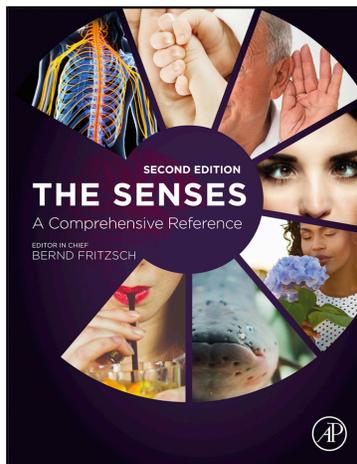


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4.22 How the Senses Guide Goal-Directed and Defensive Actions: Common Principles of Organization

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4.22.1 Abstract

Cortico-cortical connections link cortical areas in such a fashion to form information processing streams devoted to different functions, such as reaching, grasping, object construction and tool use, oculomotor intention and selective visual attention, working memory, decision making, and error and conflict monitoring. These functions are classically described as being subserved by internal models which combine sensory signals from multiple modalities with motor outflow operations. Conversely, internal models of defensive behavior aimed at the avoidance of noxious environmental events have rarely been discussed in the context of motor cognition. In this chapter we propose, instead, that injury avoidance through defensive behavior is generated by cortical areas, anatomical connections and functional motifs that are similar to those described for goal-directed actions. The similarity in functional architecture is founded not only on the wealth of entry nodes available for effective injury avoidance, but also on the outflow pathways which operate as those stemming from the cortical areas traditionally considered as devoted to purposeful actions. This view fully incorporates the brain operations underlying injury avoidance in the conceptual fame used to study and interpret cognitive-motor behavior, thus favoring the evaluation of the brain disorders affecting defensive behavior within a new perspective.

4.22.2 Introduction

4.22.2.1 The Parieto-Frontal Network for Contact-Related Actions

In the parietal and frontal cortex, a selected group of areas give rise to reciprocal cortico-cortical projections forming what has been called the “parieto-frontal network”, as well as to cortico-descending pathways. All of these cortical efferent systems are both anatomically and physiologically heterogeneous: they have different destinations, axon diameters, conduction velocities, synaptic efficacies, and underline manifold functions (see [Caminiti et al., 2017](#); [Battaglia-Mayer and Caminiti, 2019](#)). These projections have been widely discussed in relation to their role in learning and coordinating the operation of cortical areas for the formation of motor commands to be executed in the space surrounding the body. This discussion fits well with the recent reconceptualization of peripersonal space as a set of graded fields that map the value of actions that create or avoid contact between objects and the body, rather than as a portion of space of invariant geometry defined by proximity with the body or the hand reaching distance (for a review see [Bufacchi and Iannetti, 2018](#); see also [Bufacchi and Iannetti, 2019](#)). Different parieto-frontal streams are involved in the generation of different forms of behavior, such as fast reaching, object grasping and manipulation, object construction, tool use and associated mechanical problem solving, selective visual attention and oculomotor intention ([Caminiti et al., 2017](#)), as well as in encoding actions aimed at avoiding contact with objects potentially harmful for the body. The existence of such information processing lines has been inferred by combining data on the anatomical and functional properties of parietal and frontal neurons with those derived from the critical analysis of the consequences of brain lesion.

An elementary scrutiny of the basic features of such networks, mostly studied during actions based on eye-hand coordination, is that they combine information from different body parts and sensory modalities and, when transforming motor intentions into

action, their constituent neurons integrate sensory input transmitted by different sensory channels with both efferent copies of motor command and reafferent signals.

4.22.2.2 What Is the Functional Significance of the Cortical Responses Elicited by Noxious Stimuli Causing Pain?

A fundamental sensory experience throughout life is pain, which most of the time emerges as a consequence of the cortical response to the afferent volley transmitted by peripheral and central nociceptive pathways. However, the relationship between the degree of peripheral nociceptive afferent volley and pain can be notoriously weak, given the evolutionary advantage of being able, in several circumstances, to dampen painful sensations even in the presence of a strong nociceptive afferent barrage (Wall, 1982). Despite decades of research, the identification of the cortical activity giving rise to painful sensations remains elusive (Mouraux and Iannetti, 2018). A great number of studies recorded the EEG and fMRI responses elicited by transient nociceptive stimuli causing pain in humans. The majority of these studies have shown responses within a wide array of brain regions including the primary (S1) and secondary (S2) somatosensory cortices, the insula and the anterior cingulate cortex (ACC) (for a review see Iannetti and Mouraux, 2010). These responses are sometimes considered to reflect “the neural substrates of pain” (Ploghaus et al., 1999) or specific “neurological pain signatures” (Wager et al., 2013), on the basis of two facts: (i) they are consistently observed when subjects are experiencing acute pain; and (ii) their magnitude often correlates with the amount of pain experienced by the subject. However, this correlation between the magnitude of these brain responses and subjective pain is by no means obligatory, and it can be dissociated in opposite directions: these brain responses can be present when no pain is experienced, but they can also have small amplitude when intense pain is experienced. Indeed, most of these responses are also observed after equally salient, but never painful, auditory, tactile, and visual stimuli (Fig. 1) (Mouraux et al., 2011; Mouraux and Iannetti, 2009; Liberati et al., 2016). Also, when nociceptive stimuli causing pain are repeated at short and predictable intervals, a paradigm effectively dissociating nociceptive afference from stimulus saliency, these brain responses are drastically reduced in amplitude while subjective pain perception remains unchanged (Iannetti et al., 2008; Ronga et al., 2013), and only a small subset of stimulus-evoked electrocortical activity retains the ability to correlate with subjective perception (gamma-band oscillations; Zhang et al., 2012; Hu and Iannetti, 2019). Thus, given such bidirectional dissociations between most of the neural activity elicited by transient nociceptive stimuli and the presence of pain, the conclusion that this neural activity represents a pain signature is incorrect, and has generated several misconceptions (for a critical discussion see Mouraux and Iannetti, 2018; Hu and Iannetti, 2019; Iannetti et al., 2013). An alternative hypothesis about the functional significance of the cortical responses elicited by transient nociceptive stimuli is that they reflect the detection and the reaction to salient sensory input, regardless of the sensory modality through which that input is conveyed (Mouraux and Iannetti, 2018). The idea that such saliency-related responses are not related to the painful quality of the percept, but instead to the execution of appropriate behavioral responses is relevant to the issues discussed in this chapter. Indeed, as demonstrated during the execution of a simple isometric task (Novembre et al., 2018), a basic physiological mechanism links the large brain potentials traditionally elicited by salient supramodal stimuli (i.e., both nociceptive and non-nociceptive; Mouraux and Iannetti, 2009) with a modulation of motor output. This observation suggests that saliency-related cortical responses facilitate the execution of purposeful defensive actions (see also Moayedi et al., 2015). The spatial distribution across the scalp of this relationship is informative, particularly the modulation over the sensorimotor cortex ipsilateral to the somatosensory stimulus but contralateral to the hand exerting the force (Fig. 2, left panel), suggesting an effect of saliency on the corticospinal drive. It is important to note that while the scalp topography of the main negative and positive peaks of the saliency-related EEG responses is symmetrically distributed (Fig. 2, right panel), the scalp topographies of the “correlation” between these EEG responses and the modulation of the motor output is lateralized (Fig. 2, left panel). Given the existence of a number of premotor and anterior parietal areas projecting directly to last-order interneurons of the spinal cord in addition to the primary motor cortex (M1) (Dum and Strick, 1991, 2002; He et al., 1995; Rathelot et al., 2017), it is tempting to speculate that these nonprimary corticospinal projections might be modulated by saliency-related cortical activity, with the objective of preparing appropriate responses to current or future sensory input.

4.22.2.3 A Unifying Perspective on Goal-Oriented and Defensive Behavior

A crucial question arises: Beyond stereotyped reflex responses, can the avoidance of sudden and potentially noxious environmental events through immediate motor responses¹ be approached and studied through the same conceptual tools and experimental methods used for other purposeful non-defensive actions? Our hypothesis is that the avoidance of injury shares with the other action streams, so far described in the literature, the same “mental action space”—in other words a common internal model—and that the mechanisms underlying the avoidance of injury and pain are embedded in cortical processing streams with operation rules and logic similar to those underlying non-defensive actions, although these can also rely on reflexive responses (Bufacchi and Iannetti, 2018).

The framework we discuss here could be of conceptual relevance, since it implies that invariant anatomic-functional motifs of sensory-prompted motor behavior exist in the cerebral cortex, regardless of the action to be performed, be it aimed at interacting

¹With immediate motor responses we do not simply refer to stereotyped reflex responses, but to motor behaviors that, despite being urgent in nature, are not stereotyped, but dependent to a large degree on a number of contextual contingencies. A typical example of such an urgent, albeit non-stereotyped defensive response is the blink reflex elicited by electrical stimulation of the median nerve at the wrist (hand-blink reflex, HBR) (Sambo et al., 2012).

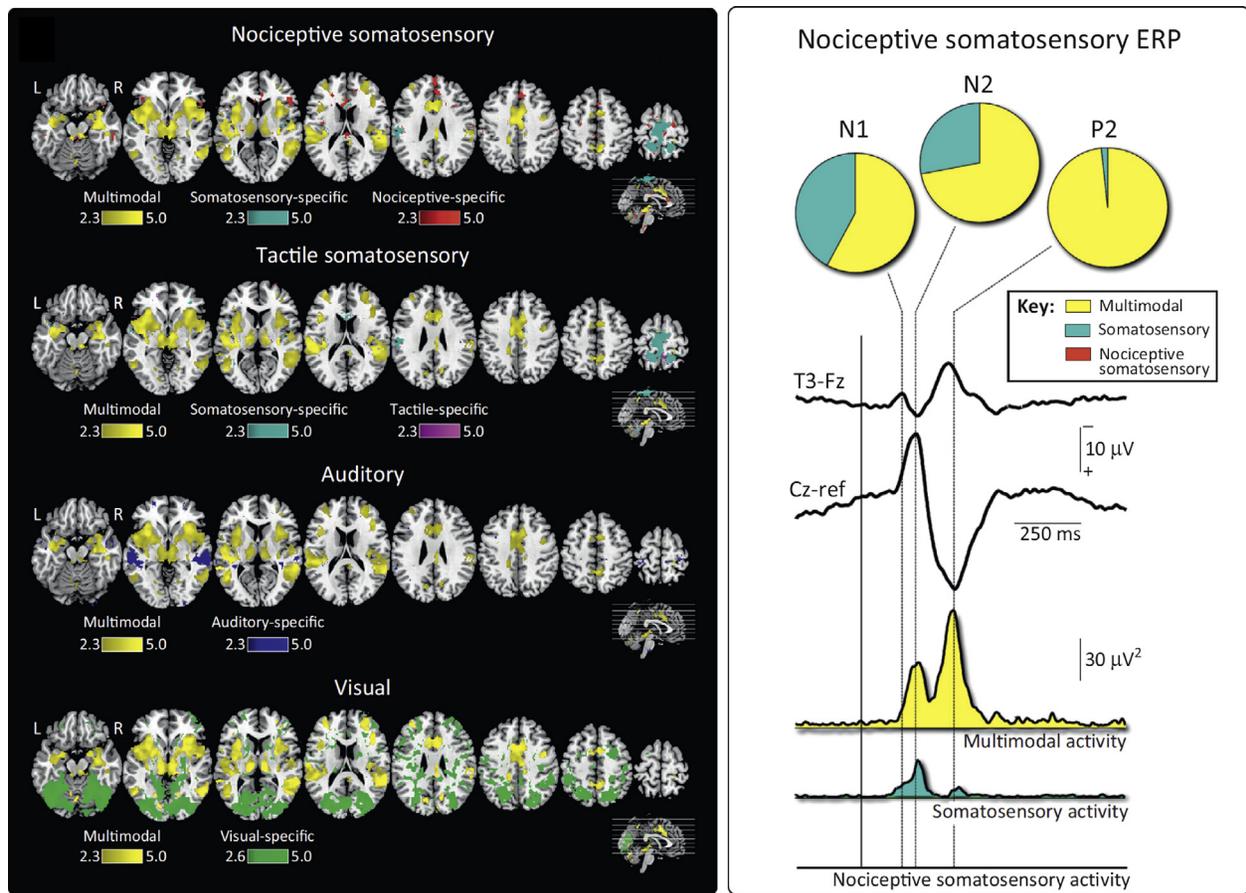


Figure 1 The left panel (data from Mouraux et al., 2011) shows the BOLD fMRI responses elicited by iso-salient and fast-rising nociceptive, tactile, auditory and visual stimuli (random-effect group analysis, voxel threshold $Z > 2.3$ and cluster threshold $P < 0.05$, corrected for multiple comparisons). Voxels responding to all four types of sensory stimuli (conjunction analysis) are shown in yellow. Voxels uniquely responding to stimuli delivered to the body (either nociceptive or non-nociceptive) are shown in cyan. Voxels uniquely responding to nociceptive somatosensory stimuli are shown in red. Voxels uniquely responding to non-nociceptive somatosensory stimuli are shown in purple. Voxels uniquely responding to auditory stimuli are shown in blue. Voxels uniquely responding to visual stimuli are shown in green. Note the large amount of spatial overlap between the responses elicited by all four modalities of sensory stimulation. The right panel (data from Mouraux and Iannetti, 2009) shows multimodal and somatosensory-specific activities contributing to the time-domain EEG responses elicited by nociceptive-specific laser stimuli. The greater part of the EEG response in the time domain is explained by supramodal brain activity (i.e., activity also contributing to the EEG response elicited by non-nociceptive somatosensory, auditory, and visual stimuli). This multimodal activity, shown in yellow as global field power, explains the largest part of the negative and positive vertex waves (N2 and P2, respectively). Somatosensory-specific brain activity (i.e., activity contributing to the response elicited by both nociceptive and non-nociceptive somatosensory stimuli, but not by auditory and visual stimuli), shown in light blue, contributes to the early, somatosensory-specific N1 wave, and to a small part of the negative vertex wave. Nociceptive-specific somatosensory activity did not contribute to the laser-evoked EEG response. The figure is adapted from Legrain, V., Iannetti, G.D., Plaghki, L., Mouraux, A., 2011. The pain matrix reloaded: a salience detection system for the body. *Progr. Neurobiol.* 93 (1), 111–124.

with visual objects or at preventing an interaction that could result in an injury, and hence in a source of pain. The existence of common mechanisms fully incorporates the avoidance of injury and pain into the field of motor cognition. Furthermore, the question posed at the beginning of this section might also be of clinical relevance, since it would determine whether the same strategies used to favor recovery of motor function after brain injury will also apply to the collapse of the cortical systems for pain avoidance. Unfortunately, virtually nothing is known about disorders of pain avoidance behavior, which to date have not been formally assessed in neurological and neuropsychological studies, remaining therefore unnoticed.

4.22.3 Parieto-Frontal Connections in Motor Cognition

The study of the design and logic of the network underlying cognitive-motor behavior is the necessary requirement for any analysis of the physiological basis of action control in general. The architecture of the network powerfully constrains its functional operations, and hence the encoding mechanisms emerging within and across cortical areas. The advancement in the study of cortical

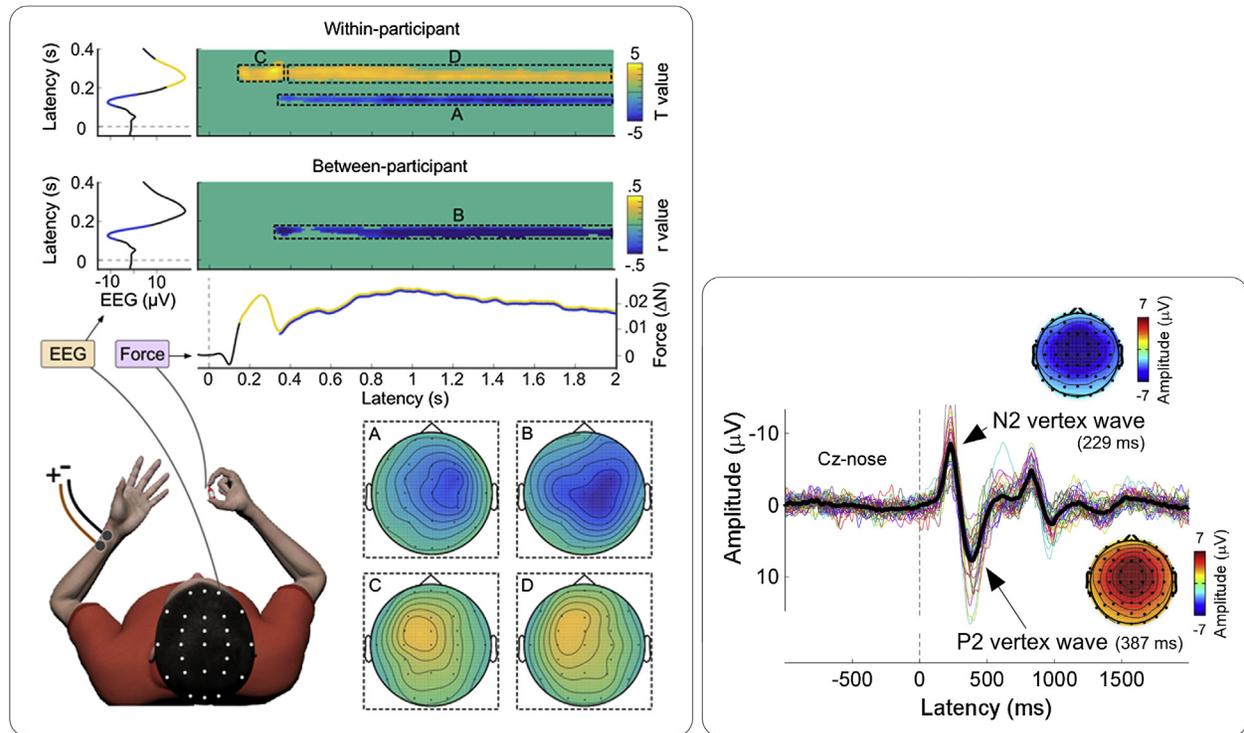


Figure 2 *Left panel:* Relationship between the time-domain 64-channel EEG responses elicited by transient somatosensory stimuli and motor output. Subjects were required to perform an isometric motor task: applying a constant force on a transducer using the thumb and index finger of the right hand, while receiving non task-relevant somatosensory stimuli on their left wrist. Top plots represent the correlation between EEG and force, for all possible pairs of time points, at electrode Cz. Note the relationship between EEG and force during both the vertex wave negativity and positivity within-participant, as well as the during the vertex wave negativity across participants. The group-level correlation with the vertex negativity (insets A and B) was lateralized toward the hemisphere contralateral to the stimulated hand (i.e., the hemisphere ipsilateral to the hand exerting the force). The correlation with the vertex positivity was strongest over the hemisphere contralateral to the hand exerting the force (i.e., the hemisphere ipsilateral to the applied stimulus) (insets C, D). These lateralized correlation topographies can be compared with the symmetrical voltage topographies (64-channel EEG) of nociceptive-evoked negative (N2) and positive waves (P2) at electrode Cz, shown in the *right panel*. Thin colored waveforms represent single-subject average waveforms, whereas the thick black line represents the group-level average waveform. *Left panel* (data from 28 participants, Novembre, G., Pawar, V.M., Bufacchi, R.J., et al., 2018). Saliency detection as a reactive process: unexpected sensory events evoke corticomuscular coupling. *J. Neurosci.* 38, 2385–2397. *Right panel* (data from 34 participants, Hu, L., Cai, M.M., Xiao, P., Luo, F., Iannetti, G.D., 2014). Human brain responses to concomitant stimulation of A δ and C nociceptors. *J. Neurosci.* 34, 11439–11451).

connectivity has elucidated key structural features of cortico-cortical and cortico-descending systems, which are very relevant for action signal processing and motor performance.

4.22.3.1 Anatomical Substrates

An undisputed observation is that cortico-cortical connections link cortical areas in a graded fashion, since any given area projects to other areas in the same or opposite hemisphere with different strength and through axons of different diameters, targeting different nodes with varying conduction velocity and synaptic efficacy (Caminiti et al., 2009; Tomasi et al., 2012). This excludes one-to-one relationships between individual areas, undermining the credibility of hierarchical communication schemes in favor of the idea of a distributed architecture with multiple parallel routes of interplay. As an example, within the parieto-frontal network, parietal areas PEip (PE intraparietal) and MIP (medial intraparietal), which form the dorsal bank of the intraparietal sulcus (IPS), are both connected, although with different strengths, with parieto-occipital and frontal premotor and motor cortices, and both PEip and MIP exchange information with at least ten other different areas (see Caminiti et al., 2017). Then, based on task demands, this information can be routed toward the functional stream more suitable for proficient processing, such as fast hand reach vs. object grasping and manipulation in the presence of affordances (Gibson, 1979), as well as defensive behavior in the presence of threatening stimuli. Successful motor performance can only be achieved by the precise selection of entry nodes, processing stream and outflow pathways.

4.22.3.2 Gradient-Like Organization of Functional Properties

Thanks to the connectivity rule described above, the parieto-frontal system is organized in a gradient-like fashion (Johnson et al., 1996; Burnod et al., 1999; Battaglia-Mayer et al., 2016). Areas located more caudally in the parietal lobe tend to

communicate preferentially, but not exclusively, with more rostral frontal areas, and vice versa, and a gradual transition of neural properties occurs in the tangential domain of both parietal and frontal cortex. This transition of properties relates to topographical features, such as the effector set in motion, that is eye vs. hand or both, as well as to the functional signals represented.

A large body of physiological evidence from studies in behaving monkeys performing actions that require eye-hand coordination indicates that cells at all levels of the network combine eye-hand signals, although with varying dominance. Neural activity-types concerning the position of the hand in space and of the eye in the orbit are distributed in a rather uniform fashion across posterior parietal and frontal premotor areas, as if to form an eye-hand matrix (for a review see Battaglia-Mayer, 2019) spanning many architectonic fields. This across-boundaries arrangement is not surprising, since the exact information about eye and hand position is crucial to estimate their distance from the target, which is a necessary information for successful saccades and/or reaching toward the target location. This information is also necessary for predicting the impact and/or the interception point of approaching and potentially harmful objects, in order to deploy the best motor plan for effective pain avoidance. Concerning the eye, it is worth stressing that beyond exploratory saccades, the angle of gaze determines the focus of overt visual attention, which is represented in area 7a (PG) by patches of activation about 800 μm wide, embedded in a matrix of eye position signals (Raffi and Siegel, 2005), which together with eye movement influence neural activity across different inferior parietal areas, such as the lateral intraparietal area (LIP) (Barash et al., 1991). In most instances, particularly during sequential actions, the position achieved by the eye after a saccade marks landmark location in space to guide the next hand movement (Land et al., 1999), as also happens for obstacles avoidance (Johansson et al., 2001).

Furthermore, physiological studies in macaques (Johnson et al., 1996; Battaglia-Mayer et al., 2001) have shown that, contrary to eye and hand position signals, other information, such as visual sensitivity and eye movement, are unevenly distributed in the parieto-frontal system, since they are preferentially represented at more caudal levels of the superior parietal cortex (areas 7 m, V6A, MIP), and in the most rostral sectors of dorsal premotor cortex (area F7), while conditional visual activity contingent on action planning for arbitrary visuomotor associations dominates in the caudal part of dorsal premotor cortex (PMd/F2). The representation of hand movement-related activity increasingly dominates as one moves rostral in parietal and caudal in frontal cortex, that is toward M1. In motor cortex, visual sensitivity is scant and highly task-dependent, since it emerges, for instance when monkeys are exposed to expanding optic flow fields (Merchant et al., 2001), as during forward locomotion. Superimposed to this gradient, there exists a second one related to the distribution of signals concerning planning and execution of eye and/or hand movement, the first more represented in caudal parietal and rostral frontal areas, the latter in an opposite fashion.

In everyday life, the eye and the hand can move in coordination, isolation, or in a spatially-decoupled manner, such as when grasping the mouse while looking at the computer screen, or when the position of the visual target to be followed is different from that of the acting hand, which happens while playing videogames, manipulating physical objects that have a pivoting point, or robotic devices during endoscopic surgery, tool use, etc. In all cases, the parieto-frontal network can offer the necessary anatomic-functional substrate to encode such complex forms of cognitive-motor behavior.

4.22.3.3 Entry Nodes of the Network and Local Computations

Different task demands can recruit a large combination of eye-hand actions and, at the same time, select specific entry nodes for information processing. Here, the term entry node refers to the area or set of areas recruited first and preferentially to fulfil the task requirements: in other words, the cortical region/s at which novel task-relevant information enter a processing stream.

Entry nodes of the network should be endowed with functional properties necessary for task satisfaction, which is precise local information about eye, hand and limbs position, and this can be generated by the parieto-frontal eye-hand matrix. Obtaining this information from remote areas in the network through cortico-cortical connections, which are formed by thin myelinated axons and by a small contingent of unmyelinated ones (Tomasi et al., 2012; Battaglia-Mayer and Caminiti, 2019), would accumulate transmission delays and should face the weak synaptic efficacy of communication in long oligosynaptic systems, some of which mainly exerts a non-driving modulatory action and necessitates spatial and temporal summation (see Novak and Bullier, 1997; Rockland, 2015). Furthermore, cortico-cortical communication occurs in a slow, temporally dispersed fashion (Caminiti et al., 2009), as a consequence of the large spectrum of axon diameters through which any given cortical area communicates with other areas in the cortex.

We consider local availability of relevant information at all nodes of complex networks as a prerequisite for the computations of local commands, and as a major achievement of cortical evolution. Such design would favor massive parallel and recursive modes of operations on top of the basic hierarchical structures of sensory channels, and would mitigate the metabolic costs associated to fast transmission along large-sized myelinated axons. Then, the advantage of temporally dispersed communication schemes is that they favor an expansion of the post-synaptic oscillatory regimes of the cortex, making a simultaneous representation and read-out of different reference frames for potential actions theoretically plausible, regardless of the nature and fusion of driving sensory signals.

One can imagine that when an intention to act is shaped, a selection mechanism will recruit the network most appropriate to encode the transition from intention to action. How this process is represented in the network could be suggested by the spatial distribution of the relevant signals within the parieto-frontal gradient that, when recruited, could provide a neural image of the information flow underlying such state transitions.

4.22.3.4 Clusters of Parietal and Frontal Areas, Information Domains, Processing Streams

The consequence of such gradient-organization, shaped by the antero-posterior arrangement of anatomical and physiological properties, is that cortico-cortically connected parietal and frontal areas share some basic functional properties. Hierarchical cluster analysis based on cortico-cortical connectivity of these areas has highlighted the statistical structure of this feature of cortical organization and has consistently shown that parietal and frontal areas sharing cortical connections tend to be grouped into functional clusters (Averbeck et al., 2009; Caminiti et al., 2017). Therefore, in the network's design clusters stay at a higher level than individual cortical areas, since they offer a multiplicity of access points, elaboration nodes and outflow paths. Thus, the functional possibilities offered by clusters outperform those offered by individual cytoarchitectonic areas, thereby providing a rich local computational reservoir to meet the task demands emerging from the manifold action choices of everyday life.

A further and more complex level of organization is that formed by functional domains (see also Kaas and Stepniewska, 2016). In fact, parietal and frontal clusters with congruent functional properties are linked by association connections. For instance, the intraparietal connections between the areas of the parieto-occipital junction (V6a, PEc and 7 m), and those of the dorsal bank of the intraparietal sulcus (MIP, PEip), shape the hand dominant domain of the posterior parietal cortex. Similarly, the cortical connections linking different frontal clusters formed by premotor areas F2, F4, SMA (Supplementary Motor Area), CMAAd/v (Cingulate Motor Areas dorsal and ventral) and M1, shape the hand motor output domain of frontal cortex. The connections linking these two domains give rise to the Dorsal Reaching System (DRS), which is recruited for fast hand reaching and its online control. The DRS provides an example of one of the processing streams embedded in the parieto-frontal network.

In a similar fashion, the somatosensory input from S1, the visual motion input from MSTd (dorsal middle-superior temporal area), the vestibular input from parieto-insular vestibular cortex (PIVC; Grüsser et al., 1990) and the combined optic flow/vestibular signals from visual posterior Sylvian (VPS) area (Chen et al., 2011) to VIP (ventral intraparietal area) shape a parietal domain related to the detection of visual objects moving relative to the head and face (Colby et al., 1993; Duhamel et al., 1998). This parietal domain shares some functional properties with ventral premotor area F4, which is connected with VIP (Fig. 3), and together might subservise a Peripersonal Action Fields System for threat avoidance (Battaglia-Mayer and Caminiti, 2019; see also Bufacchi and Iannetti, 2018). Interestingly, this system is enriched by an independent direct access to the spinal cord, thanks to descending projections from F4, which carry information at about 6 m s^{-1} (Innocenti et al., 2019). However, given the short path length of the fibers connecting F4 and M1 and the faster conduction velocity of descending spinal projections from the latter (about 15 m s^{-1} ; Innocenti et al., 2019), it is plausible that fast reactions for defensive behavior, which in general rely on parieto-frontal interactions (Cooke et al., 2003; Graziano and Cooke, 2006; Kaas and Stepniewska, 2016), mostly depend on motor cortex (Cooke and Graziano, 2004; Kaas and Stepniewska, 2016). In this context, the F4 descending projection can modulate the motor cortex outflow to spinal interneurons and/or be recruited for other ethologically relevant actions, such as reaching for food and bringing it to the

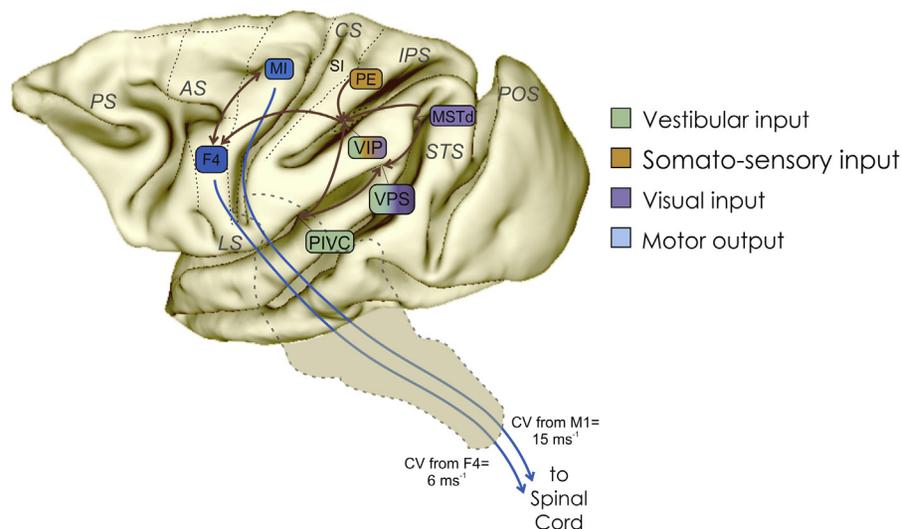


Figure 3 Peripersonal action fields system for pain avoidance and defensive behavior. Network of cortical areas and their descending motor output pathways are shown on the image the macaque monkey brain, where the main sulci have been opened to show the cortical areas located in their banks. Through cortico-cortical connections (brown arrows), area VIP (ventral intraparietal area) receives visual motion signals from MSTd (medial superior temporal area), vestibular input from PIVC (parieto-insular vestibular cortex), combined vestibular/optic flow information from visual posterior Sylvian area (VPS) and somatosensory signals from parietal area PE. VIP projects to ventral premotor area F4, which is reciprocally connected with M1 (primary motor cortex). Both these frontal areas project (blue arrows) to the motor output centers of the spinal cord, that is to ventral laminae, with axons of different diameter and conduction velocity (CV). The color coding of different information traveling in this network is shown on the right. For explanations, see text. PS, principal sulcus; AS, arcuate sulcus; CS, central sulcus; LS, lateral sulcus (Sylvian fissure); IPS, intraparietal sulcus; STS, superior temporal sulcus; POS, parieto-occipital sulcus.

mouth (Fogassi et al., 1996; Gentilucci et al., 1988) and can convey saliency-related information to the peripheral motor apparatus of the spinal cord.

Processing streams are not private routes related to just one function, but rather subserve the choice of actions of different complexity. An example is provided by those actions formed by sequences of eye and hand movement that unfold over an extended time and require constant performance monitoring, such as object construction (Chafee et al., 2005, 2007), and spatial mazes solution (Crowe et al., 2004, 2005). These studies show an important role of the inferior parietal areas PG and Opt, none of which, however, project to premotor and/or motor cortex. Therefore, how the outflow of parietal operations underlying these actions reach the motor output remains, at first glance, puzzling. Detailed analysis of the overall connectivity in the network show, instead, that area PG projects to the hand-dominant domain of the Dorsal Reaching System, through intrinsic parietal connections and therefore might “use” this route to access the motor output domain of the frontal lobe (Caminiti et al., 2017), thus specifying a potential Lateral Action and Reaching System (LARS). This would be at variance from cortical coding of tool use, which involves area PEip, since this projects in a direct fashion not only to premotor and motor cortex, but also to the last-order interneurons of the spinal cord (Rathelot et al., 2017), and could, in principle, address the spinal output centers in a direct way, bypassing motor cortex. Thus, the outflow of parietal operations concerning tool use could access motor cortex through cortico-cortical connections, and in parallel access the motor periphery via parieto-spinal connections carrying signals at about 9 m s^{-1} (Innocenti et al., 2019). This is not only an example of parallel processing of information, but also of redundancy of processing streams and outflow pathways, which are two other pillars of the edifice of motor cognition.

4.22.3.5 Redundancy and Heterogeneity in Cortical Networks

Redundancy is a general rule of most parietal and frontal areas linked by ipsilateral connections (Caminiti et al., 2017; Battaglia-Mayer and Caminiti, 2019). Redundancy, however, poses a recruitment problem, since incoming signals can be routed through different access nodes of the network. It is reasonable to assume that this selection is based on the congruency between task demands and physiological properties of the stream set in motion. Conditional motor behavior (arbitrary sensory-motor mapping) recruits a network centered on dorsal premotor cortex as putative entry node (see Wise et al., 1997 for a review), while hand reaching will probably recruit first parieto-occipital and dorsal premotor areas (Johnson et al., 1996; Battaglia-Mayer et al., 2000, 2001). However, when the task contingencies change, such as when the target for hand reaching is suddenly displaced in space during reaction or movement time, the change of target location calling for fast correction of hand trajectory is first signaled by premotor rather than by parietal cortex (Archambault et al., 2011). The late timing and prolonged duration of activation of the latter rather suggests an involvement in the state estimate of motor periphery. During action unfolding over a long time, such as object construction, one can imagine a network dynamic dependent on continuous updates and eventual re-selection of local access points, to satisfy ongoing and time-varying requests. Defensive behavior can be driven by visual motion signals about approaching objects recruiting areas MSTd and VIP, and refined thanks to the convergence of somatosensory information, provided by parietal area PE to VIP, concerning the body part that could be potentially injured (Somervail et al., 2019). Furthermore, additional sensory information consists in vestibular and optic flow signals coming from the sylvian areas discussed above (PVC and VPS). This is a clear example of heterogeneity of properties, however tuned at the service of a complex and ethologically relevant form of sensorimotor behavior.

Thus, the selection of the entry point can be updated during the temporal evolution of the task, to face novel demands, a process that can rely on the recursive signaling permitted by the reciprocity of most parieto-frontal connections.

Concerning outflow pathways, descending projections to the spinal interneurons and/or motoneurons stem not only from M1, but also from dorsal (F2) and ventral (F4) premotor cortex, from the cingulate motor areas (CMA_d, CMA_v) and from supplementary motor cortex (SMA). The recent characterization of the axon diameters and synaptic boutons of most of them has revealed that they all convey information through a wide spectrum of conduction velocities and, potentially, with varying synaptic efficacy (Innocenti et al., 2019). Furthermore, the posterior portion of the precentral gyrus, indicated as the “new M1” (Rathelot and Strick, 2009), projects in a privileged monosynaptic fashion to the spinal motoneurons for the direct control of independent fingers movement, hence of skilled hand actions.

The existence of descending pathways from most of the areas of the parietofrontal systems suggests that, because of their local nature, many computations might not require M1 as cortical output-center. Furthermore, the existence of descending projections carrying information at different speeds even within the same system, as for fast and slow pyramidal tract fibers, allows a flexible selection of the local outflow path most appropriate to satisfy the task requests (Miri et al., 2017). The local nature of command functions suggests that cortico-cortical connectivity underlies both the acquisition of motor skills as well as the orchestration of inter-areal communication to face changing task demands and to store memory traces of learned actions and associations (for a discussion see Battaglia-Mayer and Caminiti, 2019).

Redundancy, while offering manifold choices for recruitment and output operations, might also mitigate the consequences of network lesion, favoring plastic network rearrangements (Sanes and Donoghue, 2000; Ungerleider et al., 2002; Dayan and Cohen, 2011), probably within the frame of the homeostatic regulation of cortical circuits (Turrigiano, 1999; Marder and Goaillard, 2006; Keck et al., 2013).

A common feature of all processing streams so far described is the heterogeneity and richness of functions that they encode, a characteristic that has progressively emerged over the years, thanks to behavioral neurophysiology in non-human primates

and fMRI in humans (Daitch and Parvizi, 2018). This makes problematic the classical formulation of cortical connectivity beyond extrastriate visual areas in terms of dorsal and ventral streams, the “where” and “what” pathways (Ungerleider and Mishkin, 1982), and its more recent update in terms of “how” and “what” streams (Goodale and Milner, 1992). As an example, the parieto-prefrontal stream linking the caudal IPL parietal areas with posterior prefrontal areas is involved in diverse functions, including directed visual attention (7a; LIPv; Mountcastle et al., 1975; Lynch et al., 1977; Bushnell et al., 1981; Liu et al., 2010) and reorienting (area 7a; Steinmetz and Constantidinis, 1995), saliency (LIP; Colby and Goldberg, 1999; Bisley and Goldberg, 2010), novelty (LIP; Foley et al., 2014), mirror attention (LIP; Shepherd et al., 2009), visually-guided eye movement (LIPd; Barash et al., 1991; Liu et al., 2010), distributed control of reaching (area 7: Opt/PF/PFG/PGm; Mountcastle et al., 1975; Hyvärinen, 1981; Battaglia-Mayer et al., 2005), motor intention (LIP, Snyder et al., 1997; Opt/PG, Battaglia-Mayer et al., 2005), decision-making (LIP; Shadlen and Newsome, 2001; Roitman and Shadlen, 2002; Gold and Shadlen, 2007; Churchland et al., 2008; de Lafuente et al., 2015). The different visual field representations (Arcaro et al., 2011; Ben Hamed et al., 2001; Blatt et al., 1990; Galletti et al., 1999; Patel et al., 2010) of posterior parietal areas, including LIP and CIP, subserve analysis of object 3-D structure (Gnatt and Mayes, 1995; Shikata et al., 2001; Vanduffel et al., 2002; Orban, 2011), size (Durand et al., 2005), 3-D orientation axis/perspective (Tsutsui et al., 2001; Rosenberg et al., 2013), texture gradients (Tsutsui et al., 2002). These signals are all necessary for the perceptual discrimination and fine visual analysis for object and tool use. If one only considers the variety of function attributed to the prefrontal areas which are the target of cortical projections from the inferior parietal cortex, there can be no doubt that, within the general processing streams described, our understanding of cortical operations remains primitive. Therefore, any attempt to confine cortical functions within processing streams intended as private information routes is conceptually problematic since it does not capture the full complexity of parietal and frontal functions.

Heterogeneity and redundancy of representation is an additional factor making it plausible that pain avoidance shares with the action systems above discussed similar organizing principles.

4.22.4 Peripersonal Space and the Relevance of Contact-Related Actions

The complexity of the actions streams so far described, together with the richness of functions that they encode have been instrumental to the recent proposal of a novel conceptualization of peripersonal space (Bufacchi and Iannetti, 2018). Peripersonal space (PPS) is a concept used in a wide range of disciplines and derives from the observations that when stimuli occur close to the body several behavioral and physiological responses are enhanced (Hediger, 1955; Hall, 1969; Graziano and Cooke, 2006; Sambo et al., 2012). Still, a clear and univocal definition of PPS is lacking, and a great deal of terminological confusion reigns (for a detailed discussion, see Bufacchi and Iannetti, 2018). The predominant view of PPS emphasizes the spatial dimension of this concept: PPS is typically described as a single space with clear boundaries with other portions of space more distant from the body,² and defined by the proximity to the body or to certain body parts of the stimulus used to probe it. Interestingly, a careful scrutiny of the existing neurophysiological and behavioral data contradicts the description of a single, proximity-dependent space with clear boundaries.

With respect to the notion that peripersonal space has clear boundaries, it is important to consider that virtually all recordings of behavioral and physiological responses elicited by sensory stimuli presented at a range of distances from the body or a body part show a graded response. To take an example from human behavioral neurophysiology, the blink reflex elicited by intense somatosensory stimulation of the median nerve at the wrist (hand-blink reflex, HBR) is stronger when the stimulated hand is closer to the face (Sambo et al., 2012). Although variable across subjects, this proximity-dependent increase consistently follows a graded rather than a step-wise function (Sambo and Iannetti, 2013). Similarly, a number of visuo-tactile or audio-tactile bimodal neurons present in cortical structures similar to those discussed in the early part of this chapter (i.e., parietal and premotor areas) respond more strongly to visual or auditory stimuli when they are closer to the somatosensory receptive field, and this increase of response magnitude is graded rather than step-wise (Graziano and Cooke, 2006). Interestingly, some of these neurons also respond to stimuli presented far away from the body (Colby et al., 1993), or even respond less strongly to stimuli that are close to the body. The complexity of the functions subserved by the anatomical streams described in previous sections can help in reconciling these inconsistencies.

The proximity-dependent definition of PPS is a second important notion contradicted by empirical data. Indeed, there is a wealth of factors other than proximity that can modulate the magnitude of PPS-related behaviors of neurophysiological responses. These factors are both features of the stimulus eliciting the response and features not related to the stimulus. They include stimulus direction and trajectory, subject movement, but also stimulus valence, gravitational cues, and the environmental landscape (e.g., Bufacchi and Iannetti, 2018; Somerville et al., 2019). As some of us have argued in detail elsewhere (Bufacchi and Iannetti, 2018), this primacy of proximity as a factor determining PPS responses (a primacy also facilitated by the fact that those responses are considered to relate to a space) is a source of misinterpretation of many observed empirical modulations. The evidence that stimulus proximity is the most important determinant of the so-called PPS measures is lacking.

²These more distant portions of space are often confusingly called extrapersonal space. This does not bring clarity to the discourse as all space surrounding the skin is extrapersonal.

The seminal work by Mountcastle (Mountcastle et al., 1975) on the command functions of the parietal lobe offered a view of the internal representation of the action space not as an immutable geometrical entity, but rather as a construct whose configuration was defined by the action affordances available for eye-hand operations. In fact, actions within this space were reflected in neural activity only in the presence of the animal's motivation, attentive behavior, and possibility of successfully interacting with behaviorally or ethologically relevant objects.

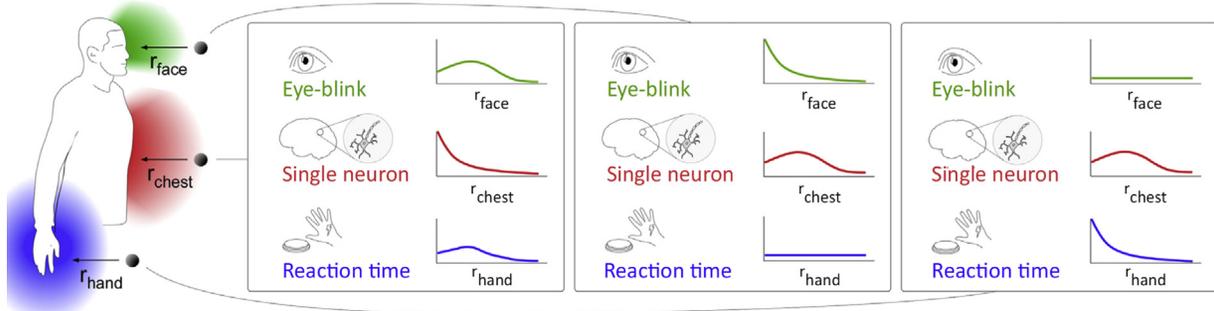
Peripersonal space is also often presented as a single space. This third aspect of the common description of PPS also does not hold when empirical evidence is carefully scrutinized. Indeed, the range of PPS-related measures is vast, ranging from single-cell recordings of cortical and subcortical neurons in primates to reaction times to audio-tactile stimuli in humans. Most of these many responses have in common that their magnitude depends largely (but by no means uniquely) on the proximity between the stimulus and the body or a body part. It is probably this fact that led these responses to be classified under the umbrella term of 'PPS'. However, different PPS-related measures depend on proximity in very different ways. For example, some measures increase in magnitude only when the stimulus is less than a few centimeters from the body, while others start increasing already when the stimulus is tens of centimeters from the body. Also, the body part to which the stimulus is close can change from measure to measure. For example, some measures depend on the proximity between the stimulus and the limb, whereas other measures depend on the proximity between the stimulus and the face (for an exhaustive discussion see Bufacchi and Iannetti, 2018) (Fig. 4). This makes it clear that talking about 'the' PPS does not help clarifying what these responses reflect.

Some of us have proposed that PPS should be conceptualized as a set of continuously graded response fields (Bufacchi and Iannetti, 2018). Each of these field describes the magnitude of a certain physiological or behavioral measure. The key question is: what is the physiological property that these different field magnitudes reflect? We have proposed that they reflect the value of some actions. Specifically, of those actions aiming to create or avoid contact between environmental objects and the body. As described elsewhere, "this framework contains three concepts with important implications: (i) a field allows PPS measures to change gradually with distance, rather than to define an in-or-out space; (ii) a set [or a class] of fields reflects the fact that there are many different PPS measures showing different response profiles; and (iii) behavioral relevance to actions aiming to create or avoid contact between objects and the body explains the functional significance of the values composing the PPS field of each action, and the fact that factors other than proximity affect PPS measures. This framework can explain seemingly anomalous empirical observations and resolve some of the definitional and conceptual issues affecting the field" (Bufacchi and Iannetti, 2018). Many PPS-related measures are indeed actions aiming to avoid the contact between objects in the environment and the body: this explains why many PPS-related measures (either behavioral or neural) are related to the head, where major sensory organs are located and avoiding the contact of potentially injurious objects is critical. The obvious example is the hand-blink reflex, aiming, by interposition, to avoid the contact between objects and the cornea. It is behaviorally advantageous that the blink strength depends on the proximity between the eliciting stimulus and the face, as well as on the presence of environmental objects that can protect or increase the harm to the eye (Sambo et al., 2012; Somerville et al., 2019).

The idea that physiological and behavioral measures traditionally associated with PPS instead reflect the value of contact-related actions fits with the framework of the interactive behavior, recently reviewed by Cisek and Kalaska (2010): rather than being the results of a serial process (from sensory input to cognitive decisions to motor output), behavior is described as a set of concomitantly active processes that define a number of motor actions and at the same time select among them. The interactive behavior framework is relevant with respect to the ideas developed in this chapter because the cortical sites where the competing actions are specified and selected are part of the parieto-frontal stream described earlier in this chapter. It is not surprising that the same parietal and premotor areas are the same cortical sites either from where "PPS-related" single neurons have been recorded or whose activity is thought to subserve the modulation of many PPS-related measures. Neurons in these areas, such as in VIP, combine and align somatosensory and visual motion signals, allowing the visual analysis of approaching objects (Colby et al., 1993; Duhamel et al., 1998) potentially colliding with different body parts, face and head in particular. VIP neurons also encode heading direction and perception (Schlack et al., 2002, 2005; Britten, 2008; Chen et al., 2011, 2013, 2016), and participate in the estimation of the numerosity of items in the visual scene (Nieder, 2016; Nieder and Dehaene, 2009; Nieder and Miller, 2004), all properties that can be of crucial relevance to approach or avoidance behavior. The outflow paths of this Peripersonal Action Fields System (PAFS) can either be the slow F4 projection to the spinal cord, which probably convey saliency-related information and/or the fast-pyramidal fibers stemming from MI, depending on the response imposed by the behavioral context. The circuit is available, since VIP projects to F4, which in turn projects to MI.

It is thus clear that the novel reconceptualization of PPS not as a representation of stimulus spatial configuration, but as behavioral relevance fits remarkably well with the idea already suggested by Mountcastle et al. (1975). Although he also suggested a primacy of proximity (intended as action space), he clearly proposed the idea that the activity of parietal neurons identifying such space for action indicates that the configuration of the action space (which, in the current reformulation, we define as the combination of several contact action value fields) is not an immutable geometrical entity. Instead, the action space configuration is highly flexible, depending on the presence and the degree of environmental threats and affordance that require coordinated hand-eye operations, locomotor activity, and whole-body displacement, among others. It is worth stressing that the deployment of such activities rests not only on sensory information traveling through all sensory channels, but also on the activation of other systems, such as those controlling the level of excitability of the cortex, the reward value, and the emotional state accompanying defensive behavior, therefore to the modulation of the core systems of the brainstem.

Panel A: Heterogeneity of PPS fields



Panel B: Additional factors modulate PPS-related measures

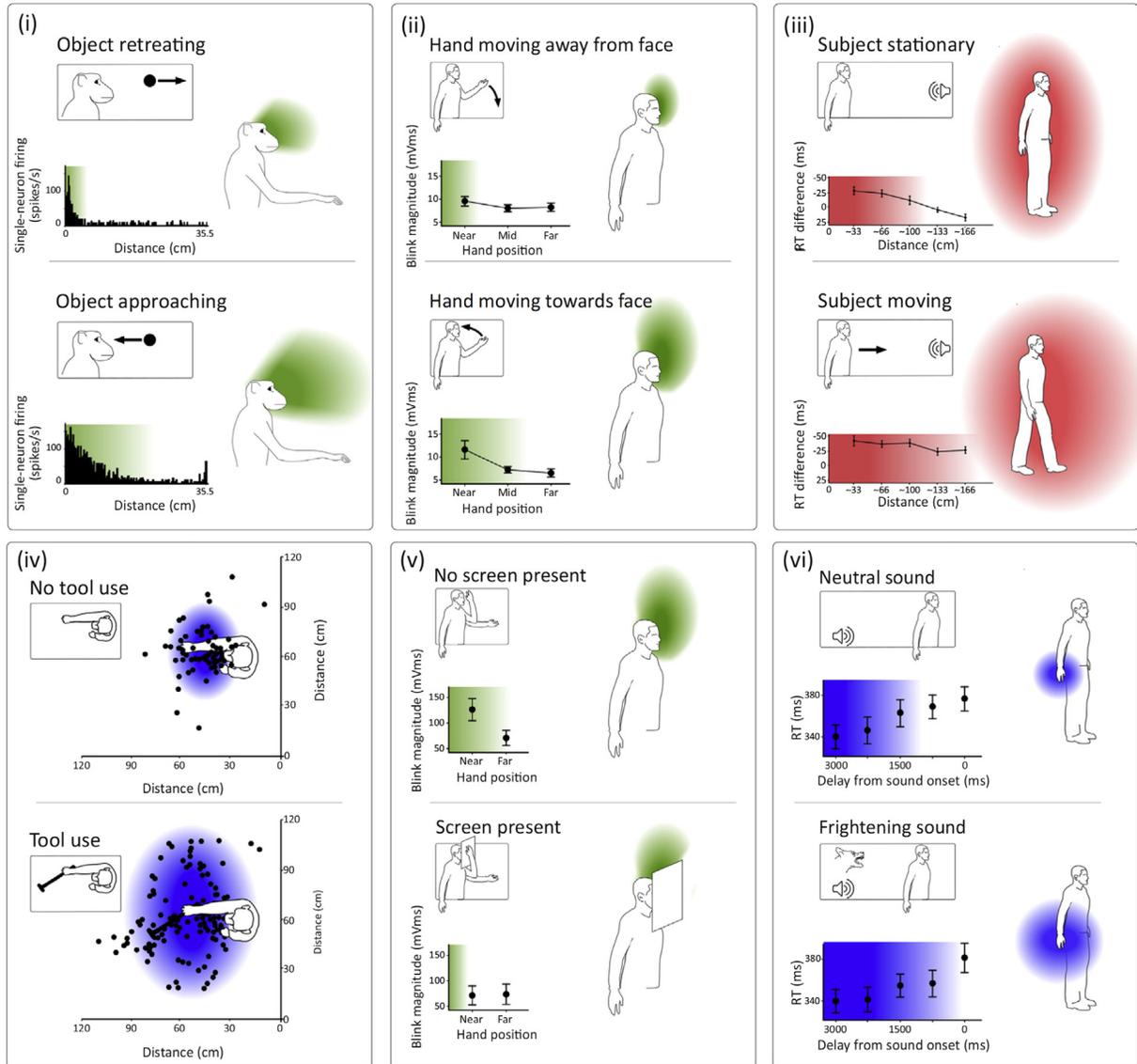


Figure 4 Peripersonal space reconceptualized not as a proximity-dependent space, but as a set of fields reflecting the relevance of actions aimed at creating or avoiding contact between objects and the body. The top panel (A) shows that there is not a single PPS, but that different “PPS-related” measures (in the figure the eye blink [green], the firing of a visuotactile single neuron with a somatosensory receptive field on the chest [red], and the reaction times to tactile hand stimuli [blue]) allow deriving different fields, each reflecting the value of the action related to the measured used. The bottom panel (B) shows that factors other than proximity modulate such value fields. These factors are both related to motion (e.g., motion of a visual stimulus, of stimulated limb, of the entire body), and independent from motion (e.g., tool use expanding response fields, screens defensive for the eye change the value of blinking, frightening sounds facilitating tactile reaction times). Reproduced with permission from Bufacchi, R.J., Iannetti, G.D., 2018. An action field theory of peripersonal space. *Trends Cogn. Sci.* 22, 1076–1090.

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