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COMPREHENSIVE REVIEW

Contribution of transcranial magnetic stimulation in assessing parietofrontal connectivity during gesture production in healthy individuals and brain-injured patients

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Summary Parietofrontal (PF) networks link the posterior parietal cortex to premotor and prefrontal areas, and are involved in the control of many motor and cognitive behaviors in healthy humans. In recent years, electrophysiological experiments have provided a better understanding of the functional specificity and temporal involvement of the PF networks' different components during the planning of visually guided upper limb movements. In particular, transcranial magnetic stimulation has been used to temporarily inactivate a cortical area (virtual lesions) or to assess connectivity using paired-pulse protocols)). This approach has shed new light on the neural mechanisms that underlie the planning stages of the reaching and grasping phases of transitive movements. Reaching and grasping were often presented as two distinct processes; in fact, the respective involvement of dorsolateral and dorsomedial networks may

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Abbreviations: AG, Angular Gyrus; aIPS, Anterior Part of the Intraparietal Sulcus; Cs, Conditioning Stimulus; dPM, Dorsal Premotor; IPS, Intraparietal Sulcus; MEP, Motor Evoked Potential; M1, Primary Motor Cortex; OA, Optic Ataxia; PF, Parieto Frontal; pIPS, Posterior Part of the Intraparietal Sulcus; PPC, Posterior Parietal Cortex; ppTMS, Paired-Pulse Transcranial Magnetic Stimulation; rTMS, Repeated Transcranial Magnetic Stimulation; SLF, Superior Longitudinal Fasciculus; SPL, Superior Parietal Lobule; SPOC, Superior Parieto-Occipital Cortex; TMS, Transcranial Magnetic Stimulation; TS, Test Stimulus; vPM, Ventral Premotor.

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depend on the movement's complexity and the need for precise coordination between the two phases. The dorsolateral parietofrontal network (linking the anterior part of the intraparietal sulcus to the ventral premotor cortex) is involved in the grasping phase (i.e. hand shape and grip force scaling), whereas the dorsomedial part (from the posterior part of the intraparietal sulcus and the superior parieto-occipital cortex to the dorsal premotor cortex) appears to be involved not only in the reaching phase but also in more complex visually guided grasping movements. Changes in parietofrontal connectivity following brain injury might explain the impairments in visually guided upper limb movements observed in patients (such as optic ataxia and the motor component of spatial neglect). Lastly, parietofrontal changes may reflect neuronal plasticity in motor function recovery.

Introduction

Prehension and object use allow us to interact with objects and our environment in daily life. These actions do not merely correspond to the execution of a motor program but encompass a number of cognitive-motor steps (from decision to action). Put simply, the movement process begins with the intention of movement and is followed by the integration of sensory information. The movements are planned, and motor programs are encoded and then executed and controlled by different feedback mechanisms. The appropriate execution of these successive steps requires the involvement of several disseminated networks. Here, we review the role of parietofrontal (PF) networks (connecting the posterior parietal cortex (PPC) to frontal regions) in the planning and online control of visually guided movements of the upper limb. These networks' physiological roles in many other behaviors have been frequently demonstrated, notably using electrophysiological methods. This is particularly true for the control of spatial attention, where the posterior part of the intraparietal sulcus (pIPS) and then the dorsal PF network have a role in the control of endogenous attention [12,44,48], emotions [31,52,85], social cognition [7], visual working memory [42], and mathematical cognition [56,67].

In animal models, the PF networks' physiological roles were long studied via invasive electrophysiological recordings of the neural substrates of visually guided upper limb movements. More recently, the development of non-invasive in vivo recording techniques in humans - particularly transcranial magnetic stimulation (TMS) — have enabled detailed studies of the roles and spatiotemporal involvement of the different PF network components in gesture processing and production in healthy individuals. Lastly, these data have shed new light on changes in PF network connectivity in disease.

In the present mini-review, we first define upper limb gestures and provide an overview of the anatomical structures and networks encompassing PF streams. We then look at how the use of TMS may be of particular value in this field, before discussing the specific involvement of PF networks in reaching and grasping movements in healthy humans. Lastly, we address connectivity changes in patients with brain damage, and look at how these alterations might be related to neuronal plasticity and impairments in gesture production.

Upper limb gestures

Humans are able to use a wide variety of objects to achieve various goals in daily life. This extended repertoire of actions must be regularly updated in response to the constraints that we have to face. Praxis corresponds to the ability to produce the right gesture for the use of a given object; along with exposure to object-specific constraints, it involves specific learning processes [81]. Many different paradigms have been used to study upper limb gestures; the paradigms can be divided into two categories, depending on whether they solely address movement of the hand to a target/object that is then grasped, or whether they also address object use (i.e. when transitive movements are performed with the goal of using a specific object in a specific task). For example, a teacup will be handled differently according to whether it contains tea or is being washed. This aspect relates to the theory of mind, and so will not be considered in the present mini-review. We shall focus here on the neural basis of visually guided reach-to-grasp movement in humans, rather than object use.

Firstly, reaching corresponds to movement of the hand (i.e. the manipulating tool) towards the object, with the goal of matching the respective locations of the hand and the target in the working space. In biomechanical terms, reaching mainly involves shoulder flexion and elbow extension when the movement is performed in the anterior peripersonal space. Secondly, grasping puts the hand and fingers in an appropriate conformation for taking hold of the object. It requires the person to analyze the features of the objects, such as its size, orientation, weight and texture, in order to adequately shape the hand and adjust grasping speed and grip force. It mainly involves pronation-supination movements of the forearm, adequate, stable positioning of the wrist, and a hand aperture that depends on the type of grasp. In summary, one can draw a parallel between upper limb function and a crane moving its bucket (i.e. its manipulating tool) to the target with its arm, and then grabbing the load. Although reaching and grasping are described as two

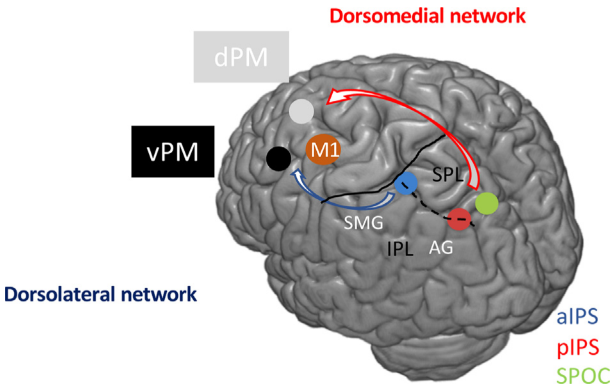

Figure 1 Components of parietofrontal networks in humans. aIPS: anterior part of the intraparietal sulcus; pIPS: posterior part of the intraparietal sulcus; SPOC: superior parieto-occipital cortex; dPM: dorsal premotor cortex; vPM: ventral premotor cortex; SPL: superior parietal lobule; IPL: inferior parietal lobule; AG: angular gyrus, SMG: supramarginal gyrus. The solid line indicates the post-central sulcus, and the dotted line indicates the intraparietal sulcus.

separate components, their interdependence is revealed by changes in finger aperture during the reaching phase of prehension and the influence of disturbance of one phase on execution of the other [8,32].

Anatomy of the PPC and parietofrontal networks

The PPC is located within the parietal lobe, behind the post-central sulcus. It is divided into a medial region, the precuneus, and a lateral part. In turn, the lateral part of the PPC is divided into superior and inferior parietal lobules, which are separated by the intraparietal sulcus (IPS) (Fig. 1). The inferior lobule encompasses the angular gyrus (AG, Brodmann area 39) and the supramarginal gyrus (Brodmann area 40). Macroscopically, the superior parietal lobule (SPL) is a single structure but it consists of two architectonically regions (Brodmann areas 5 anteriorly and 7 posteriorly).

Here, we shall focus on three areas within the lateral part of the PPC (Fig. 1). The anterior part of the intraparietal sulcus (aIPS) is defined as the region located at the intersection between the post-central sulcus and the IPS [26]. The pIPS is located at the intersection between the IPS and the parieto-occipital sulcus [39]. The superior parieto-occipital cortex (SPOC) is defined as the region along the medial surface of the parietal lobe, anterior to the parieto-occipital sulcus, posterior to the subparietal sulcus, and medial to the IPS [78].

The PPC is anatomically connected to ipsi- and contralateral hemispheric structures. Within the hemisphere, the aIPS, the pIPS and the SPOC are mainly connected to premotor and prefrontal regions via the superior longitudinal fasciculus (SLF) [83]. This voluminous tract is composed of three different branches. The most dorsal branch (SLF-1) links the SPOC and dorsal frontal regions (and particularly the dorsal premotor (dPM) cortex). The SLF-2 is the most voluminous part; it joins the pIPS and the AG to the dPM cortex and the dorsolateral prefrontal cortex. Lastly, the SLF-3 (also referred to as the ventral branch) links the aIPS and the ventral premotor cortex (vPM). Overall, two main PF networks can be identified: the dorsolateral stream connecting the aIPS to the vPM cortex, and the dorsomedial stream connecting the pIPS and the SPOC to the dPM cortex (Fig. 1). Interhemispheric connections are mediated by transcallosal tracts crossing the posterior part of the corpus callosum (regions 4 and 5) [86].

Why use TMS in this field?

In non-human primates, in vivo recordings using microelectrode arrays have allowed to build a precise model of the spatial and temporal involvement of the PPC and the premotor areas during the different phases of upper limb gesture production (for review, see [38]). In humans, since invasive in vivo recordings cannot be easily performed, non-invasive electrophysiological (EEG, non-invasive brain stimulation) and imaging techniques are required.

Neuroimaging studies have demonstrated that the PF networks are specialized in the planning of visually guided upper limb movements. In particular, neuroimaging activation studies have evidenced a high degree of specialization of the aIPS [9,30,49,54] and the vPM cortex [9,49] in the grasping phase. Other studies have shown that the discrimination of an object's intrinsic properties (but not its location) is governed by the aIPS and the vPM cortex [9,45,55]. Concerning the reaching phase, fMRI activation studies have shown that the SPOC and the pIPS are selectively activated during the preparation of movement [9,14,25,49]. Interestingly, much the same parietal activations are noted during motor imagery of upper limb reaching movements, along with dPM activation [60].

However, fMRI's poor time resolution prevents precise studies of the temporal involvement of the different brain areas in movement processing, and this imaging technique cannot be used to interfere with neural activation. In contrast, TMS meets the latter criterion, and a variety of protocols have been used in this field [68]. Firstly, TMS can be used to modulate a region thought to be involved in a given behavior, either by prevent activity by silencing neurons (''virtual lesion'' or temporary inactivation protocol) or by adding supplementary ''noisy'' activity to ongoing processes [72]. Effects can first be achieved online, i.e. by delivering a single pulse or a short train of high frequency TMS pulses, enabling an assessment of the participation of the targeted region in the ongoing behavior and of the moment in behavior production during which the region is involved, with high temporal resolution (less than a millisecond), and a spatial resolution of 1.5 to 2 cm^2 for a standard 70 mm figure-of-eight coil (better with smaller coils) [74]. Effects can also be assessed offline for up to one hour after the end of the session [57,84], i.e. after a period of repeated transcranial brain stimulation (rTMS), either by increasing (with high frequency (>5 Hz) rTMS or an intermittent theta burst mode) or decreasing cortical excitability (with low frequency (<1 Hz) rTMS or a continuous theta burst mode). Paired-pulse TMS (ppTMS, also referred to as twin-coil TMS) can be used to assess effective connectivity (i.e. the directional influence that one neural system exerts over another [27]) between a cortical brain region and the primary motor

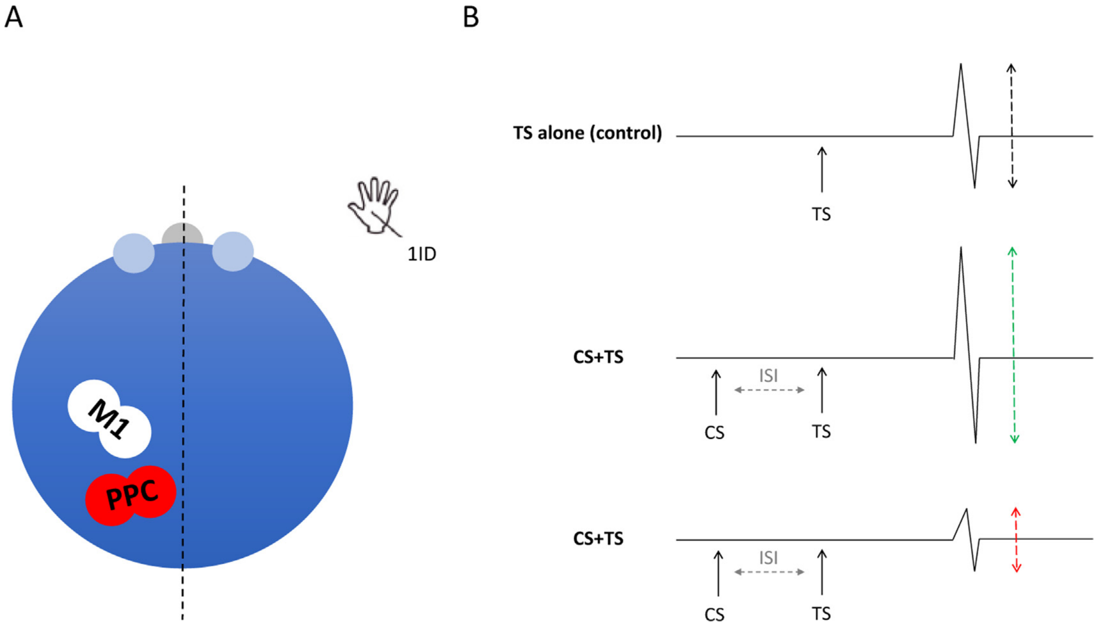

Figure 2 A ppTMS protocol for assessing PF networks (PPC-M1 connectivity). A. A schematic representation of how the probes are positioned over M1 (delivery of the test stimulus, TS) and the PPC (delivery of the conditioning stimulus, CS). B. In the control modality, only the TS is delivered over M1. In the conditioned modality, the CS is first delivered over the PPC, and then the TS is delivered after a fixed interstimulus interval (ISI). Facilitation corresponds to an increase in the amplitude of the motor-evoked potential, whereas inhibition corresponds to a decrease.

cortex (M1) at rest or during gesture production [51,66]. In this paradigm, a test stimulus (TS) applied over M1 gives rise to a motor-evoked potential (MEP) whose amplitude reflects corticospinal excitability. Prior to the TS, a conditioning stimulus (CS) is applied at a fixed interstimulus interval (ISI) with a second stimulator over the region thought to be connected to M1. The CS may result in facilitation (if the MEP amplitude increases) or inhibition (if the MEP amplitude decreases), or may have no influence on M1 (Fig. 2). Advantageously, ppTMS can be used to test multiple hypotheses by varying the CS's cortical target and intensity, and the ISI. Usually, the intensity of the TS is supraliminal (in order to evoke MEPs) and that of the CS is infraliminal. The influence of the ISI provides information on the nature of connections underlying the observed effect: if an effect is observed for a short ISI, then the connections are likely to be direct, short pathways, whereas an effect of a longer ISI reveals longer and/or indirect pathways (i.e. with several nodes) [66]. Whatever the protocol used, since targeted brain areas (in the premotor cortex as in the PPC) are close to each other, small diameter coils should be preferred in order to specifically target one site without modulating the adjacent region [74].

The role of parietofrontal networks in the planning and control of visually guided reaching and grasping movements

Although the kinematic interdependence of the reaching and grasping phases is undebated, the phases' respective neural bases have not been fully characterized. In Jeannerod et al.'s initial model [37], each phase is considered to be an independent process: the reaching phase depends on the target's extrinsic properties (mainly its position in working space), whereas the grasping phase depends on the object's intrinsic properties (size, shape, texture, etc.). For many years, this dual processing theory had been supported by evidence of neural segregation between the dorsolateral network involved during the grasping phase and the dorsomedial network involved in the reaching phase. However, recent data have challenged this view, and have shed new light on the dual function of the dorsomedial stream. This mini-review will only address the key aspects of the neural bases of reaching and grasping; for an exhaustive review, we refer the reader to other publications [75,79,81].

The dorsolateral network's function in gesture planning

Data from the literature on the dorsolateral network (involved in the grasping phase in non-human primates as in humans) are homogeneous [18]. Studies using different TMS protocols have confirmed the effective connectivity between the aIPS, the vPM cortex and M1, and have identified a sequential activation and interaction in the movement planning phase. Temporary inactivation of the aIPS during movement planning is responsible for modifications in hand shaping and force scaling [15,16]. These two grasping parameters appear to be independently mediated by the aIPS. Indeed, the consequence of inactivation depended on the latter's time of occurrence: when applied 270 to 220 ms before contact of the hand with the manipulandum, the CS specifically altered hand shaping, whereas only grip force scaling was affected when the CS was delivered later (170 to 120 ms before contact) [16]. Furthermore, the two processes appear to differ in their lateralization; although grip force scaling was altered by a unilateral lesion in the left aIPS, a bilateral lesion was required to impair hand shaping. In another study, Davare et al. showed that temporary inactivation of either the left or the right vPM cortex during movement planning also altered the positioning of fingers on the target, whereas the recruitment of intrinsic hand muscles was affected only when both vPM cortices were virtually lesioned [17].

Several ppTMS studies have explored the effective connectivity between the aIPS, the vPM cortex and M1 in healthy humans. At rest, a CS applied over either the aIPS [1,39,45,46,77,78] or the vPM cortex [19] exerted an inhibitory influence on M1 for short ISIs (4 ms for the aIPS, and 6 to 8 ms for the vPM). This inhibition might reduce competition between alternative movements planned in parallel during movement preparation [4,11,78]. Interestingly, the inhibition changed to facilitation (at the same ISI) when the CS was delivered over the aIPS during the preparation of a grasping movement, regardless of whether or not is was combined with a reaching movement [45,77,78]. Lastly, applying a TMS pulse stimulation over the vPM cortex (temporarily inactivating the latter) between the CS over the aIPS and the TS (i.e. a triple-pulse TMS protocol) suppressed the inhibition elicited at rest; this demonstrated the crucial role of parietal connections to the vPM cortex in the modulation of M1 [45,71].

In conclusion, both the vPM and the aIPS (via the vPM) have an influence on the control of the grasping phase of visually guided upper limb movements. Hand shaping seems to be planned first, and then force scaling.

The dorsomedial network's functions in gesture planning

The dorsomedial network's influence during planning of the reaching phase

The dorsomedial network's importance in the planning and online control of reaching movements has been clearly demonstrated. Although there are fewer virtual lesion studies of the pIPS and the SPOC than of the aIPS, the research has revealed these areas' influence on the planning of reaching movements in humans [21,22,73]. In addition, Busan et al. evidenced, by modulating the pIPS, the SPOC and the dPM cortex during the planning of reaching movements, that visuomotor information is probably processed in parallel in these regions of interest [5,6].

At rest, the connections between the pIPS and the SPOC and between the dPM cortex and M1 (as evidenced by ppTMS protocols) differ from those observed for the dorsolateral network. At rest, M1 excitability was not modified when the CS was applied over the SPOC [78] but increased when the pIPS was stimulated at an ISI of 6 ms [39,46]. This facilitation appears to be due to the asymmetry of parietal interhemispheric connections, with the right pIPS exerting a strong inhibitory effect on the left pIPS via short-latency connections through the corpus callosum [44]. Indeed, the facilitation of M1 excitability observed when the CS is applied over the left pIPS is suppressed when the right pIPS is stimulated before the CS, but not *vice versa*. Interestingly, the degree of this asymmetry was correlated with the severity of pseudoneglect (i.e. a leftward bias in line bisection tests) in healthy subjects. During the planning of a reaching movement, the pIPS and the SPOC behave in the same way in ppTMS studies; MEPs are facilitated when the CS is applied over either the former [47] or the later [77,78]. Although the pIPS and the SPOC show similar patterns in ppTMS studies, they do not have the same role in reaching planning; the SPOC appears to be involved in the encoding of reach goals, whereas the pIPS and the angular gyrus may be involved in the encoding of reach vectors [79,80].

Does the dorsomedial network have a role in the grasping phase?

In line with findings in non-human primates [24,62], there is evidence to suggest that the posterior part of the PPC and the dorsomedial network both have roles in the planning of the grasping phase and in grasping-reaching integration, in addition to their well-known involvement in the reaching phase.

Electromyographic activation patterns during reach-to-grasp movements provided the initial (indirect) evidence of neural coupling between reaching and grasping. In fact, the first dorsal interosseous muscle (a key muscle for precise thumb-index gripping) is activated as expected during the grasping phase but is also activated during the reaching phase [47]. Furthermore, the excitability of the hand's intrinsic muscles is modified when the subject's shoulder position is changed passively [23].

Grol et al. were the first to highlight (using activation fMRI) the dorsomedial network's role in the planning of grasping movements [30]. Whereas grabbing a small object activated only the aIPS and the vPM cortex, grabbing a large object increased activity in the dorsomedial network. Later research confirmed that the dorsomedial network is recruited when grasping movements are complex or when the subject must choose between different types of grasp [28,65,76].

Data from TMS experiments in this field are scarce. Davare et al. first demonstrated that temporary inactivation of the left dPM cortex (but not the right) during the planning of a grasping movement impaired the coupling between gripping and lifting a manipulandum — suggesting that the dPM cortex acts during the grasping phase [17]. In a ppTMS study, Vesia et al. studied changes in SPOC-M1 connectivity during the planning of different types of reach-to-grasp movements (pointing, a thumb-index grip, and a palmar grip) [77]. Their results confirmed that the dorsomedial network has a causal role in planning complex, visually guided grasping movements.

Overall, the literature does not support the existence of segregated brain circuits for reaching and grasping. On the contrary, the dorsomedial and dorsolateral networks' respective contributions may depend on the complexity of the movement and the need for precise coordination between reaching and grasping.

Parietofrontal networks and upper limb function after brain injury

Stroke often leads to impairments in upper limb function. Although paresis and muscle hypertonia are the main causes of these impairments, other defects can be involved. In particular, disruption of PF networks (either by an intra-network lesion or a remote lesion that disrupts network function) might be responsible for post-stroke gesture impairments. Firstly, optic ataxia (OA) is a good model of how a lesion limited to the SPL or the IPS disturbs the reaching phase. Optic ataxia is defined as difficulty in reaching targets in the absence of sensory cues other than visual guidance, and which cannot be explained by visual, proprioceptive, motor or coordination disorders [64]. In contrast to apraxia (i.e. the impaired production of learned behaviors), OA is a model visuomotor coordination disorder that affects the reaching phase of visually guided movements. When the person attempts to reach an object, dysmetria results from visual perceptual impairments that have the same kinematic features as in cerebellar ataxia. However, in contrast to cerebellar dysmetria, the dysmetria in OA is markedly reduced or may even disappear when the person uses haptic cues (e.g. movement guidance by external contact) or auditory cues. The symptoms usually worsen when movements are guided by peripheral vision, and OA is sometimes combined with psychic paralysis of gaze and a spatial disorder of visual attention (Balint's syndrome). Lesions associated with OA are located in the SPL and around the IPS, predominantly in the right hemisphere [29,40]. Three main mechanistic hypothesis for OA have been suggested:

- a visuomotor impairment, i.e. impaired sensorimotor integration that is specific for visually guided reaching [59,64];
- a disturbance in visual orientation and thus altered ability to adequately judge the location of an object in space [53];
- an impairment in the online control of movement by visual feedback [61].

The role of the PPC (particularly that of its most caudal part) in the development of OA has been highlighted by inducing virtual lesions (using TMS) of the pIPS in humans [20] and the parietal reach region (the homologue of the SPOC and the pIPS) in monkeys [35]. In contrast, lesions limited to the aIPS in the human impair the precise coordination of finger movements during grasping but do not impair reaching [2,9].

Spatial neglect is another example of how a connectivity defect in the PF networks might impair gesture. This condition is defined as failure to acknowledge or explore stimuli on the contralesional side [33]. Even though the perceptual features of spatial neglect are most frequently apparent, the condition also includes a directional hypokinesia component (i.e. an impairment in initiating or completing movements in the leftward direction) [34,41]. This is evidenced by a longer reaction time when the target is located in the neglected (contralesional) hemispace and slower, less ample movements towards the contralesional space. It has also been shown that spatial neglect is related to a hemispheric imbalance between the activities of the two PPCs and, more broadly, between dorsal attention networks (DANs). Firstly, Koch et al. used ppTMS to reveal hyperexcitability of PF networks (from the pIPS) in the intact left hemisphere in patients with spatial neglect. This hyperexcitability was correlated with the degree of visual neglect [43,48], and downregulation of the hyperexcitability (via an inhibitory rTMS protocol) led to a reduction in the severity of the neglect. These results are consistent with those obtained in fMRI neuroimaging studies; disconnection between the DANs (involved in the control of endogenous visual attention, and the structures encompassing the dorsolateral network) and the ventral attention network (involved in the control of exogenous attention) within the lesioned hemisphere resulted in increased activity within the contralesional DAN [12]. An exhaustive presentation of connectivity disorders in neglect is beyond the scope of this mini-review (for a review, see [13]). The data on connectivity in spatial neglect mainly concern the perceptual modality; hence, future connectivity studies should focus on spatial neglect's motor aspects.

Another aspect of PF network connectivity relates to the networks' relationship with neural plasticity and their potential roles in motor recovery after stroke. In fact, recent studies of functional and structural connectivity have evidenced alterations in the ipsi- and contralateral connections between the PPCs and the lesioned M1 (via PM cortex) during the subacute and chronic phases of stroke [36,58,69,70,82,87]. In addition, a recent connectivity study using EEG demonstrated that parietofrontal coupling was stronger in hemiparetic stroke patients compared to controls and correlated with the residual motor deficit [3]. Taken together, these observations suggest that the PF networks may have a role in motor impairment and recovery after stroke. Furthermore, the PPC exerts a direct influence on M1 and upper limb movements; excitatory modulation of the PPC by non-invasive brain stimulation is able to enhance M1 excitability [63] and PPC-M1 connectivity [10], and modify movement timing in healthy subjects [50]. Nevertheless, the functional significance of these connectivity changes remains to be demonstrated because the latter do not appear to be related to the level of motor impairment [1,36,69,70].

Lastly, better knowledge of the neural bases of reach-to-grasp planning and control in health and disease may facilitate the development of brain computer interfaces or neural prostheses capable of compensating for motor impairment in disabled people.

Conclusion

Parietofrontal networks are key structures in the planning and online control of visually guided upper limb movements. Although reaching and grasping phases of movement were initially thought to involve segregated neural circuits, TMS studies have demonstrated that the contributions of the dorsomedial and dorsolateral networks may vary according to the complexity of the movement and the need for precise coordination between reaching and grasping. Whereas the dorsolateral network is activated at various times in the grasping phase (for hand shaping and force scaling), the dorsomedial network is activated during the planning of the reaching phase and during more complex visually guided grasping movements. Changes in PF connectivity following brain injury can account for the impairments in visually guided upper limb movements observed in patients, such as OA and the motor component of spatial neglect. These changes may also reflect neuronal plasticity during the recovery of motor function, although this remains to be proven. Lastly, better knowledge of motor planning in patients and healthy individuals may facilitate the development for brain computer interfaces capable of compensating for motor disability.

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The authors declare that they have no competing interest.

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