 2020).

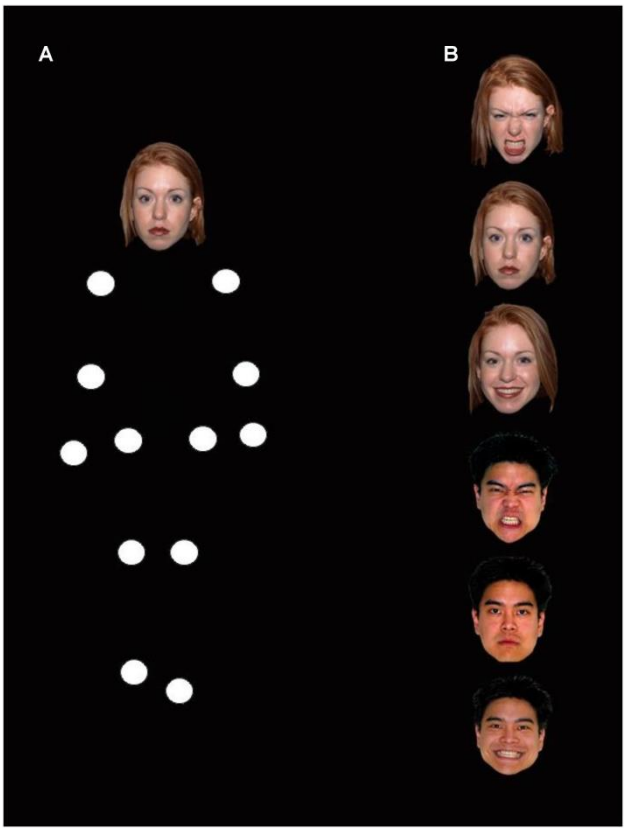

Figure 3.8 *Human-like point-light avatar adopted by Cartaud and colleagues. The male or female avatars could have neutral, angry or happy facial expressions, and they moved towards the participant crossing its frontal parallel axis on the right or left side. From Cartaud et al., 2018.*

A result that seems to go in the opposite direction comes from the study by Dureux and colleagues (Dureux et al., 2021). In a virtual reality context, participants saw male and female faces with angry, neutral or happy expressions presented statically at different distances from the face. The task in this case does not focus on distance, but requires discriminating the sex of perceived faces as quickly as possible. What is observed at the behavioral level is a faster and more accurate discrimination for faces with happy expressions presented in near space, compared to both neutral and angry faces. By fitting a Gaussian and a sigmoid curve to the data, in both cases a peak (Gaussian) or an inflection point (sigmoid) is observed closer to the body for angry faces, followed by faces with neutral expression and, associated with a greater extension of the PPS, happy faces. These results, observed both with correction of the stimuli for retinal size and without, thus in conditions of ecological visual perception, seem to indicate that expressions of anger are associated with a reduction in the extension of the PPS, contrary to what has been observed in the studies described above (Cartaud et al., 2018, 2020; Ruggiero et al., 2016). However, a first aspect to consider concerns the stimulations used (static faces against moving avatars and / or participants): the movement aspect could interact with the influences of emotional expressions, altering the results. The second aspect, on the other hand, have been already

extensively discussed in this manuscript: while Dureux and colleagues use a task that is not explicitly focused on the distance of stimulations, the previously described studies use reachability and comfort judgment tasks, focused on the spatial dimension. In fact, if we consider studies that used tasks similar to that of Dureux and colleagues, strong similarities are observed: Pellencin and colleagues, in a visual-tactile detection task, observe a greater extension of the PPS towards partners perceived as moral compared to others perceived as immoral (Pellencin et al., 2018). The opposite pattern, once again, emerges towards moral or immoral partners using a reachability or comfort distance task (Iachini, Pagliaro, et al., 2015). It is therefore likely that different tasks can capture different aspects and nuances of the PPS representation, and the visual unisensory task of Dureux and colleagues seems to capture the same features as other multisensory tasks (Pellencin et al., 2018). In addition to these behavioral measures, this study investigated two physiological responses: pupil dilation and heart rate. The first measure made it possible to record greater pupillary dilation in response to faces with expression of anger, and this increase in physiological response seems consistent with what was observed by Cartaud and colleagues (Cartaud et al., 2018, 2020). The second measure, recorded during a passive viewing task, instead reported an increase in heart rate in the presence of faces presented in the near space, but this measurement was not modulated by the emotional expression.

In a related study, Vieira and colleagues sought to investigate the neural basis of the regulatory response of interpersonal distance as a function of a wider range of emotions, and how this neural activity is modulated by different levels of empathy (Vieira et al., 2017). In this study participants had to perform three different tasks: the first was a computer-based stop-distance task with respect to faces that could express anger, happiness, sadness, fear, or neutrality; the second, in the fMRI scanner, required to provide a measure of discomfort following the perception of the same faces, approaching or moving away from the participant. Finally, after exiting the scanner, participants had to perform a stop-distance task with a real partner approaching or moving away. The results of the two stop-distance tasks are coherent and correlated with each other: a greater distance is observed for the looming stimuli than for the receding ones, with a strong modulation as a function of emotions. Particularly, negative emotions (anger, fear and sadness, in this order) pushed the participants to keep greater distances, while the expression of happiness brought back the

shorter distance. The same sequence is observed in the ratings of the perceived discomfort in the scanner, confirming that the greater negativity of the perceived expression pushes to maintain a wider margin of safety. Furthermore, these results are related to the level of empathy, but specifically for the expression of fear: the lower the participant's level of empathy, the shorter the distance maintained with respect to the frightened face. Finally, this study allowed to investigate the neural basis of these behavioral reactions. Confirming the greater salience of stimuli in looming towards the body compared to receding ones, greater activations for the approaching faces were found at the level of the amygdala, inferior and superior parietal lobule, insula, prefrontal cortex and occipital, temporal and parietal visual cortices, independently by the displayed emotion. An interesting aspect, however, concerns the cerebral activations at the level of the dorsomedial prefrontal cortex, of the orbitofrontal cortex, of the temporo-parietal junction (inferior parietal lobule and supramarginal gyrus in particular) and of the bilateral insula: in these regions, faces of anger or joy elicited a maximal response (for the insula, only for looming faces). It is therefore interesting to observe that anger and happiness, the two emotions related respectively to maximum and minimum distance and maximum and minimum discomfort, similarly modulate the activity of prefrontal regions, of the temporo-parietal junction and of the insula. This seems to be evidence in support of the dual approach / avoidance function of the PPS: while anger can be considered a threatening stimulus, to be avoided, the expression of happiness stimulates interaction, a form of approach.

Of particular interest in the study that will be presented at the end of the chapter is the reaction to a particular emotion: *fear*. As previously described, a pre-existing fear can influence the representation of the peripersonal space, expanding it (A. M. de Haan et al., 2016; Taffou & Viaud-Delmon, 2014). The same can happen for those forms of fear induced by conditioning, making an initially harmless stimulus a threat (Åhs et al., 2016). Finally, also on a social level, the perception of an expression of fear has an important adaptive meaning: a frightened face close to us communicates the proximity of a threat that we cannot yet see, and therefore pushes us to explore the surrounding space in order to anticipate the danger (Ellena et al., 2020).

But what happens in our brain when we are scared?

3.3 Fear learning and its neural correlates

Considering the dynamism and richness of the world around us, the ability to learn in a flexible way the threatening or appetitive character of a stimulus is an essential advantage for survival. It is thanks to a mechanism of this type that, as children, we learn that the flame of the candles on the cake is not something pleasant to touch. Once the flame-pain pairing has been learned, we don't need to repeat the experience or ask ourselves if the next candle will hurt as much as the first: we are able to create associations between stimuli and consequences and store them in memory, in order to recognize the future threat based on what we have learned. The “switch” that allows us to "recall" the unpleasant experience whenever we encounter such a threatening stimulation is fear.

This emotion, as often happens, has marked and easily identifiable physiological responses, which can occur with greater or lesser intensity: dry mouth, sweating, heart pounding, tension in the chest and gastrointestinal sensations are just some of the markers that characterize the expression of fear. The pattern of autonomic responses, on the other hand, consists of a strong activation of the sympathetic nervous system, which induces an accelerated heartbeat, peripheral vasoconstriction, increased skin transpiration and increased electrodermal activity (Harrison et al., 2013; see Garfinkel & Critchley, 2014 for review). As we have already noted, the measure of these responses is often used as an index of the intensity of the emotions experienced by the participants (Åhs et al., 2016; Cartaud et al., 2018, 2020; Dureux et al., 2021).

Fear fills a highly adaptive role, allowing us to recognize and avoid stimuli that are dangerous for our safety. To be adaptive, however, the fear-learning system must be flexible: in the course of life we will experience and come into contact with very different stimuli and events, and it is therefore essential to have a mechanism capable of creating and modifying associations between different stimuli to develop new fears or eliminate some obsolete ones. It is for this reason that one of the most studied aspects of human fear is how new fears can be learned, what is the cognitive mechanism underlying such learning and what its consequences are.

One of the most used paradigms for this purpose is certainly fear conditioning (Pavlov, 1927; Rescorla, 1988; and see Duits et al., 2015; and Suarez-Jimenez et al., 2020 for meta-analyses on the effects of fear conditioning in patients with anxiety disorders). In a protocol of this type, an initially neutral stimulus, which we will call conditioned stimulus (CS), is associated with another capable of spontaneously eliciting a response: the unconditioned stimulus (US). For example, whenever we apply a small electric shock (US) to the participant's hand, we present a red light (CS) that anticipates his arrival. If initially the participants are afraid of the electric shock, due to the unpleasant tingling, with the repetition of its association with the visual stimulus they will begin to show physiological reactions of fear as soon as they perceive the red light. This happens thanks to the creation of an associative link between CS and US: the light "means" shock. However, for the formation of this associative bond to be successful, certain circumstances are fundamental. First, the CS must be informative: if visual stimulus and shock are two associated and contiguous events, but uncorrelated in time, it will be impossible to establish a relationship between them. Conversely, if the presence of CS is temporally informative of the presence of US, the conditioning process will be successful (see Figure 3.8, Rescorla, 1968, 1988). The strength of a conditioning effect, therefore, depends on how many occurrences of the US happen during the presentation of the CS, but also on how many occurrences of the US occur outside that presentation. If the probability of receiving the shock during and outside the presentation of the red light is the same, there will be no valid reason to associate the two stimuli, and therefore there will be no associative learning (Rescorla, 1968). The temporal contiguity of CS and US, therefore, is a necessary but not sufficient condition for associative learning (see Rescorla, 1988 for review).

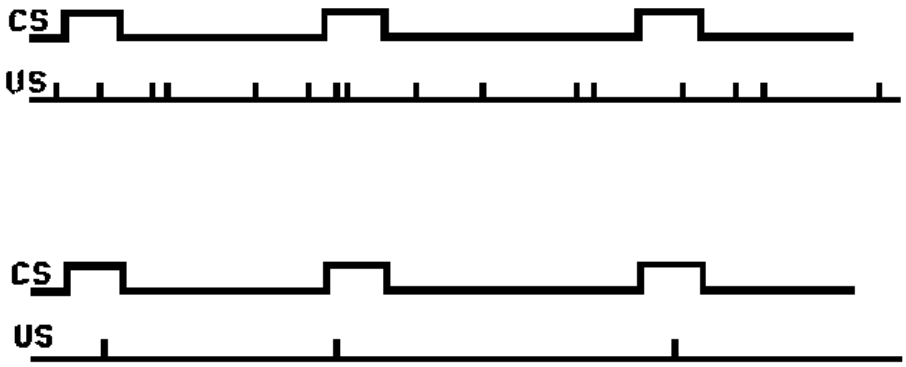

Figure 3.9 *Schematic representation of two possible temporal relationships between conditioned and unconditioned stimuli (CS and US respectively). In the upper scheme, a temporally non-informative relationship: the US can arrive in an unpredictable way when the CS is present or when it is absent. In this case, no conditioning effect. In the lower scheme, however, the relationship between the two stimuli is informative: the US is applied only in the presence of the CS, whenever the latter is present. In this case, conditioning will be successful. From Rescorla, 1988*

Once fear conditioning has been successful, the presentation of the CS alone will therefore be able to elicit the same physiological responses produced by the US. However, the repetition of the conditioned stimulus not associated with the electric shock will lead to a phenomenon of *extinction* of the learned fear: multiple occurrences of CS, deprived of the threat of the US, will induce a more or less rapid loss of the physiological response of fear. This extinction is an adaptive mechanism, which allows us to inhibit the defensive reaction in the face of obsolete, no longer current threats. During the extinction process, indeed, fear memories are not eliminated, but rather replaced with a inhibitory safety memory that can be specific to a context or type of stimulus (Quirk, 2002). The failure of the extinction of these fears, indeed, is considered a source of excessive fear at the basis of anxiety disorders (Cooper & Dunsmoor, 2021; Duits et al., 2015; Marin et al., 2017; Milad & Quirk, 2012; Suarez-Jimenez et al., 2020). Another phenomenon linked to the conditioning of fear, and which can lead to pathology, is *generalization*. This phenomenon is usually adaptive, as it allows us not to have to touch all the flames we encounter to remind us of the unpleasant effects of the first candle. However, an over-generalization can induce conditioned fear reactions towards a set of non-threatening stimuli, linked to CS only for some more or less marked similarity aspects. As with failed extinction, over-generalization can also cause pathological levels of anxiety (Craske et al., 2009; Ehlers & Clark, 2000; Foa et al., 1989; and see Webler et al., 2021 for review).

At the neural level, neuroimaging studies in humans revealed a strong bilateral involvement of the amygdala (Dunsmoor et al., 2007; Fischer et al., 2000; Herry & Johansen, 2014; LaBar et al., 1998; and see Sehlmeyer et al., 2009 for a meta-analysis) in the formation of conditioned fear, and this result is in line with what has been observed in animal models (Herry & Johansen, 2014; LeDoux, 1996). Most of the results concerning the neural basis of fear learning through conditioning, indeed, come from studies on rats. In particular, it has been observed that the response from the amygdala tends to decrease over time, with the succession of presentations of the conditioned and unconditioned stimuli (Fischer et al., 2000; LaBar et al., 1998; Phelps et al., 2001). This time-dependent effect seems to confirm that the formation of the initial association between CS and US occurs at the level of the amygdala, and that its response tends to decrease once the link is established.

It therefore seems legitimate to affirm that the cardinal structure of the neural circuit underlying the fear learning processes is the amygdala. Evidence from studies on humans and rats shows that its lateral nucleus (LAn) represents an important site of neural plasticity through which fear learning takes place (Davis & Whalen, 2001; Ehrlich et al., 2009; Fanselow & Poulos, 2005; LeDoux, 2000; Maren & Quirk, 2004; Pape & Pare, 2010). The neurons of this nucleus, which receive auditory, somatosensory and nociceptive multisensory information (Johansen et al., 2010; Romanski & LeDoux, 1993; Uwano et al., 1995), have connections with the auditory thalamus and other areas of the cortex which are reinforced during fear learning processes (Davis & Whalen, 2001; Ehrlich et al., 2009; Fanselow & Poulos, 2005; LeDoux, 2000; Maren & Quirk, 2004; Uwano et al., 1995). It is thanks to these projections that the integration between the information of the CS and the US can take place, and this explains the response evoked by the presentation of the CS at the level of the LAn and the basal nucleus of the amygdala (BAn), directly connected to the above (Aggleton, 2000; Amano et al., 2011; Herry et al., 2008; Pitkänen et al., 1997).

Furthermore, the amygdala is not only a destination for sensory information from the thalamus, neocortex, hippocampus and olfactory cortex, but also a starting point for projections to brain structures involved in the activation of fear reactions, such as the bed nucleus of stria terminalis for the activation of stress neurons, the lateral hypothalamus for the activation of the sympathetic nervous system or the periaqueductal gray for the freezing responses (LeDoux, 1996).

Its importance is such that amygdala lesions can cause impaired recognition of facial expressions of fear (Adolphs et al., 1994) and a deficit in fear conditioning (LaBar et al., 1995). This is consistent with the results obtained from neuroimaging studies on healthy humans, which report a greater activation of this structure during the presentation of fearful faces (Morris et al., 1996) or during fear conditioning protocols (Knight et al., 1999; LaBar et al., 1998).

Although the amygdala thus appears to be the pivotal structure and the gateway to the neural network underlying fear conditioning and the expression of fear (see J. J. Kim & Jung, 2006 for review), other subcortical structures and regions of the cortex are involved. A prime example is the cortex of the insula, directly interconnected with the amygdala (Büchel, 2000; Sehlmeyer et al., 2009) and involved in the consolidation of fear memories (Bermudez-Rattoni et al., 1991).

The hippocampus also seems to be involved in some types of conditioned fear memory, and in particular in the memory of contextual cues; the evidence supporting this hypothesis derives mainly from studies on rats, and shows that hippocampal lesions can preclude the retention capacity of contextual CSs during a fear conditioning process, while discrete cue conditioning does not suffer any deficit (Anagnostaras et al., 1999; Burwell et al., 2004; J. J. Kim & Fanselow, 1992; Maren et al., 1997). However, considering that different subregions of the hippocampal cortex are involved in different behavioral aspects - e.g. spatial-related behaviors are more related to the subdorsal region, while anxious behaviors seem more a specificity of the ventral subregion (see Bannerman et al., 2004 for review), it is conceivable that different aspects of fear conditioning may involve different subregions of the hippocampus. The perirhinal cortex, connected to the hippocampus, seems to be involved in the early consolidation and storage of contextual memory processed by this latter (Bucci et al., 2000; Burwell, Bucci, et al., 2004), causing the same deficit in contextual fear memory in case of damage (Bucci et al., 2002, 2021).

Finally, always from rat models, there is evidence in favor of the involvement of the cerebellar vermis in the implementation of autonomic and behavioral responses to external threats. Crucially, lesions of the vermis cause an abolishment of the conditioned autonomic response (the modulation of the heart rhythm in particular) without affecting the unconditioned responses (Supple & Leaton, 1990) and producing an inhibition of the

freezing behavior in front of predators (Supple et al., 1987). In rabbits, the recording of vermis neurons activity showed more marked responses in the presence of informative (CS+) rather than non-informative (CS-) auditory stimuli; this activation also correlated with the magnitude of the conditioned autonomic response (Supple et al., 1993). These results appear to support the involvement of cerebellar vermis in modulating fear-related behaviors.

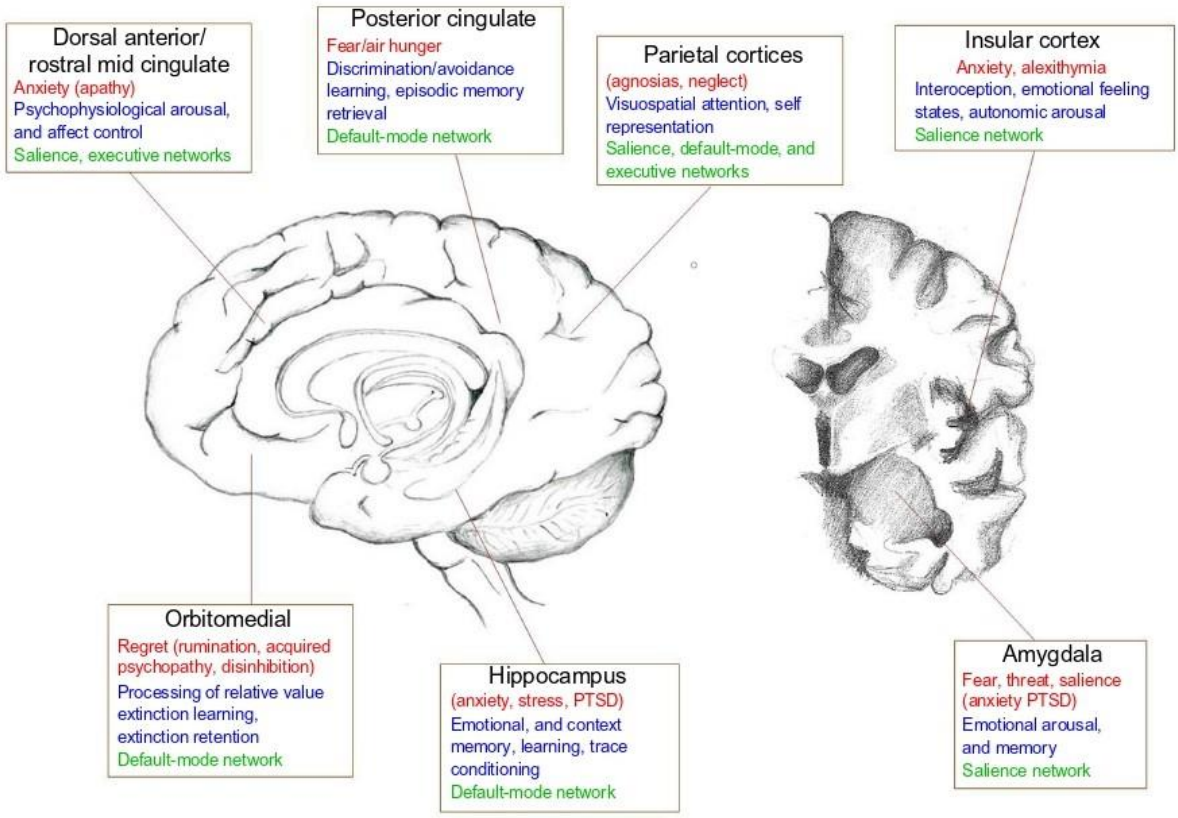

Figure 3.10 *Diagram showing the brain areas involved in fear learning, fear memory and fear extinction processes. In red the contribution of the different areas to specific fear processes, in blue their general involvement in the cognitive and / or affective processing of information. In green, finally, the belonging of these regions to different networks, such as the salience network (regulation of dynamic changes in the activity of other brain networks) or the default network (brain activity during the state of rest). Abbreviation: PTSD - post traumatic stress disorder. From Garfinkel & Critchley, 2014.*

While all the regions described are involved in different aspects of fear conditioning, from the formation of CS/US associations, to the consolidation of fear memory up to the implementation of behavioral and autonomic responses, the extinction of fear learning seems to require the involvement of more frontal areas. As described above, when CS is no longer predictive than US, that stimulus no longer poses a threat, and the memory of the CS-

US association is actively inhibited (see Myers & Davis, 2002 for review). Considering the role of the prefrontal cortex (PFC) in the inhibitory control of maladaptive behaviors, it is likely to find the key area for the inhibition of the conditioned fear response in this region. The existence of inhibitory projections directed towards subcortical structures such as amygdala and hypothalamus (Fuster, 2015), able to reduce the neural response of the latter (Quirk et al., 2003; Rosenkranz & Grace, 2001, 2002) and conditioned behavioral response (Milad et al., 2004; Milad & Quirk, 2002) supports further this hypothesis. Also in humans, activation of PFC inhibits the activity of amygdala neurons (Kim et al., 2003; Ochsner et al., 2002), thus supporting the idea of a distinction between neural networks for fear learning and fear extinction.

Considering the adaptive importance of fear and its defensive function, some studies have already begun to investigate the relationship between this emotion and the representation of peripersonal space. As described above, specific phobias can induce a modulation of the extent of PPS (A. M. de Haan et al., 2016; Taffou & Viaud-Delmon, 2014), as well as high levels of anxiety (Lourenco et al., 2011; Sambo & Iannetti, 2013). Even in the absence of a pre-existing phobia, threatening stimuli can alter the processing of multisensory information in the space around the body (Ferri et al., 2015; Somervail et al., 2019). Finally, even initially neutral stimuli can undergo re-evaluation processes following fear conditioning, and thus be able to influence the PPS representation (Åhs et al., 2016).

However, all of these studies directed the employed threatening stimuli towards a part of the body (hand or head especially) that did not change its position in space. Since the body-part centered reference frame is a fundamental feature of the PPS, if the encoding of threatening stimuli and the learning of new associations between CS and US take place within this spatial representation, we should expect a hand-centred fear learning, that can be revealed, for example, through the remapping of the physiological response of fear (i.e. the increased skin conductance response). The "value" of a threat, indeed, is not the same for all the parts of the body, increasing as the distance with a specific body-part decrease. It would therefore be crucial for the PPS representation to take into account the position of the threatening stimuli as a function of the location and movements of the different parts of the body.

To test this hypothesis, we used a fear conditioning protocol in which initially neutral visual stimuli (CS) are associated with unpleasant electrocutaneous stimulations, but only when presented near the position of the threatened hand. In this way, we could investigate the effect that the movement of the hand can have on the CS / US association thus created.

Associative learning in peripersonal space: Fear responses are acquired in hand-centred coordinates

(Journal of Neurophysiology, 2021)

J Neurophysiol 126: 864–874, 2021.
First published August 11, 2021; doi:10.1152/jn.00157.2021

american physiological society

JNP JOURNAL OF NEUROPHYSIOLOGY

RAPID REPORT

Higher Neural Functions and Behavior

Associative learning in peripersonal space: fear responses are acquired in hand-centered coordinates

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Abstract

Space coding affects perception of stimuli associated to negative valence: threatening stimuli presented within the peripersonal space (PPS) speed up behavioral responses compared with nonthreatening events. However, it remains unclear whether the association between stimuli and their negative valence is acquired in a body part-centered reference system, a main feature of the PPS coding. Here we test the hypothesis that associative learning takes place in hand-centered coordinates and can therefore remap according to hand displacement. In two experiments, we used a Pavlovian fear-learning paradigm to associate a visual stimulus [light circle, the conditioned stimulus (CS)] with an aversive stimulus (electrocutaneous shock) applied on the right hand only when the CS was displayed close (CS+) but when not far from it (CS−). Measuring the skin conductance response (SCR), we observed successful fear conditioning, with increased anticipatory fear responses associated with CS+. Crucially, *experiment I* showed a remapping of these responses following hand displacement, with a generalization to both types of CS. *Experiment II* corroborated and further extended our findings by ruling out the novelty of the experimental context as a driving factor of such modulations. Indeed, fear responses were present only for stimuli within the PPS but not for new stimuli displayed outside the PPS. By revealing a hand-centered (re)mapping of the conditioning effect, these findings indicate that associative learning can arise in hand-centered coordinates. They further suggest that the threatening valence of an object also depends on its basic spatial relationship with our body.

NEW & NOTEWORTHY Associative fear learning takes place in hand-centered coordinates. Using a Pavlovian fear-learning paradigm, we show that the anticipatory skin conductance response indicating the association between the negative value and an initially neutral stimulus is acquired and then remapped in space when the stimulated body part moves to a different position. These results demonstrate the relationship between the representation of peripersonal space and the encoding of threatening stimuli. Hypotheses concerning the underlying neural network are discussed.

associative learning; fear learning; hand-centered space; peripersonal space; skin conductance

INTRODUCTION

The portion of space close to our body, termed peripersonal space [PPS (1)], represents a safety zone against close or threatening approaching stimuli (2–4). Early studies in nonhuman primates revealed that fronto-parietal neurons code for objects in this region thanks to multisensory receptive fields (RFs), displaying tactile RFs centered on a specific body part (e.g., the hand) and visual ones overlapping and anchored to them (1, 5–8). Neuroimaging evidence in humans highlighted a similar circuit involving the ventral and anterior intraparietal sulcus, the ventral and dorsal premotor cortices, and the putamen (9–15), dedicated to the integration of visual, tactile, and proprioceptive signals in body part-centered reference frames. PPS interfaces perception to action, allowing us to protect our body and interact with the surrounding environment. This view is supported by behavioral evidence: responses

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Submitted 6 April 2021 / Revised 27 July 2021 / Accepted 27 July 2021

to touches delivered to parts of the body are boosted when a visual stimulus is presented near compared to far from them (16, 17). This feature allows PPS to support both goal-directed reach-to-grasp actions and rapid detection of near threats. Threatening stimuli within PPS can be more dangerous, their proximity to the body coming with reduced time available to react. Accordingly, anticipating the position of a threat with respect to our body would spare time to respond (18). Several studies have documented the relationship between aversive stimuli and PPS representation: be it acoustic (19, 20) or visual (16, 21), perception of a negatively connoted stimulus within PPS is boosted, in keeping with other behavioral (22, 23) and neural (24–28) findings. Thus, there is evidence that threatening stimuli are encoded according to their distance from the body (21, 24). However, a critical question remains open: does the association of a negative valence to a stimulus occur within a body part-centered reference frame? If this were true, one would predict that a learned association would remap as a function of the displacement of the body part involved. This would indicate a role of PPS representation in associative learning, implementing an efficient mechanism to encode threats close to the body.

To test this hypothesis, we ran two experiments adopting a Pavlovian associative learning protocol assessing whether humans learn the negative value of a stimulus within a reference frame centered on a specific part of the body (e.g., the hand). In particular, we used associative fear learning, where an initially neutral stimulus [conditioned stimulus (CS)] is associated with an aversive stimulus [unconditioned stimulus (US)]. After repeated associations, the presentation of the CS alone begins to produce in the subject the autonomic responses generally produced by the US.

MATERIALS AND METHODS

Participants

Twenty-one (12 females; mean age ± SD: 26.6 ± 3.44 yr) and forty-one (28 females; 24.8 ± 4.87 yr) participants took part in *experiment I* (within-subject design) and *experiment II* (between-subject design), respectively. Two subjects were excluded because they were nonresponders [no skin conductance response (SCR) fluctuation]. All participants reported normal/corrected-to-normal vision, normal tactile sensitivity, and no history of psychiatric disorders. Except for two left-handed and one ambidextrous participant in *experiment II*, all participants were right-handed by the Edinburgh handedness test. They gave their written informed consent before the study, which was approved by the national French ethics committee (CPP SUD EST IV France) and was in line with the Declaration of Helsinki.

Stimuli and Apparatus

Participants sat at a table, in a dark room, with the head on a chinrest (30 cm high). A projector (Panasonic PT-LM1E_C) controlled by Presentation displayed visual stimuli on the table. A fixation cross (2.5 cm) was projected aligned to the participant's sagittal axis. Two-dimensional (2-D) circles (diameter 2.5 cm, duration 6 s) were presented in either a yellow (CS_{yellow}; RGB = 0,255,127) or purple (CS_{purple}; RGB = 255,0,127) hue, in one of two visual positions, 20 cm to the right (CS_{yellow_right}, CS_{purple_right}) and to the left (CS_{yellow_left}, CS_{purple_left}) of the body's sagittal axis, respectively, equidistant from the fixation cross and 20 cm from the participant's body (Fig. 1). Depending on the condition, either color was associated with a US, an electrocutaneous stimulation (2,000 μs, 400 mV) delivered to the right index finger via a constant-current stimulator (DS7A; Digitimer, UK) through a pair of disposable pregelled electrodes (1.5 × 1.9 cm, Neuroline; Ambu, Denmark). Intertrial interval jittered between 12 and 15 s (21, 22, 29).

We recorded the SCR signal through Ag/AgCl electrodes (EL507; BIOPAC, Goleta, CA) filled with isotonic gel (0.5% chloride salt) and applied on the second phalanx of the second and third fingers of the left hand, placed under the table on an armrest. A MP-150 BIOPAC Systems SCR module amplified this signal, recorded at a rate of 1,000 Hz.

Procedure

Participants had to stare at the fixation cross during *experiment I*, involving three phases: familiarization (8 trials), learning (48 trials) and test (24 trials).

As illustrated in Fig. 1, the right hand was placed ipsilaterally on the table, 24 cm rightward of the sagittal body's axis, during the familiarization and learning phases. In the test phase, the hand was moved 16 cm to the left of the sagittal body's axis, granting an identical distance between hand and CS across postures (4 cm).

Before familiarization, the intensity of tactile stimuli was set through an ascending staircase procedure: participants had to judge tactile shocks with a number between 1 (not unpleasant) and 7 (very unpleasant but not painful). At each stimulation, intensity was increased by steps of 1 μA. The procedure terminated when the participant judged the unpleasantness at 7 for two consecutive pulses, and the corresponding intensity was applied during the learning phase. If participants judged the stimulation as "painful," intensity was decreased in 0.5-μA steps, until a double evaluation of "7" was reached. The mean intensity was 8.9 ± 5.6 μA (mean ± SD) for *experiment I* and 7.5 ± 4.1 μA for *experiment II*.

The familiarization phase had a twofold purpose: familiarizing participants with the procedures and obtaining color and position SCR baselines. Two stimuli per color and position were presented, without any tactile stimulation.

In the learning phase, the conditioned color (CS+) was counterbalanced across participants. Twelve repetitions of each color were randomly displayed in the right (close to the hand) and left (far from the hand) visual positions. In ~80% of the CS+ hand-close trials, this visual stimulus was associated with the US (10 of 12 trials). Since the duration of the US was 2 ms, in these trials the onset of the US occurred 5.998 s after the onset of the visual stimulus. Four CS types are therefore defined: $CS+_{right}$, $CS+_{left}$, $CS-_{right}$, and $CS-_{left}$. Both the CS− and $CS+_{left}$ were never associated with the US.

In the test phase, visual stimulation was identical, but the hand was positioned close to the circles presented on the left side. It should be noted that no electrocutaneous stimulation was delivered during this phase, making any variation of the

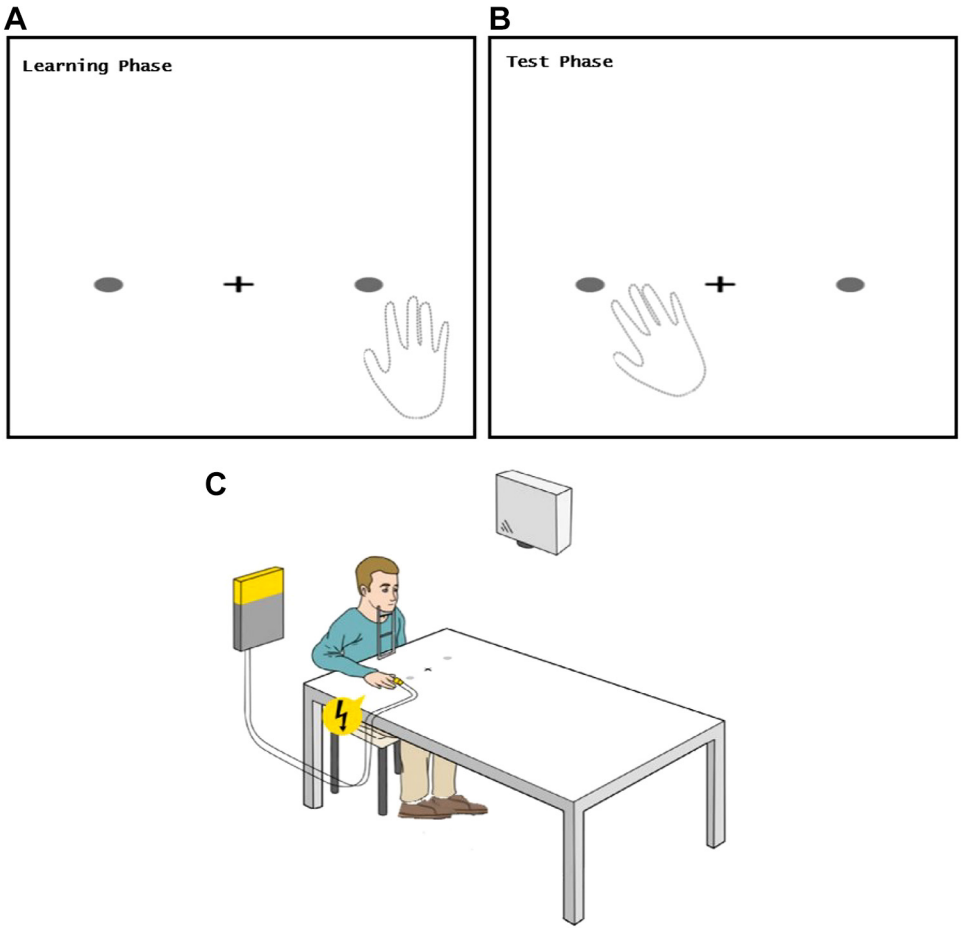

Figure 1. Experimental setup. *A*: positions of right hand, fixation cross, and visual stimuli during learning phases of *experiments I* and *II* and in the 2nd test phase of *experiment II*. *B*: positions of right hand, fixation cross, and visual stimuli during the test phase in *experiment I* and the 1st test phase in *experiment II*. *C*: representation of the experimental setup during learning phases. Tactile stimulation in this phase was applied to the right index finger and was associated to conditioned stimuli (CS+) such that tactile offset corresponded to visual offset.

SCR due only to the previously learned association. Six repetitions per CS type were randomly presented.

Before the learning phase, participants were warned of the possible presence of tactile stimuli but had no information about the CS/US contingency. At the end of the test phase, participants were debriefed.

In *experiment II*, visual and tactile stimuli were identical to *experiment I*, but participants underwent five phases: familiarization (4 trials), 1st learning (24 trials), 1st test (6 trials), 2nd learning (24 trials), and 2nd test (6 trials). Their right hand was placed ipsilaterally during the familiarization, the learning phases, and the 2nd test phase (Fig. 1). In the 1st test phase, their hand was placed on the same left position as *experiment I*.

Similarly, in the two learning phases, 12 repetitions of the visual stimulus of the selected color were presented in each position of visual stimulation (12 CS_{right}, 12 CS_{left}). Only CS_{right}, presented close to the hand, coterminated in 80% of cases (10 of 12 trials) with the US (CS+), whereas CS_{left} was never associated with it (CS−).

In the 1st test phase, as in *experiment I*, participants had their right hand close to the left visual positions. Depending on the group, six repetitions of the same CS were presented close to the hand (in the same left position as the learning phases) or 40 cm farther away (to ensure the same distance previously existing between the right and left stimulations). This between-subjects design allowed subjects to experience stimulation either within or outside the perihand space. In the 2nd test phase, six repetitions of the CS were presented near or 40 cm far away from the right hand (depending on the group of the 1st test phase), positioned ipsilaterally. Thus, we replicated the experimental conditions of the 1st test phase in terms of distance of visual stimuli from the hand. However, in this test phase visual stimuli were of the opposite color to the conditioned one: if the participant had been shown only yellow stimuli now the visual stimuli were purple, and vice versa.

Analyses

Experiment I.

Trials were averaged to obtain four scores per participant (CS_{yellow_right}, CS_{purple_right}, CS_{yellow_left}, CS_{purple_left}). Separate analyses were performed for each phase on SCR waveforms with AcqKnowledge software. We measured the SCR for each trial as the base-to-peak amplitude difference in skin conductance (in microsiemens) in the 0- to 6-s time window following CS onset. The recorded SCR waveform was smoothed at 100 points and then resampled at 15 samples/s; then, raw SCR scores were square-root transformed to normalize the distribution (29), and then, to reduce variance due to individual differences, we divided these scores by the participant's maximal response (30, 31).

To estimate baseline SCR, we performed a Color (yellow/purple) × Side (left/right) repeated-measures ANOVA on

square-root SCR scores in the familiarization phase. In both the learning and testing phases, we carried out a first ANOVA with Color (yellow/purple) as factor to verify possible SCR differences related only to the chromatic aspect. Subsequently, we performed a Side (left/right) × Association (CS+/CS−) × Trial (from 2 to 12) repeated-measure ANOVA on SCR scores of the learning phase, excluding the first trial of each condition in order to analyze only the responses following the subject's first experience with electrocutaneous stimulation. In the test phase, considering the rapid extinction of this kind of conditioning effect (32–34), we performed a Trial (from 1 to 6) × Side (left/right) × Association (CS+/CS−) ANOVA on the SCR scores.

Experiment II.

Preprocessing of SCR data was identical to *experiment I*. Because the between-subject design may require us to compare potentially different absolute values, we performed a preliminary ANOVA on the individual maximum values in response to stimuli falling near and far from the hand in the two test phases, with Position (close/far) and Phase (1st test/2nd test) as between and within factors, respectively. This revealed a significant main effect of Position ($F_{1,38}$ = 6.31, P = 0.02, η_p^2 = 0.143), confirming that the maximum SCR obtained with Far stimulations (mean ± SE = 0.12 ± 0.03) was lower than that of Close stimulations (0.24 ± 0.03). Because of this, and at odds with *experiment I*, here the square-rooted SCR (not divided by the maximum value) was entered into the analysis and averaged to obtain, depending on the experimental phase, two average scores per participant: CS_{right}/CS_{left} or CS_{close}/CS_{far}

As in *experiment I*, we ran a repeated-measure ANOVA on SCR values of the familiarization phase, considering Position (left/right) as within factor and Color (yellow/purple) as between factor. This analysis allows assessment for possible differences before the conditioning process, related to basic spatial or chromatic aspects.

For the same reason, we performed a *t* test to compare the effect of Color between groups in each learning phase. We then performed an ANOVA with Position (left/right) and Trial (from 2 to 12) as within factors on SCR scores, excluding the first trial of each condition in order to analyze only the responses following the subject's first experience with US.

In the 1st and 2nd test phases we performed an ANOVA on square-rooted SCR scores with Position (close/far) and Trial (from 1 to 6) as between and within factors, respectively.

Data and materials are available online (https://osf.io/ryhms/?view_only=9bbd1a5d84ff4b2c9a7568ba1bd0da9f).

RESULTS

Experiment I

In the familiarization phase, no significant main effect (Color: $F_{1,19}$ = 0.41, P = 0.53; Side: $F_{1,19}$ = 1.82, P = 0.19) or interaction (Color × Side: $F_{1,19}$ = 0.94, P = 0.34) emerged, indicating comparable amounts of SCR for stimuli differing in color or position before conditioning.

In both learning and test phases, the ANOVA on Color reported nonsignificant effects (learning: $F_{1,19}$ = 2.12, P = 0.16, test: $F_{1,19}$ = 0.04, P = 0.85). We thus collapsed the two levels of this factor in the subsequent analyses, investigating the differential impact of CS+ and CS− independently of color. In the learning phase, the ANOVA highlighted significant main effects of Side ($F_{1,19}$ = 15.35, P < 0.001, η_p^2 = 0.45), Association ($F_{1,19}$ = 7.83, P = 0.01, η_p^2 = 0.29), and Trial ($F_{3.83,72.82}$ =5.64, P < 0.001, η_p^2 = 0.23). Considering the trial, post hoc comparisons corrected for false discovery rate (FDR) showed higher responses for the second trial compared with all the others (all P < 0.05 except 2nd trial vs. 3rd trial, P = 0.07). The response trend is similar between the four stimulation combinations (Side × Association; Fig. 2*C*). Furthermore, Side and Association interacted ($F_{1,19}$ = 5.94, P = 0.02, η_p^2 = 0.24): FDR-corrected post hoc comparisons showed higher SCR for CS+ on the right (mean ± SE = 2.97 ± 0.46) compared with those on the left (2.36 ± 0.38, P < 0.001) but no difference for CS− (P = 0.13; Fig. 2*A*). This confirms the emergence of a conditioning effect, specific to the CS+ displayed close to the hand.

We then analyzed the test phase to ascertain the hand-centered mapping of this effect. In the Trial × Side × Association ANOVA, the only significant term, observed for the first trial (P = 0.002; Fig. 2*D*), was the Trial × Side interaction ($F_{3.93,74.69}$ = 3.45, P = 0.01, η_p^2 = 0.15), revealing that early stimuli presented on the left now evoked a greater SCR (mean ± SE = 5.83 ± 0.86) than those presented on the right (4.72 ± 0.71).

Experiment II

In the familiarization phase, neither the main effect of Color ($F_{1,38}$ = 0.21, P = 0.65) nor that of Position ($F_{1,38}$ = 1.44, P = 0.24) was significant, as their interaction was nonsignificant ($F_{1,38}$ = 0.36, P = 0.55). Again, before conditioning, stimuli differing by color or position evoked comparable SCR. Similarly, the Welch two-sample *t* tests in both the 1st and 2nd learning phases did not show significant differences between colors (1st: $t_{37.09}$ = 1.05, P = 0.30; 2nd: $t_{37.96}$ = 0.052, P = 0.96), which we thus collapsed in the subsequent analyses.

The Position (right/left) × Trial (from 2 to 12) ANOVA of the 1st learning phase highlighted a significant main effect of both factors (Position: $F_{1,39}$ = 37.62, P < 0.001, η_p^2 = 0.49; Trial: $F_{5.48,213.65}$ = 6.72, P < 0.001, η_p^2 = 0.15). In particular, it was possible to observe that the conditioning was successful, as the SCR for CS+ (mean ± SE = 0.336 ± 0.03) was greater than that for CS− (0.249 ± 0.03). This confirms that participants learned the association between visual stimuli close to the hand and the US (Fig. 3*A*). FDR-corrected post hoc comparisons showed greater responses for the 2nd trial compared with all the others (all P < 0.01) and for the 3rd trial compared with all the trials between the 6th and the 11th (all P < 0.05). The response trend is similar for the two stimulus positions (Fig. 3*C*).

In the 1st test phase (hand displaced leftward), the Position (close_left/far_left) × Trial (from 1 to 6) ANOVA showed a significant effect of both the within (Trial: $F_{3.37,128.1}$ = 5.53, P < 0.001, η_p^2 = 0.13) and the between (Position: $F_{1,38}$ = 10.40, P = 0.003, η_p^2 = 0.22) factors. Similar to *experiment I*, FDR-corrected post hoc comparison revealed a significantly higher SCR in the 1st trial compared with all the others (all P < 0.05) except the 2nd trials, which in turn was statistically greater than the 3rd, 4th, and 5th trials (all P < 0.05; Fig. 3*D*). Moreover, the significant effect of Position showed higher SCR for the stimuli presented close to the hand (mean ±

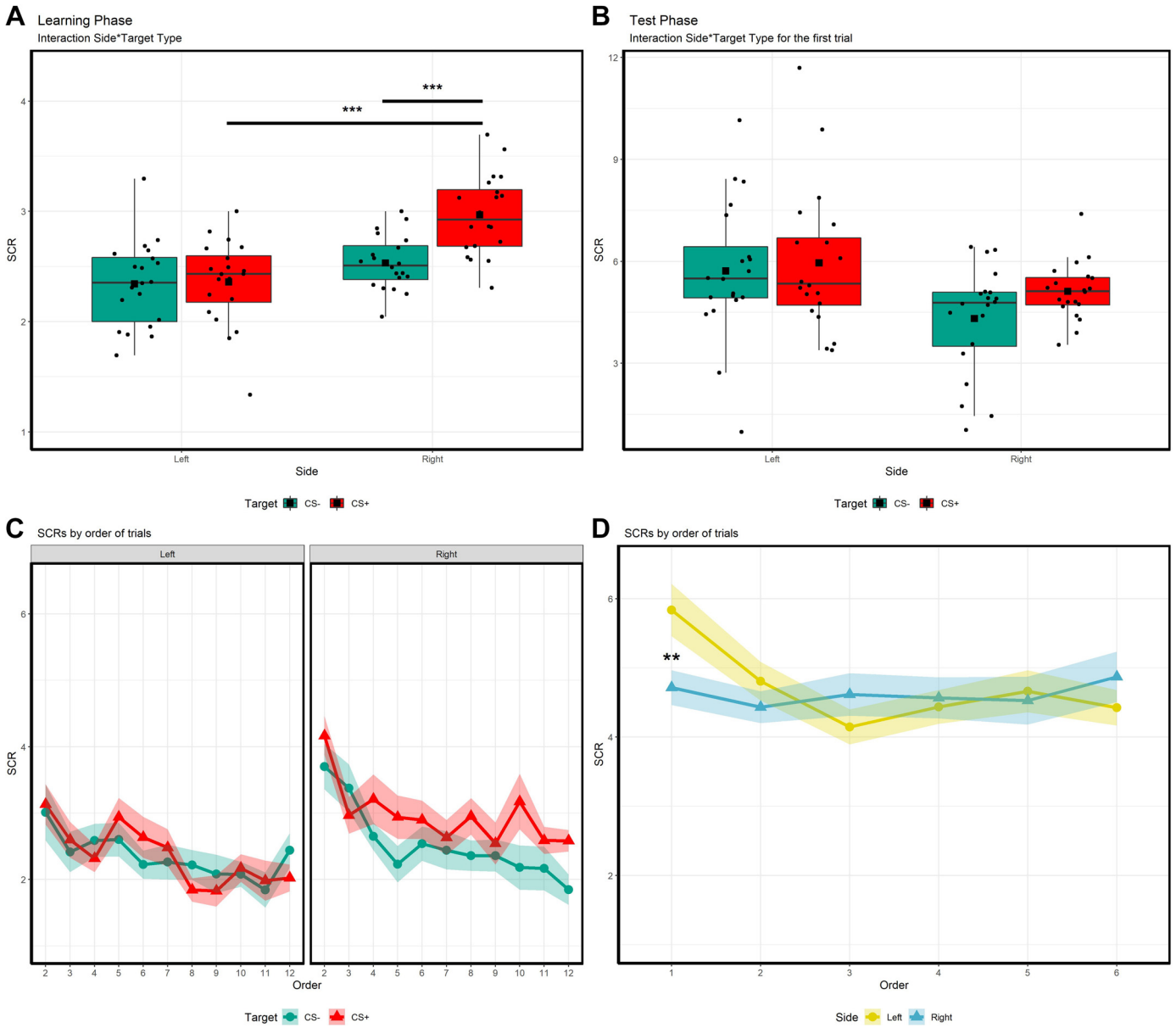

Figure 2. *A* and *B*: mean skin conductance response (SCR) to conditioned (CS+) and control (CS−) stimuli presented on the right or on the left side during the learning phase (*A*) and the 1st trial of the test phase (*B*) of *experiment I*. Error bars show SE. Significant differences: ***$P < 0.001$. ●, Individual means; ■ sample mean per condition. *C*: representation of the SCR pattern for the 4 experimental conditions (Side × Association Type) of the learning phase of *experiment I* as a function of the presentation order of the trials. *D*: SCR pattern for stimuli presented on the left and on the right in the test phase of *experiment I*. Significant differences: **$P < 0.01$.

SE = 0.392 ± 0.04) compared with those far from it (0.215 ± 0.04; Fig. 3*B*). This result confirms those of *experiment I*'s test phase, highlighting a remapping of the associative fear learning in a hand-centered fashion. The Position × Trial interaction did not reach significance ($F_{3.37,128.1} = 1.76$, $P = 0.15$).

The Position (right/left) × Trial (from 2 to 12) ANOVA on the SCR scores of the 2nd learning phase showed a significant main effect of Position ($F_{1,39} = 40.36$, $P < 0.001$, $\eta_p^2 = 0.51$), indicating greater responses for stimuli presented close to the hand (mean ± SE = 0.322 ± 0.02) compared with those presented on the left of the table (0.242 ± 0.02; Fig. 4*A*). Neither the main effect of Trial ($F_{6.58,256.59} = 1.04$, $P = 0.40$) nor the Position × Trial interaction ($F_{6.72,262.23} = 1.56$, $P = 0.15$) was significant. These results on one side confirmed the reestablishment of the conditioning effect, and on the other showed the absence of an order effect (Fig. 4*C*).

Finally, the Position (close_right/far_right) × Trial (from 1 to 6) ANOVA on SCRs scores of the 2nd test phase displayed a significant main effect of both Position ($F_{1,38} = 6.73$, $P = 0.01$, $\eta_p^2 = 0.15$) and Trial ($F_{3.16,119.97} = 10.44$, $P < 0.001$, $\eta_p^2 = 0.22$) and their interaction ($F_{3.16,119.97} = 3.1$, $P = 0.027$, $\eta_p^2 = 0.08$). FDR-corrected post hoc comparison showed higher SCRs for stimuli presented close to the hand compared with those presented far from it. This difference was significant in the 1st ($P = 0.007$) and 2nd ($P = 0.004$; Fig. 4, *B* and *D*) trials. All the other differences were nonsignificant.

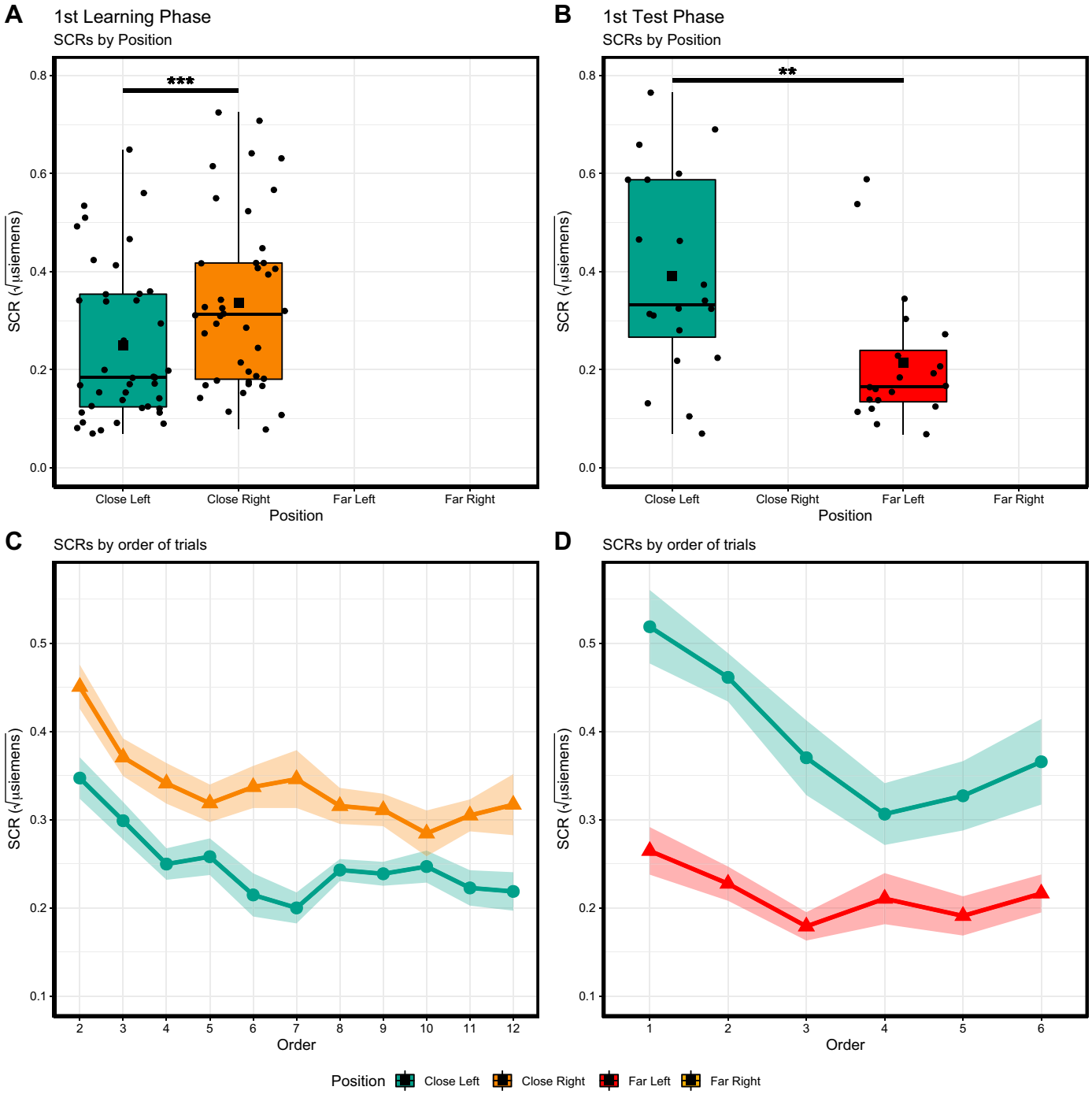

Figure 3. *A*: mean skin conductance response (SCR) to conditioned (CS+) and control (CS−) stimuli presented on the right or on the left side, respectively, during the 1st learning phase of *experiment II*. *B*: the same responses, but to stimuli presented close to or far from the hand during the 1st test phase of *experiment II*. Error bars show SE. Significant differences: $^{**}P < 0.01$, $^{***}P < 0.001$. ●, Individual means; ■, sample mean per condition. *C*: representation of the SCR pattern for the 2 positions of visual stimulation of the 1st learning phase of *experiment II* as a function of the presentation order of the trials. *D*: SCR pattern for stimuli presented close to or far from the hand in the 1st test phase of *experiment II*.

DISCUSSION

This study provides empirical support to the hypothesis that humans can learn to react to nearby fearful stimuli by establishing stimulus-response associations within a hand-centered reference system. Consistent with the body part-centered nature of PPS mapping (10, 11, 17, 35–37), here we report that acquired fear responses "follow" the hand to a new position. Because of this remapping, previously innocuous stimuli are then regarded as threatening ones, merely by virtue of their spatial "vicinity" status.

Learning is a skill that allows us to shape and adapt our behavior according to the events of the external world (38). A particular type of learning is the one that concerns fear,

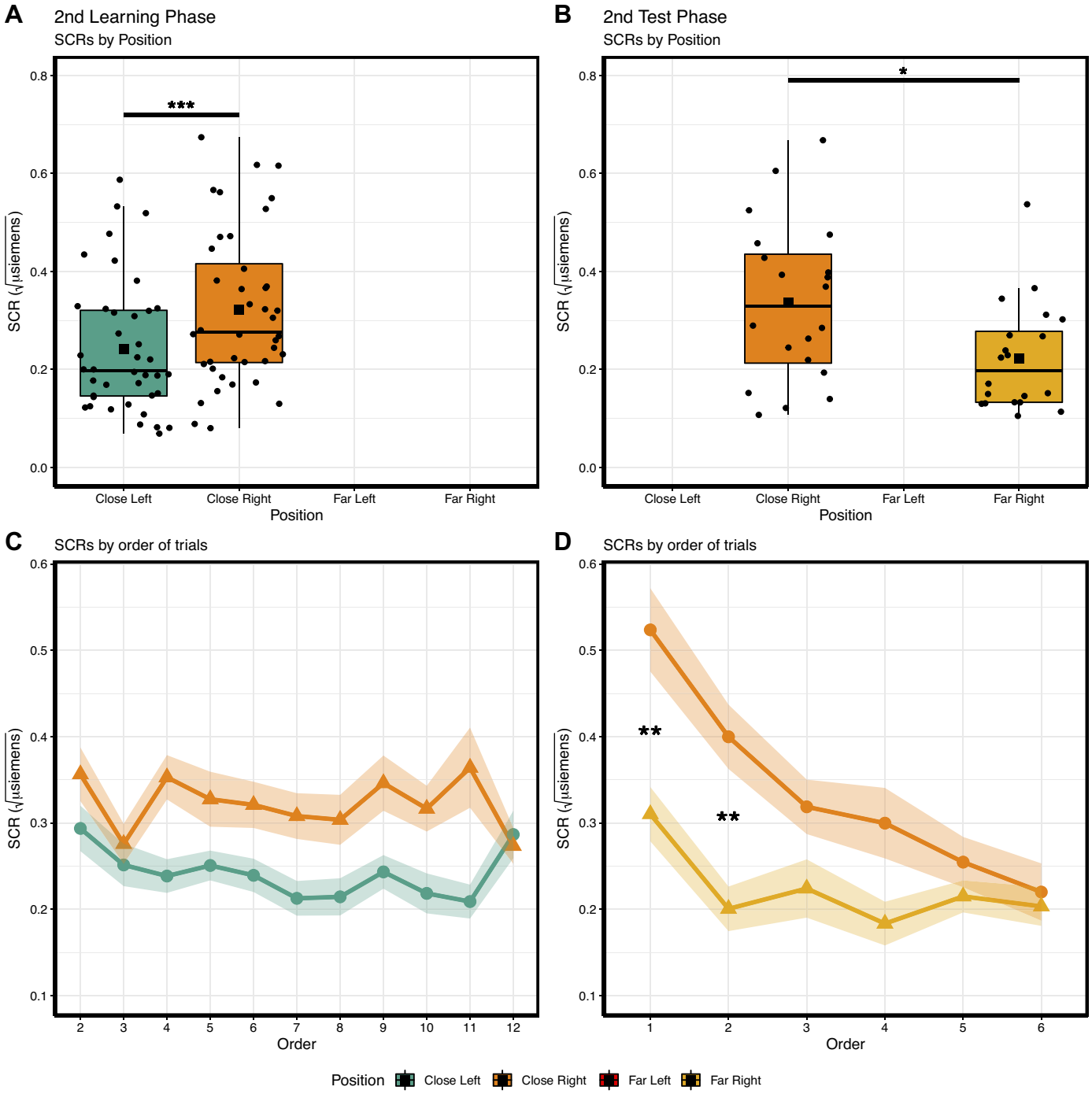

Figure 4. *A*: mean skin conductance response (SCR) to conditioned (CS+) and control (CS−) stimuli presented on the right or on the left side, respectively, during the 2nd learning phase of *experiment II*. *B*: the same responses, but to stimuli presented close to or far from the hand during the 2nd test phase of *experiment II*. Error bars show SE. Significant differences: **P* = 0.05, ****P* < 0.001. ●, Individual means; ■, sample mean per condition. *C*: representation of the SCR patterns for the 2 positions of visual stimulation of the 2nd learning phase of *experiment II* as a function of the presentation order of the trials. *D*: SCR patterns for stimuli presented close to or far from the hand in the 2nd test phase of *experiment II*. Significant differences: ***P* < 0.01.

considered as the set of unconscious and measurable physiological responses to threat (see Ref. 39). Previous studies have shown the influence of aversive stimuli on the extent of the PPS: coherently with its defensive function, its extension increases when facing threatening stimuli directed toward the body, allowing us to anticipate danger and plan an appropriate response (16, 19–21). However, these studies used stimuli aversive by nature, in some cases finding an effect only in the presence of a corresponding and preexisting phobia (19, 20) or individual idiosyncratic reaction. Indeed, here we found that nearby stimuli are not threatening per se. Although these stimuli are known to boost multisensory

J Neurophysiol • doi:10.1152/jn.00157.2021 • www.jn.org

processing when presented close compared with far from the hand (16), here the SCR did not vary for this sheer metric feature. This finding suggests that although PPS representation may code space for a defensive function, this may be not the default one. In stark contrast, when nearby stimuli start being associated to aversive ones, their metric dimension becomes relevant.

In *experiment I* we observed that the anticipatory fear response occurs in the learning phase only for the CS+ and only for the conditioned position, demonstrating that participants learned the CS+/US contingency. In the test phase, the hand being displaced in a novel, unconditioned position, a greater anticipatory fear response was associated to visual stimuli displayed in that near-hand position. This was true despite the fact that participants never experienced unpleasant stimulations associated with a CS in this novel hand position. This clearly indicates that the CS+/US association took place in a reference frame centered on the hand and not in a more general egocentric spatial reference system. So far, studies of fear learning in PPS have tested, broadly speaking, egocentric stimuli: toward the head (19, 20) or the hand (16, 40), which were kept in the same position. These studies showed a modulation of PPS representation and supported its defensive role. Our results considerably widen this perspective, indicating not only that an external threat is encoded as a function of its position relative to a specific body part but that the spatial relationship between them is maintained when that body part moves in space. Compatible with the dynamic properties observed in the domain of voluntary actions (41–43), here we additionally report that PPS allows us to learn new associations of stimuli in body part-centered coordinates.

Interestingly, this remapping showed some degree of generalization. Participants generalized the learned association to another, unconditioned stimulus, provided it was close to the new position occupied by the hand. This effect could not be due to insufficient differentiation of the stimuli used, because participants clearly differentiate between CS+ and CS− during the learning phase. It cannot be due to the simple spatial proximity between visual stimulus and hand either, as in the familiarization phase, before any conditioning takes place, this effect did not emerge. In addition, in the learning phase, the observed effect was clearly specific for the CS+ and not for any nearby visual stimulus. It might instead reflect an adaptive learning mechanism: moving the hand in space, the position of the threat is remapped, but in the absence of further information, all stimulations in the "dangerous" position are considered as a potential threat. Alternatively, the fear response observed only in the 1st trial of the test phase could be driven by novelty, the new experimental context. This possibility would be consistent with the order effect observed also in the learning phase of *experiment I*: regardless of the type of stimulus, the response rapidly decays after some trials. However, the results of *experiment II* speak against this alternative and instead support our hypothesis of hand-centered remapping and generalization of the CS/US association. If the effect observed in *experiment I* was mainly related to novelty, then the 1st test phase of *experiment II* should reveal similar responses between the near-hand and far-hand groups, contextual novelty being comparable. Yet the fear response was greater when visual stimuli appeared near the hand, rather than far from it. Furthermore, in the 2nd test phase of *experiment II* two previous effects are replicated: the effect of greater response for stimulations within PPS and that of the generalization of this response. In this phase, both stimulations are novel by the feature of color, and they have never been associated with US. Yet, again, fear responses were higher when stimuli were presented in the position previously associated with them, close to the hand. Therefore, novelty effects can be observed but do not account for our findings.

It is noteworthy that no order effect was observed in the 2nd learning phase of *experiment II*. We might speculate that this relates to the level of uncertainty, varying with the growing confidence participants may acquire regarding the CS/US association: higher drifts may appear in the early stages of learning (and testing) when any stimulation could lead to the US. Through repetitions, uncertainty lowers, as well as the response magnitude. In the 2nd learning phase (*experiment II*), participants' uncertainty may be lower since the beginning, which could result in less signal drift. This possibility deserves dedicated testing in future studies.

These findings provide previously unavailable evidence that humans encode new and arbitrarily learned associations of nearby stimuli within a body part-centered reference frame. This might reflect an adaptive mechanism: a threatening stimulus inside PPS is more dangerous for the part of the body more proximal to its position. Its detection in relation to this body part therefore becomes more relevant for the preparation of adequate avoidance responses. This is in agreement with the findings of Makin and colleagues, who argued the existence of a neuronal "fast track" capable of bypassing some stages of the processing of visual information relative to the hand (44) and to the position of objects in hand-centered coordinates (45). Learning to associate the threatening valence of a stimulus with respect to the threatened body part could contribute to make this fast update (~70 ms), by exploiting direct cortical and subcortical pathways (46). By coding information about the threats and the hand in a common reference frame, PPS would allow the online control of action and the ability to perform quick hand-object interactions. Although our study highlights this characteristic for threatening stimuli, the same mechanism can be hypothesized for stimuli having a positive value (rewards), which already seem to be coded differently according to their distance from the body (47, 48). Furthermore, here we investigated the influence of a visual stimulus on the perception of an electrocutaneous stimulation, but the reverse path is also conceivable: Filbrich and colleagues (49) have brilliantly demonstrated how a nociceptive stimulation applied to the hand affects the temporal judgment performance of visual stimuli presented close to or far from it. It is possible to say, in a more general way, that the defensive function of the PPS prioritizes the processing of multisensory information coming from the threatened part of the body.

The potential neural mechanism underlying hand-centered learning of the valence of nearby stimuli is worth discussing. Fear learning involves a network of regions including the anterior cingulate cortex, the anterior insula, the hippocampus, and the amygdala (see Ref. 50 for review), an important hub for the processing of fear and fear learning (51–54). Specifically, the lateral and basal nuclei of the amygdala are

the primary sensory input centers of these processes (52, 53, 55, 56), receiving multisensory information of auditory, somatosensory, nociceptive (57–59), and visual (60, 61) origin. These nuclei display enhanced responses to conditioned auditory stimuli in fear-learning protocols, and this modulation may occur for conditioned visual stimuli, through their direct connection with the visual nuclei of the pulvinar (61). According to a hypothesis, this pathway could represent a fast alerting system (52), capable of attributing an emotional value to incoming visual information, even before accessing conscious awareness. This idea is coherent with the defensive function of PPS: the closer the threat is to the body, the faster the response must be. A possible connection of the network underlying the representation of the PPS and that of the fear response, therefore, could represent an important adaptive mechanism.

At what point the PPS and fear learning circuits communicate with each other is not yet clear. The pulvinar, thanks to its important connection with the different portions of the intraparietal sulcus, the posterior medial intraparietal area (62; see 63 for review), and the putamen (64), could prove to be the hub of this communication. These areas are part of the fronto-parietal network underlying the PPS coding (9–13, 15), involved in planning reaching, grasping, and defensive movements (65). It therefore seems legitimate to suggest that its communication with a network of areas capable of evaluating and learning the threats present in the surroundings may help ensuring greater chances of survival. Activity of the left ventral premotor cortex (PMv) may also contribute to the phenomenon newly reported here. In addition to being an important region for the representation of PPS (10, 11), this area has shown strong activations in response to threatening stimuli presented near the body (24). In this perspective, further neuroimaging studies are necessary to better understand how the dialog between these systems may take place.

ACKNOWLEDGMENTS

We thank M. Martinuzzi for help with data acquisition in *experiment I*.

GRANTS

This work was supported by the Labex/Idex (ANR-11-LABX-0042) and by grants from the ANR-16-CE28-0015 and ANR-19-CE37-0005 to A.F. C.B. was supported by a grant from the Swedish Research Council (2015-01717) and ANR-JC (ANR-16-CE28-0008-01).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.Z., R.S., A.F., and C.B. conceived and designed research; A.Z. performed experiments; A.Z. analyzed data; A.Z., A.F., and C.B. interpreted results of experiments; A.Z. prepared figures; A.Z. drafted manuscript; A.Z., R.S., A.F., and C.B. edited and revised manuscript; A.Z., R.S., A.F., and C.B. approved final version of manuscript.

ENDNOTE

At the request of the authors, readers are herein alerted to the fact that additional materials related to this manuscript may be found at https://osf.io/ryhms/?view_only=9bbd1a5d84ff4b2c9a7568ba1bd0da9f. These materials are not a part of this manuscript and have not undergone peer review by the American Physiological Society (APS). APS and the journal editors take no responsibility for these materials, for the website address, or for any links to or from it.

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Discussion

Lo duca e io per quel cammino ascoso
intrammo a ritornar nel chiaro mondo;
e sanza cura aver d'alcun riposo

salimmo sù, el primo e io secondo,
tanto ch'i' vidi de le cose belle
che porta 'l ciel, per un pertugio tondo.

E quindi uscimmo a riveder le stelle.

Dante Alighieri

The last forty years of research on peripersonal space have taught us that our body is nothing more than a metaphor for the planet we live on. Seen from the Moon, the Earth looks just like a large blue-green stone immersed in a totally uniform black space. However, it is not true that the "black space" it is really uniform: the region that surrounds it takes on characteristics that are very different from the more distant regions, and the further one moves away from its surface, the more the distinctive characteristics of that which we call atmosphere tend to "fade". The importance of this "bubble" around the Earth is such that only thanks to it are we allowed to survive, and every time a foreign element penetrates inside it, coming from a more distant region of space, we are alarmed and we try to understand as quickly as possible if this intruder could be a danger. Our body is that blue-green stone: although the space around us seems to be completely uniform, both to our eyes and to external observers, the region that surrounds us most closely represents an envelope of fundamental importance, whose limits are not clearly defined but tend to fade with increasing distance. It is within this “atmosphere” that our daily life takes place, made up of interactions with the objects and people around us. This "bubble" with indefinite borders was baptized peripersonal space (PPS) exactly forty years ago by Rizzolatti and colleagues (Rizzolatti et al., 1981a, 1981b). The first evidence to support a distinction between the space near and far from the body comes from electrophysiological studies in the macaque, in which it was possible to observe that single neurons in the premotor (Fogassi et al., 1996; Graziano et al., 1994, 1997a; Matelli & Luppino, 2001; Rizzolatti et al., 1981a, 1981b; see Cléry et al., 2015 for review) and parietal cortices (Avillac et al., 2005; Bremmer et al., 2013; Colby et al., 1993; Duhamel et al., 1997, 1998; Guipponi et al., 2013; Schlack, 2005), as well as in the putamen (Graziano & Gross, 1993), showed responses to visual or auditory stimuli presented in the region surrounding a given tactile RF on the animal's body. The response of these neurons is stronger as the distance of the stimulus from the body reduces. Thus, these neurons were able to make our body "interact" with the surrounding space, responding not only to tactile stimuli presented on a specific part of the body, such as the hand, arm, head or larger areas, but also to visual or auditory stimuli close to this body region (Colby et al., 1993; Rizzolatti et al., 1981a, 1981b). Furthermore, his multisensory integration takes place within a body-part-centered reference frame: the movement of the hand in space causes a remapping not only of the tactile receptive fields of the neurons that respond for that part of the body, but also of the visual or auditory ones

anchored to the former (Fogassi et al., 1992, 1996; Gentilucci et al., 1983; Graziano et al., 1994; Graziano & Gross, 1998a).

In this way, the multisensory representation of the space around our body is always updated regarding the position of the different parts of the body, the position of external stimuli and the spatial relationship between them. Over time, studies on patients and healthy humans have revealed that the PPS representation is not only the prerogative of macaques. Also for the human being the spatial region surrounding the body takes on a special character, as the stimuli presented closer to the body are able to improve behavioral performances, whether in multisensory (Canzoneri et al., 2012; A. M. de Haan et al., 2016; Serino, et al., 2015) or unimodal conditions (Blini et al., 2018). Neuroimaging evidence then strengthened the link between human and non-human primate's PPS, not only observing that stimuli presented within-PPS elicit activations along a fronto-parieto-subcortical network (Bremmer et al., 2001; Brozzoli et al., 2011, 2012a, 2013; Gentile et al., 2011, 2013; Makin et al., 2007), as in macaques (Colby et al., 1993; Duhamel et al., 1997, 1998; Graziano et al., 1994; Graziano & Gross, 1993; Rizzolatti et al., 1981a, 1981b), but highlighting that such neural responses are body-part-centered, responding consistently with the position of, for example, the hand (Brozzoli et al., 2012a). If, on the one hand, these results seem to provide a coherent parallel with what was observed in the monkey, on the other hand the comparison between the recording of single neuron activity and the BOLD activations in fMRI is not entirely fair. If it is true that fMRI can approach (but not equal) the level of spatial definition of electrophysiological studies thanks to techniques such as adaptation (Grill-Spector et al., 1999, 2006), the difference regarding the extent of the investigated activations remains. Even using multi-site recording techniques, electrophysiology studies cannot investigate brain activations at such a widespread level as that of fMRI ones. This could explain the discrepancy observed by the first fMRI study that investigated the neural basis of PPS in macaque monkeys: Cléry and colleagues, in addition to confirming the involvement of the neural areas described by the electrophysiological literature (VIP and F4 in particular, see Cléry et al., 2015 for review), identified a wider network, which includes previously non-documented premotor (F5, FEF, SEF), somatosensory (S2) and parietal (AIP) areas (Cléry et al., 2018). Furthermore, a critical difference is highlighted regarding area 7b, electrophysiologically associated with the coding of stimuli in the near space (Hyvärinen,

1981; Hyvärinen & Poranen, 1974; Hyvärinen & Shelepin, 1979; Jiang et al., 2013; Leinonen et al., 1979; Leinonen & Nyman, 1979) but showing preferential responses for far stimuli in Cléry's study. The same has been reported for the LIP area, which electrophysiological studies indicate as presenting preferential responses to visual fixations within PPS (Genovesio & Ferraina, 2004; Gnadt & Mays, 1995), but reporting preferential responses to extrapersonal stimuli in the fMRI study (Cléry et al., 2018). It therefore seems that the use of fMRI techniques brings not only confirmations, but also some questions. Strengthened by this first step to bridge the gap between human and non-human primate's brain activity recordings, the first study presented in this manuscript (Chapter I) tried to directly compare the PPS networks of the two species, using a similar experimental protocol. Regarding the macaque PPS network, the results support the idea that the coding of stimuli close to the body is not limited to the F4, putamen, VIP and IPS regions (Colby et al., 1993; Duhamel et al., 1997, 1998; Graziano et al., 1994; Graziano & Gross, 1993; Rizzolatti et al., 1981a, 1981b), but involves a much wider network of areas, bilaterally. While the results described confirm what Cléry and coworkers observed (Cléry et al., 2018), on the other hand these two first fMRI studies on macaque's PPS report some discrepancies. The first concerns one of the areas classically included in the non-human primate's PPS network: the parietal area 7b. If in the previous study this region seemed to show preferential responses to far space stimuli, this is not observed in the results of our study, which instead seem to confirm what was reported in the electrophysiological studies. This could be related to the different experimental setup, as close-to-the-face stimulation in our study was closer (~2 cm) than that used by Cléry and colleagues (~15 cm). Although these distances fall within PPS, indeed, it is possible that the closest of the two falls within what we could define "ultra-near space". Some neurons of the VIP area, for example, show a preference for stimuli within this ultra-near area (Colby et al., 1993), and evidence at the human behavioral level also seems to support this distinction (Sambo & Iannetti, 2013). However, there is no evidence in the electrophysiological literature regarding the existence of ultra-near space neurons in area 7b yet. This could also be the reason behind the second discrepancy between the two fMRI studies, concerning the activation of LIP for far stimuli in the study by Cléry and colleagues (Cléry et al., 2018) and for near stimuli in our study. Being only the first steps in this line of research, these inconsistencies can only stimulate new studies and open new perspectives. As well as encouraging are the similarities found between the two studies: going beyond the

fronto-parietal network already known in the literature, both studies report a preferential activation for close-to-the-body stimuli in regions such as AIP and F5. Both of these areas are not, to date, included in the canonical fronto-parietal network underlying the PPS representation. However, AIP has strong homologies and interconnections with area 7b (Matelli & Luppino, 2001; Rizzolatti & Luppino, 2001), and reports neurons sensitive to structural features of 3D objects and their graspability (Murata et al., 2000; Sakata & Taira, 1994). Similarly, F5 also seems to preferably respond to within-reach stimuli and as a function of different hand-grasping configurations (Bonini et al., 2014; Murata et al., 1997; Raos et al., 2006; and see Cléry et al., 2015 for review). It is therefore possible that these areas are involved in the encoding of within-reach stimuli, as well as the parietal area 5, identified in our study as part of the pattern of neural areas involved in decoding the difference between near and far stimuli. Indeed, this region seems to present neurons capable of encoding the movements of the upper limbs in a body-centered coordinate system, taking into consideration the starting point and the end point of the movement (Buneo & Andersen, 2006; Lacquaniti et al., 1995). Similarly, the MIP area has been associated in the literature with the planning and execution of reaching movements (Colby, 1998; Eskandar & Assad, 1999; Johnson et al., 1996; Marconi et al., 2001; Rizzolatti et al., 1997b), being within what is called the parietal reach region, located between MIP and V6A (R. A. Andersen & Cui, 2009; Batista et al., 1999; Bhattacharyya et al., 2009; Buneo et al., 2002; Chang et al., 2008; Scherberger & Andersen, 2007). Again, this region is not part of the originally described fronto-parietal network of PPS, but is significantly activated in response to stimuli near the face in our study. Also in humans, brain regions associated with the coding of reaching movements include the medial bench of the IPS (the human MIP, Beurze et al., 2007, 2009; DeSouza et al., 2000; Grefkes et al., 2004; Hagler et al., 2007; Medendorp et al., 2003; Prado et al., 2005; Tosoni et al., 2008), the parieto-occipital junction (Beurze et al., 2009; Connolly et al., 2003; Culham et al., 2008; Monaco et al., 2011; Pitzalis et al., 2013; Prado et al., 2005; Tosoni et al., 2008; Zettel et al., 2007) and the dorsal premotor region (PMd, Kertzman et al., 1997; Lara et al., 2018; Picard & Strick, 2001; Prado et al., 2005; see Filimon, 2010 for review). All these regions, even if not in a systematic way, appear in the results of our study among those encoding the distance of the visual stimulus. These findings are not inconsistent with the theoretical and functional distinction between PPS and arm reaching space (ARS), directly addressed by the behavioral study in Chapter II. At the level of

brain activations, identifying responses simultaneously in PPS and ARS areas is linked to the fact that what is found within-PPS is also reachable. A 3D visual stimulus presented a few centimeters from the face or hand is not coded only as "existing" in the region near the body, but becomes salient because the interaction with it becomes more probable: we can touch it, manipulate it, avoid it, and depending on its intrinsic meaning (thinking of appetitive or threatening stimuli) we can be attracted or frightened. But all this implies the involvement of a brain network that goes far beyond the connection between the areas of the intraparietal sulcus and the premotor cortex. If we hypothesize that these regions are able to record the position of stimuli in body-part-centered coordinates, they will then need to communicate with other brain areas to implement planning for an effective response, which may require eye movements (LIP, in both monkeys and humans: Colby et al., 1996; Corbetta et al., 1998) or reaching / grasping movements with the upper limbs (F1, F5, AIP, MIP, areas 5 and 7 in monkeys, see Nelissen & Vanduffel, 2011; IPL, PMv and inferior frontal gyrus in humans, see Hardwick et al., 2018), and to do this it is necessary to evaluate the 3D characteristics of the stimulus and the configuration that the hand will have to assume to grasp it (AIP and F5 in the monkey brain; hAIP and premotor cortex in humans, see Castiello, 2005). And the coding of these aspects could take place automatically, preventing the fMRI studies conducted so far from identifying specifically the PPS network and discriminating it from other "intervening" networks. However, the fact that these two networks present high levels of mutual communication does not necessarily mean that the two representations they support are functionally equivalent. The study illustrated in Chapter II compares a task of reachability judgment and one of tactile detection, gold standard in the study of ARS and PPS respectively, using an experimental setup as similar as possible. The 10 positions of visual stimulation cover all the reachable space and expand beyond its limit, while the participant's right hand, on which the tactile stimulation is applied, can be positioned closer or further away from the body, next to different sites of visual stimulation. What is observed in the tactile detection task, in which the participants have to ignore the visual stimuli, is a facilitation of the performance that follows what has already been observed in the literature (A. M. de Haan et al., 2016; Serino et al., 2015; or see Canzoneri et al., 2012; and Teneggi et al., 2013 for examples of audio-tactile facilitation): when the irrelevant visual stimulus is close to the part of the body that receives the tactile stimulus, the response is faster. Furthermore, the results support and clearly show the hand-centered coding of visual

stimulations: the displacement of the hand causes a remapping of the facilitation, as if it remained "anchored" to that specific part of the body (an aspect that recalls the overlapping visuo-tactile receptive fields, Graziano et al., 1994; Rizzolatti et al., 1981a, 1981b). This characteristic feature of the PPS representation, however, does not emerge with the task of reachability judgment, in which the participants judge the reachability of the visual stimulus, ignoring the tactile one. In this second case, the positions of the hand and of the visual stimulus do not affect the performance: not only visual stimuli close to the hand do not boost the reaction times, but there is no advantage even for all reachable versus non reachable visual stimuli. While it is true that this study cannot tell us anything about the underlying brain activations, on the other hand it seems to provide evidence to support the functional distinction between ARS and PPS, due to different fundamental characteristics: PPS appears to be sensitive to the multimodality of stimuli, which are encoded in body-part-centered coordinates, whereas ARS does not (although it is possible that the distance of the stimuli is encoded with respect to the trunk or shoulder). Is it possible that the presence of a specific task for one of the two spatial representations could be the key to bringing out the distinction between them also at the fMRI level?

The studies conducted so far on PPS and ARS have indeed focused only on one of the two representations, presenting unisensory (Brozzoli et al., 2011, 2012a, 2013; Cléry et al., 2018; Holt et al., 2014; Makin et al., 2007; Quinlan & Culham, 2007; Schaefer et al., 2012) or multisensory stimuli (Bremmer et al., 2001; Ferri et al., 2015; Gentile et al., 2011, 2013; Huang et al., 2012; Sereno & Huang, 2006) close to different body-parts in order to observe their respective brain responses or by asking participants (human or non-human primates) to perform reaching movements (Beurze et al., 2009; Filimon et al., 2007, 2009; Lara et al., 2018; Prado et al., 2005), pointing (Connolly et al., 2003), grasping (Hinkley et al., 2009) or observing / imagining such movements (Filimon et al., 2007). Given their close relationship, it would be important to compare the two types of tasks within the fMRI scanner, trying to use experimental conditions as similar as possible and testing different parts of the body, in order to better understand the neural basis of these two different spatial representations. Indeed, in the fMRI study reported in Chapter I, 3D visual stimuli presented near different parts of the body are observed to induce both specific and common neural responses, and it is therefore possible, as previously mentioned, the two spatial representations refer to

different spatial coordinate systems. As for PPS, the results of the comparison between body-parts in the human sample confirm the existence of a common "core" of activation underlying this representation. Considering the activations of both participants, a preferential activation for close to the body stimuli is observed at the level of the left intraparietal sulcus and the surrounding superior parietal areas, regardless of which part of the body is stimulated. This region is indeed often reported in the fMRI literature of PPS, in relation to close to the hand stimulations (Brozzoli et al., 2011, 2012a; Gentile et al., 2011, 2013; Makin et al., 2007), to the face (Bremmer et al., 2001; Holt et al., 2014; Huang et al., 2012; Sereno & Huang, 2006) or to other body-parts (Huang et al., 2012), and is one of the areas also reported from the meta-analysis by Grivaz and colleagues (Grivaz et al., 2017). Our results seem to confirm that these intraparietal and superior parietal regions are involved in encoding the distance of stimuli from all parts of the body tested, suggesting the idea of a "whole-body" PPS. However, the network of areas supporting this representation could be wider than the one described: one of the two participants reveals areas of joint activation also at the level of the SMG, bilaterally. Further studies are therefore necessary to clarify this discrepancy, due to the small size of the sample and the analyses at the individual level (in our study, a choice dictated to ensure a fair comparison with the analyses on non-human primates). In addition to this core network underlying a hypothetical whole-body PPS, it is interesting to observe the specific activations in response to stimulations close to the hand, the face or the trunk. Previously cited studies investigated these parts of the body separately (see Grivaz et al., 2017 for discussion), and this prevented direct comparison of the neural basis of the body-part-centered coding of PPS. The studies that tried to directly compare different body districts (Huang et al., 2012; Sereno & Huang, 2006) focused on small portions of the PPS network (especially at the parietal level). In our study, however, a salient specificity is observed at the level of the most frontal areas of this network. In particular, the premotor regions seem to be associated only with close-to-the-face or to-the-hand stimuli, with a junction area and two well-discriminable specific regions: one anteriorly to the conjunction, with specific responses for stimuli within head-based PPS, and one posteriorly, specific for the peri-hand space. This is in line with the results from electrophysiology, which report premotor neurons characterized by multisensory receptive fields centered on the hands and face (Rizzolatti et al., 1981a, 1981b) or involved in hand-to-mouth movements (Gentilucci et al., 1988).

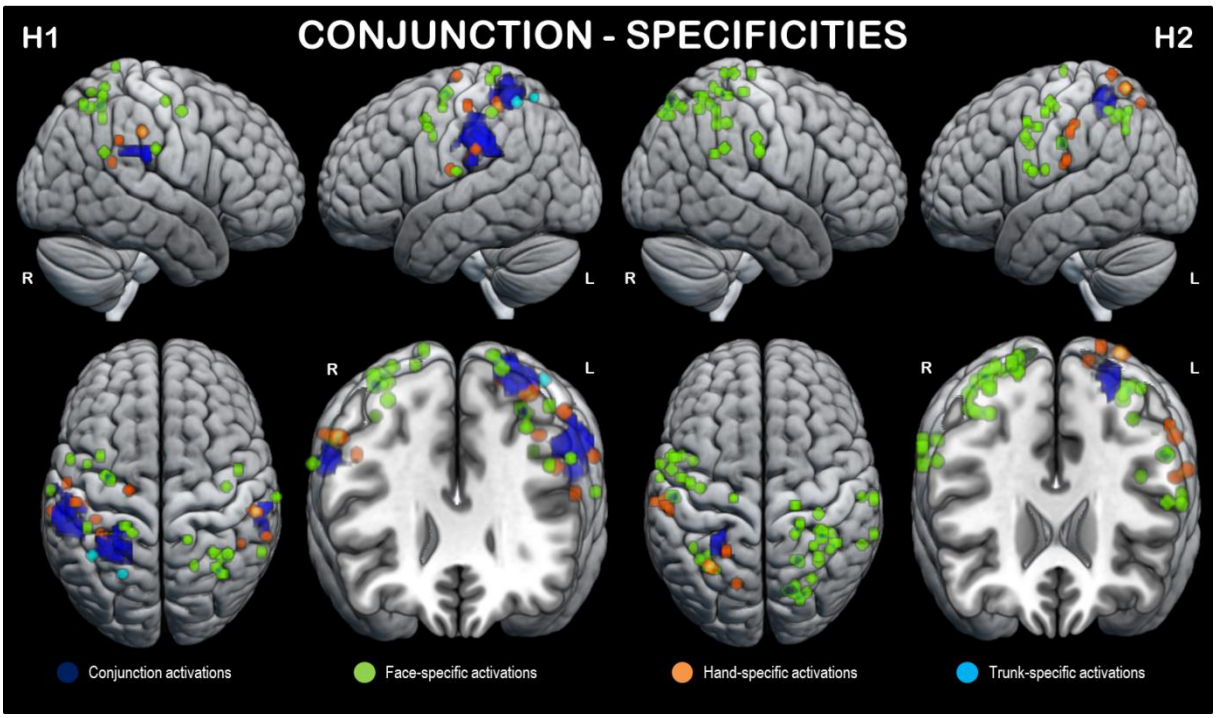

Figure 4.1 *Specific activations induced by visual stimuli close to the face (green), the hand (orange) or the trunk (light blue) in the human participants of the fMRI study described in Chapter I. Regions of conjunction between the activations of the three body parts are illustrated in dark blue.*

Our findings are therefore consistent with previous fMRI studies that reported fronto-parietal activations in response unimodal visual stimuli close to the hand (Brozzoli et al., 2011, 2012a; Makin et al., 2007), and provide further support to hand-centered remapping observed both at neural (Brozzoli et al., 2012a) and behavioral level (study presented in Chapter II). Considering the conjunction between face, trunk and hand reported both at the parietal and supramarginal level, it is possible that this remapping occurs thanks to populations of neurons with receptive fields specifically centered on the hand, and located in these premotor regions. These neuronal populations could then be involved in the remapping of the skin responses of learned fear observed in the study described in the third chapter. In this study, using a fear conditioning protocol, we observed that the repeated association of an initially neutral stimulus (conditioned stimulus, or CS) with an aversive stimulus (unconditional stimulus, or US) leads to an anticipatory fear response, as demonstrated by an increase in skin conductance. In particular, the two experiments show that this response is present only when the CS is presented near the hand, the position associated with the US, and does not occur in the case of CSs far from the hand. Furthermore, a hand-centered remapping of this response is observed: displacing the hand

on the table, the anticipatory fear response remains anchored to the hand, associated to CSs located near the new position of the hand and within the peri- hand space. Previous studies have succeeded in demonstrating that an aversive visual (A. M. de Haan et al., 2016) or auditory (Ferri et al., 2015; Taffou & Viaud-Delmon, 2014) stimulus is able to influence the processes of multisensory interaction within-PPS, leading to an apparent "extension" of the latter towards the threat. Åhs and colleagues also showed that the stimulus does not necessarily have to possess aversive characteristics in an innate way, but it can be a conditioned stimulus, which following the conditioning process will be able to elicit enhanced skin conductance responses in case of invasion of the participant's PPS (Åhs et al., 2016). However, none of the previous studies show that this fear learning process is body-part centered. The results of our study highlight the relationship between the representation of PPS and learning processes, opening the way to new questions. Is it possible to establish body-part centered associations using appetitive stimuli, or is the link between PPS and learning processes only for defensive purposes, and therefore linked to aversive stimulations? The different encoding of "positive" stimuli as a function of distance from the body (O'Connor et al., 2014, 2021) seems to suggest a rather universal relationship, more associated to the repetitive association of the CS and US than to the positive or negative valence of the conditioned stimulus. Moreover, the results show that the remapping of the learned association involves a generalization of the fear response even to previously unconditioned stimuli, but sharing the closeness to the hand with the CS. How plastic is this learning? The visual stimuli we used were very simple, devoid of intrinsic meaning. It is therefore possible that the simple spatial position was sufficient to induce generalization. Can the use of more complex stimuli, with their own positive or negative value, for example, bring out a more specific type of learning?

Going beyond the study of behavioral effects, our results push towards an investigation of the neural basis of the link between PPS and fear learning processes (or, in a broader view, learning processes in general). By bringing a protocol similar to that described in Chapter III inside the scanner it would be possible not only to observe possible additional activations compared to those observed for the peri-hand space in the study of Chapter I, but through connectivity analysis it would be possible to identify the potential link between the PPS network and the fear learning network. Where does the connection between these two

systems take place? An ideal candidate appears to be the amygdala, via the pulvinar. The amygdala is indeed the fulcrum of fear learning processes, essential both for the acquisition and storage of fear memories (thanks also to the communication with the hippocampus) and for the implementation of fear responses (Radwanska et al., 2002; Repa et al., 2001). The lateral nucleus of the amygdala is the structure of reception of sensory information, through projections both from the thalamus (which transmits faster and less complex information, probably involved in the most rapid defensive reactions) and from the cerebral cortex (Garrido et al., 2012; Garvert et al., 2014; LeDoux, 1994, 2000; McFadyen et al., 2017). This nucleus then has direct and indirect connections (Pitkänen et al., 1997) with a second amygdalar nucleus, the central one, responsible for the physiological expression of fear. Moreover, strong interconnections have been observed between amygdala and the ventral and medial prefrontal cortex (S. Chen et al., 2021), whose theta activity is increased in patients and healthy humans that capture the link between the CS and the unconditional stimulus. The hypothesis is that this PFC-amygdala-hippocampus circuit communicates with the PPS network through the pulvinar; the medial (multisensory) and inferior (visual) portions of this subthalamic nucleus show indeed connections both with the amygdala and with the posterior parietal cortex, in humans and non-human primates (Abivardi & Bach, 2017; Grieve et al., 2000; Tamietto et al., 2012). Baizer and colleagues, in particular, observed in rhesus monkeys a direct connection between the pulvinar and the ventral and lateral intraparietal areas (VIP and LIP, Baizer et al., 1993), characterized by a preference for near-body multisensory stimuli (VIP, Bremmer et al., 2001; Colby et al., 1993) and for fixations in the near space (LIP, Genovesio & Ferraina, 2004; Gnadt & Mays, 1995). The pulvinar seems particularly important for the implicit processing of fear-related information: hemianoptic patients without blindsight and with spared pulvinar report a facilitation of the response for visual stimuli presented in the preserved visual field if, simultaneously, faces with expressions of fear are presented in the blind hemifield (Bertini et al., 2013, 2018a, 2018b). If the pulvinar is damaged by the lesion, this facilitation disappears, indicating that fear-related information in the blind hemifield can no longer reach the amygdala. These results are in agreement with the role played by the colliculus-pulvinar-amygdala circuit in the unconscious and rapid processing of salient and emotionally connoted stimulations (Garrido et al., 2012; Garvert et al., 2014; McFadyen et al., 2017; Tamietto & de Gelder, 2010). The physiological fear response and the same defensive function of the PPS could rely

on to this axis of neural communication: the amygdala has direct connections with the periaqueductal gray (PAG, see Critchley & Harrison, 2013 for review), a brainstem nucleus involved in defensive behaviors (Assareh et al., 2016; Bandler et al., 2000) showing enhanced activity in response to threatening stimulation approaching the body (Coker-Appiah et al., 2013; Mobbs et al., 2007, 2009). This structure seems to be involved in the implementation, for example, of freezing and flight responses in monkeys (Carrive, 1993; Koba et al., 2016), but also in the expression of fear and anxiety in humans (Hermans et al., 2013), and it is also a synapse point in the path of information from PMd to the adrenal medulla, involved in the behavioral response to external threats (Dum et al., 2016). It therefore seems that the communication between different neural systems can explain not only the results of the study reported in Chapter III, indicating a relationship between PPS and learning, but also the defensive nuance of this spatial representation, aimed at preserving bodily integrity. And it is precisely the possible threat to the integrity of the body that reveals a further link between the PPS representation and the amygdala. Fourcade and colleagues, in a recent study, used an experimental virtual reality protocol in which a threatening (spider) or neutral (toy car) stimulus was presented on a fake arm, positioned coherently with the participants' right arm. Associated with this visual stimulation, a tactile stimulus was applied to the real arm through different electrostimulators, to give the impression that the touch was moving in a coherent or incoherent way with the visual stimulation (Fourcade et al., 2021). Participants reported a greater sense of ownership towards the virtual arm in case of congruent visual-tactile stimulation, correlated to an enhanced activity of the posterior parietal cortex (area 7a, in SPL). This result confirms what has been observed in the literature on rubber hand illusion, whose sense of illusory ownership seems to be linked to the activity of a brain network that includes two crucial nodes of the neural representation of the PPS (the posterior parietal cortex and the premotor cortex) plus the extrastriate body area (EBA), located in the middle temporal gyrus (Ehrsson et al., 2004, 2005; Limanowski & Blankenburg, 2015). The most interesting aspect is that Fourcade and colleagues report enhanced activity of the amygdala in response to threatening stimulation, as would be expected from the core structure of the fear network, but this response was modulated by the strength of the illusion of ownership, with increased activity in case of congruent threatening visuo-tactile stimulation. There seems therefore to be a link between the activity of the posterior parietal cortex, involved in the visual-tactile integration and

encoding of the internal representation of the body (Limanowski & Blankenburg, 2016), and that of the amygdala, as if to indicate an enhanced perception of aversive stimuli when such stimuli are perceived as a threat to bodily integrity. The defensive response is not just a reaction to a threatening stimulus, but a reaction to a potential danger to one's body (Fourcade et al., 2021), or to what is perceived as such.

To complete the picture, the social function of the PPS is also not exempt from communication with the amygdala. Indeed, this structure seems to have a fundamental role in the regulation of interpersonal distance during social interactions (Dureux et al., in preparation; Kennedy et al., 2009; Schienle et al., 2015; Vieira et al., 2017). Supporting the interconnection between the PPS network and the amygdala, it has been observed that theta burst stimulation (TBS) applied to the PMv or posterior IPS is able to modulate the amygdalar response to emotional whole-body actions: if in the absence of TBS the amygdala response in front of whole-body angry or neutral actions does not report significant differences, the stimulation applied in the premotor or superior parietal region induces an enhanced response for angry actions (Engelen et al., 2018). This seems to be consistent with what Fourcade and colleagues described (Fourcade et al., 2021): actions of anger can represent a danger if they are directed towards one's body, in relation to the activation of the PPS network. Moreover, this modulation was also observed at the level of other areas of the superior parietal lobule and in particular in the region of conjunction between the SPL and the occipital lobe (POS), an area involved in the coding of reaching movements (Beurze et al., 2009; Connolly et al., 2003; Culham et al., 2008; Monaco et al., 2011; Pitzalis et al., 2013; Prado et al., 2005; Tosoni et al., 2008; Zettel et al., 2007). The studies by Vieira and colleagues expanded the neuroimaging literature on the social function of PPS, observing that the presentation of social stimuli (faces with different emotional expressions) approaching the participant's body induces an enhanced response at the level of the amygdala, IPS, fusiform face area and temporo-parietal junction (SMG), regardless of the emotion expressed by the face (Vieira et al., 2017, 2020). When these faces displayed threatening expressions, additional activations at the level of the PMv and PAG were found, as well as an increased connectivity between these two regions (Vieira et al., 2020). These results, which confirm what Holt and colleagues have already observed in one of the first studies on social PPS (Holt et al., 2014), include another interesting aspect, which is the

involvement of the insula. This area, whose electrical stimulation causes approach or social withdrawal behaviors in the monkey (Caruana et al., 2011), is closely interconnected to the amygdala, both in humans and in non-human primates (Mufson et al., 1981; Uddin et al., 2017). Vieira and colleagues observed enhanced activity of the insula in response to faces with expressions of anger or happiness in looming towards the body (Vieira et al., 2017, 2020), and this involvement of the insula also appears to be present in the formation of a sense of body ownership and agency (Grivaz et al., 2017; Uddin et al., 2017). For this reason, it is possible that the insula is also part of the network of areas recruited from the representation of the space near the body, as also highlighted by neuroimaging (Schaefer et al., 2012) and EEG studies (Bernasconi et al., 2018).

Trying to "summarize" the different nuances and functions of the PPS in a single and unambiguous definition, referring to what is present in the literature, is not an easy task. Depending on the tasks used, the research groups involved and the starting hypotheses, PPS assumes multiple different identities: a working space in which we interact with the objects around us (de Vignemont & Iannetti, 2015; Rizzolatti et al., 1997a), a defensive space to preserve the integrity of our body (Graziano & Cooke, 2006; Sambo et al., 2012), a space of social interaction, which helps us to regulate the distance between us and those around us (Iachini et al., 2014; Teneggi et al., 2013), or the space of our Self, not necessarily corresponding to our physical body but corresponding to the position in space that we think our body is assuming (Noel et al., 2015; Serino, 2019). Not considering the possibility that PPS is represented by a set of different fields in which the distance of a stimulus from the body is only one of the ingredients of the final recipe (Bufacchi & Iannetti, 2018). Yet, to address these different functions, the different research groups and studies refer to the same literature.

To conclude this doctoral dissertation, I will therefore try to provide a definition of the concept deriving from these (few) years of immersion in this literature (this means that the scientific part of the manuscript is finished, and we are now entering the free world of speculation). What do the different descriptions, definitions and functions of the PPS (or reaching space, working space, defensive space, space of the Self, social space and so on) have in common? What is the variable present in all articles with "peripersonal space" in the abstract?

It is the distance between the body (or its parts) and a stimulus. Stimulus that may be unimodal or multisensory, social or non-social, appetitive or aversive, threatening or not. We can stimulate a part of the real body or it can be rubber, virtual or even a metal tool. Distance matters. But I would not define peripersonal space as a space, unequivocally exposing it to parallelisms and confusion of definition (is PPS larger/narrow than the reaching space? And what about the defensive space? Is the social PPS different from the previous two, or is it just a nuance dictated by the emotional context?). Why not define it as a peripersonal mechanism (PPM) for encoding external stimuli? A mechanism that records the position of the different parts of the body and the stimuli that surround them, thanks to which goal-directed actions, defensive reactions, social interactions and body awareness can interact harmoniously: if I see a spider on the table, while my hands slide on the keys of the computer keyboard, the PPM will register that my hands are close to a stimulus, which is approaching over and over. At that point, without the intervention of the fear and defense network, my hands would remain next to the spider. Is this a defensive peripersonal space, because there is a spider and it is close to me? And what if that spider is my pet tarantula? Does it become a working space, just because my hand approaches the puppy, or maybe a social space, because nobody would deny that their pet is able to interact better than humans?

The distinction becomes complicated when we consider stimuli that could call two or more "functions" at a time. Instead, everything becomes simpler considering the existence of a basic mechanism capable of monitoring and encoding the position of our body and of what surrounds it, interacting with other processes / spaces / networks according to the context.

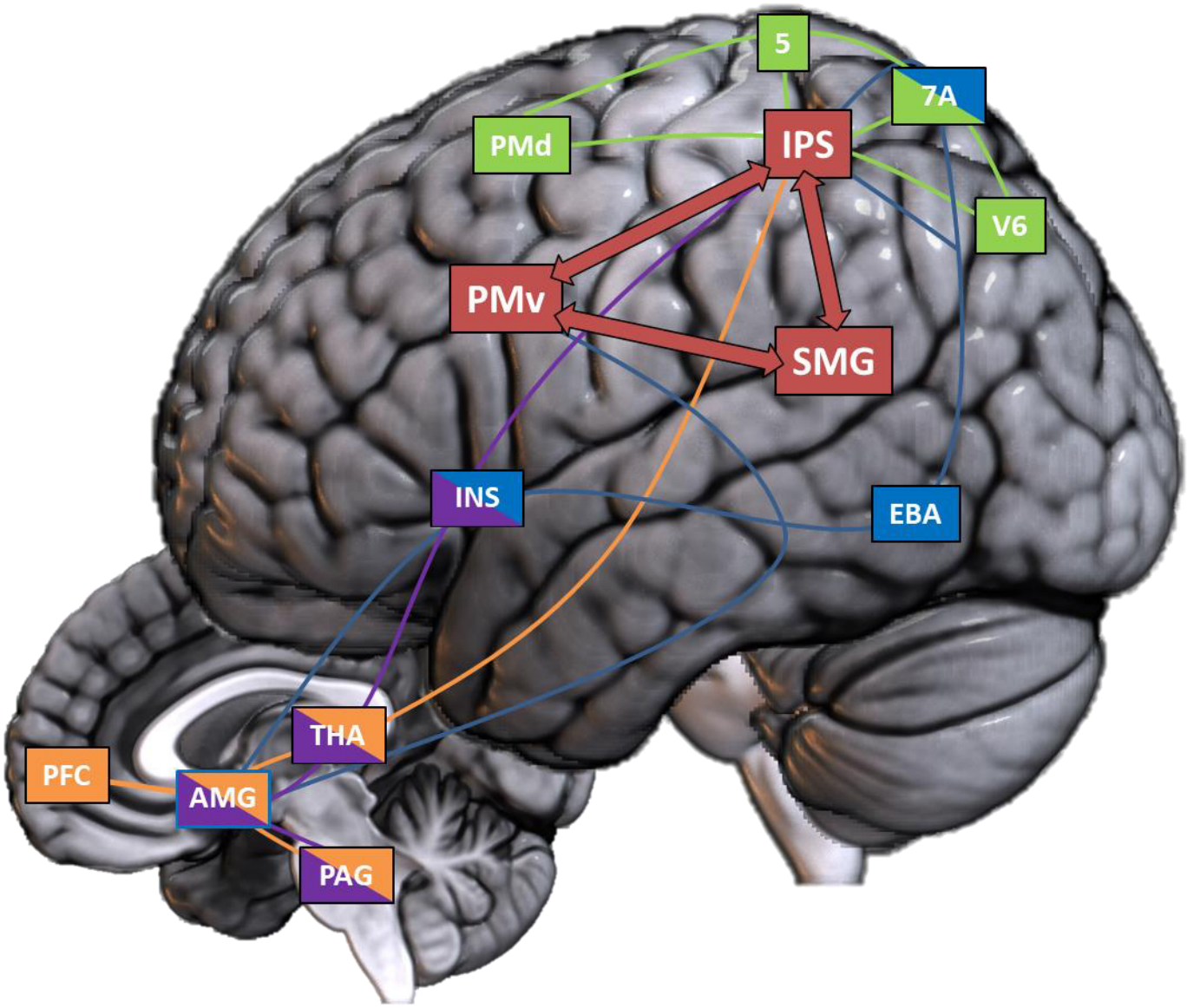

Figure 4.2 *Schematic representation of the main activation nodes of brain networks involved in the coding of reaching movements (green), in fear learning processes (orange), in the sensation of body ownership (blue, considering the exemplary case of RHI) and in the response to stimuli threatening (social and nonsocial, purple). The areas of the PPS core network, the common basis for the various networks described, are shown in red. Abbreviations: IPS=intraparietal sulcus, SMG=supramarginal gyrus, PMv/PMd=ventral/dorsal premotor cortex, EBA=extrastriate body area, THA=thalamus (pulvinar), AMG=amygdala, Ins=insula, PFC=prefrontal cortex (ventro-medial), PAG=periaqueductal gray.*

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