

INTERMANUAL COORDINATION: FROM BEHAVIOURAL PRINCIPLES TO NEURAL-NETWORK INTERACTIONS

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Locomotion in vertebrates and invertebrates has a long history in research as the most prominent example of interlimb coordination. However, the evolution towards upright stance and gait has paved the way for a bewildering variety of functions in which the upper limbs interact with each other in a context-specific manner. The neural basis of these bimanual interactions has been investigated in recent years on different scales, ranging from the single-cell level to the analysis of neuronal assemblies. Although the prevailing viewpoint has been to assign bimanual coordination to a single brain locus, more recent evidence points to a distributed network that governs the processes of neural synchronization and desynchronization that underlie the rich variety of coordinated functions. The distributed nature of this network accounts for disruptions of interlimb coordination across various movement disorders.

One of the most impressive features of human beings is their ability to produce a bewildering variety of coordinated behaviours that involve the upper and/or lower limbs. The motions of the limbs are coordinated in a task-specific manner, with a seemingly unlimited temporal and spatial diversity. Many coordination patterns are cyclical, such as walking, riding a bicycle, swimming and rowing. These patterns are characterized by synchronized or alternated movements of limb pairs. Other tasks require differential contributions of each limb for goal accomplishment, such as tying your shoelaces, opening a bottle or playing a musical instrument. Elementary coordination patterns seem to be present at birth, as seen in the supine newborn that shows synchronous or alternating kicking actions of the legs. Other behaviours require years of intensive practice to be performed skilfully.

Here, I discuss some elementary coordination rules that underlie this variety of movement patterns. These basic rules or principles become readily apparent when trying to perform different movements simultaneously. Try, for example, to tap a regular rhythm with one hand and an accelerating rhythm with the other hand. Although doing each of these separately is very simple,

their combined performance results in substantial interference. This indicates that principles of interlimb coordination are unique and cannot be inferred from the laws of single-limb movements. This interference is not only restricted to movements with a different temporal structure, but is also observed when performing spatially different movements, such as when trying to draw a circle and an ellipse or a triangle simultaneously. These examples show that temporal and spatial parameters of movement constrain the coordination of limb movements, resulting from a basic synchronization tendency¹⁻⁸. Synchronization is ubiquitous in biological systems, and often seems to be the default mode of operation of the central nervous system⁹⁻¹¹. But many coordinative functions require that this tendency be overcome, reflecting plastic changes that are associated with skill learning. The study of the principles that underlie basic patterns of interlimb coordination, as well as our ability to overcome them, is being achieved by integrated efforts from the behavioural sciences and the neurosciences. Although many questions remain unanswered, a basic understanding of the coordination principles and their neural basis has begun to emerge.

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Basic modes of interlimb coordination

What are the most typical default coordination modes that are available in the animal world? The analysis of relative phase has been particularly helpful in answering this question. Relative phase (Φ) is used to quantify and characterize coordination modes; this principal variable is obtained by subtracting the phase angles of both limb motions ($\Phi = \theta_{\text{Limb1}} - \theta_{\text{Limb2}}$). It is generally agreed that, even though other modes exist, locomoting (quadrupedal) animals and humans show a basic tendency towards in-phase ($\Phi = 0^\circ$) or anti-phase ($\Phi = 180^\circ$) coordination of the limbs with a prevalent 1:1 frequency-locking mode¹². How in-phase and anti-phase are defined depends on the particular limb combination and the plane in which the limb motions occur. They can be expressed relative to an intrinsic (egocentric) or extrinsic (allocentric) reference frame. For example, during cyclical movements of both upper limbs (homologous) in the horizontal plane, two dominant modes — known as mirror-symmetric and parallel coordination — are evident (FIG. 1a). The symmetrical mode is characterized by extending and flexing both limbs together through simultaneous activation of the same muscle groups ($\Phi = 0^\circ$). The parallel mode requires alternated activation of the same muscle groups ($\Phi = 180^\circ$). These basic modes are observed when moving together both arms, both wrists, the fingers of both hands or both legs, underscoring their generic nature.

Research on cyclical bimanual movements in humans has shown that the in-phase mode is usually more accurate and stable^{10,13–18}, and requires less attention than the anti-phase mode¹⁹. If a subject performs a movement in the anti-phase mode, increasing movement frequency will ultimately result in a phase transition towards the mirror-symmetrical mode. The converse transition does not occur under speed stress^{10,14}. Relative-phasing patterns that deviate from in-phase and anti-phase coordination are more difficult to perform, often requiring intensive practice. So, during movements of the homologous limb pairs (both arms or both legs), mirror-symmetrical or in-phase movements with respect to the longitudinal axis of the body are more stable and accurate than any other phase relationship. This fact is denoted as the egocentric constraint¹⁶.

With respect to coordination of the upper and lower (non-homologous) limbs, such as simultaneous movements of the wrist and foot, or forearm and lower leg, the most preferred and stable pattern is characterized by moving both limbs in the same direction in extrinsic space (isodirectional, $\Phi = 0^\circ$) (FIG. 1b). Conversely, movements in different directions (antidirectional, $\Phi = 180^\circ$) generally seem to be more difficult to sustain^{20–23}. This is referred to as the allocentric constraint, denoting a general preference for performing movements in the same direction in extrinsic space¹⁶. This constraint is also evident during coordination of the homologous limbs, even though it is subordinate to the egocentric constraint. More specifically, coordination patterns of the upper limbs that involve simultaneous activation of the same muscle groups and isodirectional movements in extrinsic space are more accurate and stable than any

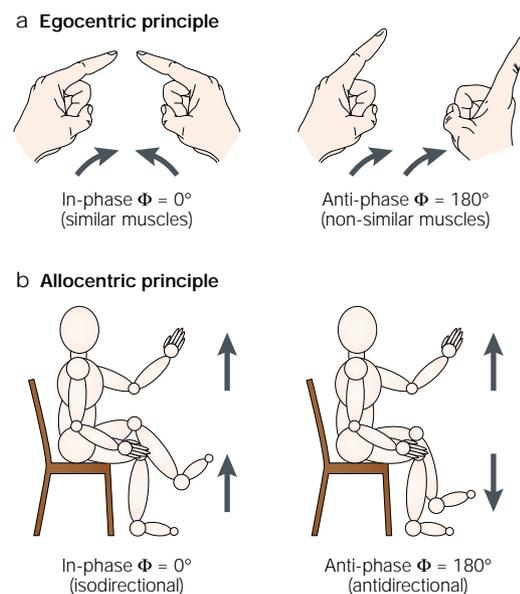


Figure 1 | Basic coordination constraints: the egocentric and allocentric principles. **a** | The egocentric principle refers to a preference for moving according to mirror symmetry, which involves activating similar muscle groups simultaneously. **b** | The allocentric principle refers to a preference for moving the limbs or limb segments in the same direction in extrinsic space. Φ , relative phase.

alternative patterns^{16,17}. Preferred neuromuscular and perceptual aspects could underlie these basic coordination constraints. In this respect, an interesting parallel can be drawn with visual perception, in which mirror-image symmetry on the one hand and perceptual grouping of isodirectional stimuli on the other hand are more salient than alternative symmetry or grouping principles²⁴. The aforementioned constraints pertain to only basic coordination modes. The type of coordination pattern that performers will ultimately show is task specific and context dependent. For example, in two-legged locomotion, anti-phase coordination between homologous limb pairs is the preferred mode to preserve balance in a gravitational field.

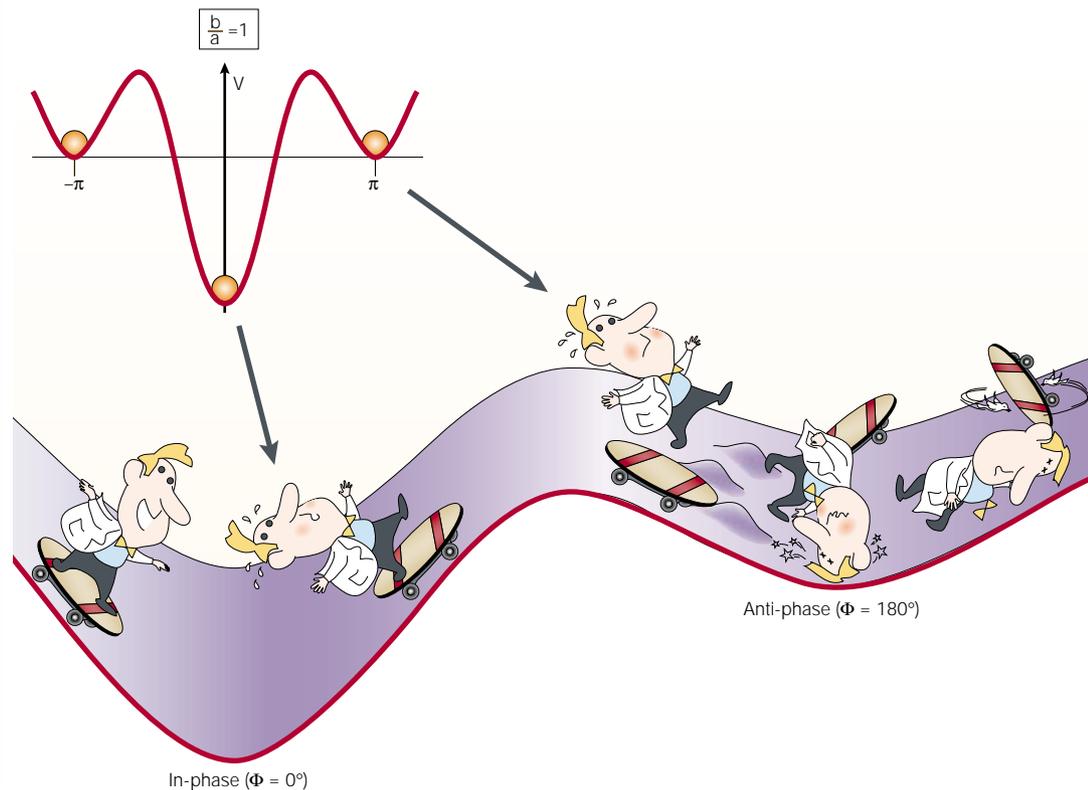
When comparing homologous and non-homologous limb coordination in seated humans, relative-phase accuracy and stability is higher between homologous than non-homologous limb pairs^{22,23,25,26}. This coupling strength might be mediated by physical properties, referring to the degree of inertial (dis)similarity between limb pairs. However, when correcting for inertial differences by limb loading, differences in coupling accuracy between homologous and non-homologous limb pairs remain evident²⁷. This is indicative of differential pathway strength between neural assemblies that are involved in limb control. The observations converge with animal research in which coordination within fore- or hindlimb girdles is often less variable than coordination between both girdles²⁸.

Two dominant frameworks — dynamic pattern theory (DPT) and neural crosstalk (BOX 1) — have provided the theoretical foundations for the principles of

Box 1 | Dynamic pattern theory and neural crosstalk

Dynamic pattern theory (DPT) searches for general principles of pattern generation in complex biological systems^{10,30}. Qualitative changes in patterns that are described by collective variables (such as relative phase, or Φ) are elicited by relevant control parameters (such as cycling frequency). The dynamics of the system are captured formally by an equation of motion of the collective variable. The theoretical strategy is to map empirically stable coordination patterns onto attractors of the collective variable dynamics. This is exemplified for movements of the two hands operating at a common frequency (a). The observed in-phase and anti-phase coordination patterns can be mapped onto point attractors at $\Phi = 0^\circ$ and $\Phi = 180^\circ$. The behaviour of the system can be visualized by identifying Φ with a black ball or a skater moving in an energy landscape that is defined by the function V , in which $V(\Phi) = -a \cdot \cos(\Phi) - b \cdot \cos(2\Phi)$, known as the Haken–Kelso–Bunz (HKB) model of coordination²⁹. By changing the ratio b/a , which is inversely related to cycling frequency, one can travel through an evolving landscape, going from a bistable (in- and anti-phase) to a monostable (in-phase) regime (not shown). The basin of attraction or local minimum is lower at $\Phi = 0^\circ$ than at $\Phi = 180^\circ$. When the skater moves within the $\Phi = 0^\circ$ basin, his movements will be very stable and regular, and external perturbations will not easily affect his pattern or push him over the hill. More pattern variation will be observed when the skater is in the $\Phi = 180^\circ$ basin. With increasing speed, he might eventually get out of this basin and end up in the nearby, more stable basin at $\Phi = 0^\circ$. The converse route is less likely. This has been confirmed experimentally for the case of bimanual finger coordination, in which the in-phase coordination mode is more stable than the anti-phase mode. Increasing cycling frequency affects the stability of the anti-phase mode more than the in-phase mode, eventually resulting in a transition from anti-phase to in-phase coordination, and intentionally switching from in-phase to anti-phase coordination is more difficult than vice versa. In the DPT approach, learning corresponds to the stabilization of a novel attractive state through practice (such as $\Phi = 90^\circ$)^{31,32}.

The neural-crosstalk approach pertains to pathways that promote neural interactions between command streams, resulting in patterns of (mutual) interference between limb motions. These interactions can occur at various levels of the central nervous system, from cortical to spinal. With respect to bimanual coordination, these neural pathways refer to information exchange between the hemispheres through the corpus callosum. Research on patients with resections of the corpus callosum indicates that temporal and spatial movement features might normally be exchanged between hemispheres. In addition, there are direct and indirect routes from the motor cortex to the spinal cord — the lateral and ventral corticospinal tracts. Most axons of the lateral corticospinal tract cross in the medulla and terminate primarily in the lateral portions of the ventral horn of the spinal cord. This pathway is concerned primarily with contralateral control of precise and fractionated movements of distal parts of the limbs. The ventral tract runs uncrossed through brainstem centres and enters primarily the medial regions of the spinal cord. These fibres terminate ipsilaterally or contralaterally and are involved in the control of axial and proximal limb muscles. Accordingly, each half of the brain has full contralateral control over arm, hand and finger movements, but has ipsilateral control over arm movements³⁸. This implies that the limbs might receive discordant efferent commands from both hemispheres.



interlimb coordination. DPT aims for a mathematical formalization of the coordination principles, modelling rhythmic movements as a system of coupled nonlinear oscillators^{10,29,30–32}. Both the observable behaviour and the global dynamic properties of the brain are formalized using the same theoretical principles, which refer to self-organization and pattern formation³³. The basic premise of neural crosstalk is that interactions occur between command streams within a highly linked neural medium. These will give rise to patterns of mutual interference between concurrent limb motions at different stages of movement planning and organization^{4,7,34–38}. Although both perspectives have developed in relative isolation and have focused on different aspects of coordination, they are not necessarily incompatible.

Spatial and temporal constraints in coordination. An important strategy to reveal the basic principles of interlimb coordination or, more generally, the limitations of the central nervous system in controlling more than one task, is to perform different movements simultaneously. The archaic response tendencies or coordination modes that the system settles into when stressed might also reflect what the most easily potentiated pathways of neural wiring are. Limitations in control are reflected in spatial and temporal features of movement. Although time and space are often difficult to distinguish, it is possible to develop tasks that differ in their spatial requirements while preserving temporal compatibility, and vice versa.

Spatial constraints become easily apparent. When drawing lines of different amplitude, one with each hand, the tendency for the amplitudes to become similar to each other emerges — a tendency called assimilation^{4–6,35,37}. Not only amplitude, but also movement direction, constrains coordination. Drawing parallel lines with both arms in front of you is easy, whereas drawing orthogonal lines is more likely to give rise to interference in the directional specifications of both limbs^{1,17}. Compared with normal subjects, patients in whom the corpus callosum has been severed have less difficulty in simultaneously producing movements with divergent directional requirements^{39–41} (FIG. 2). This indicates that directional specifications might be exchanged between the hemispheres through the corpus callosum. Temporal coupling during movements with a prominent discrete event (such as finger tapping) seems to be preserved in patients who have undergone callosotomy^{42,43}, but is disrupted during continuous circle drawing movements⁴⁴. In addition, when tasks require intensive collaboration and exchange of information between the upper limbs that goes beyond basic in-phase coupling, callosotomy patients do not perform so well^{45,46}.

When studying various orientation combinations within the broader workspace of the performer, it is possible to obtain an idea of the reference frames within which interlimb interference emerges. When expanding the basic notion of the egocentric principle that I discussed previously, a radial egocentric reference frame emerges. In this frame, cyclical movements of both upper limbs along radial axes that expand from the performer's

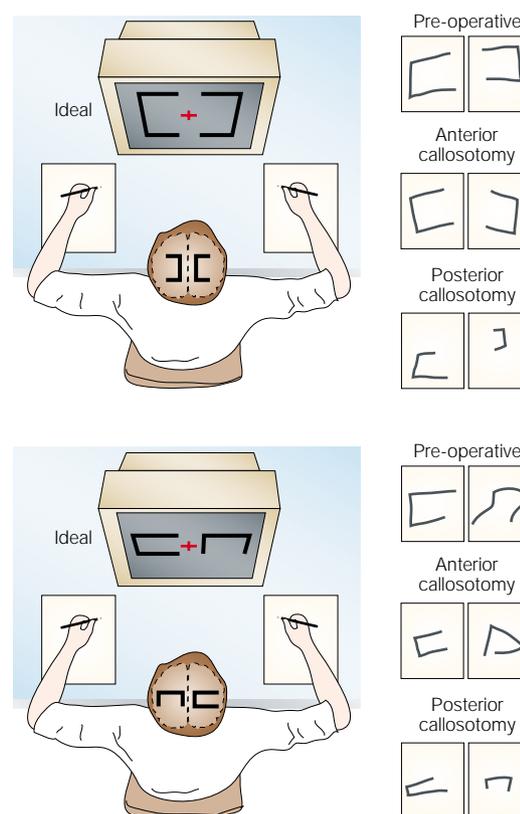


Figure 2 | Differences in directional interference in a patient with resections of the corpus callosum, before and after surgery. Bimanual drawing performance is shown before (pre-operative) and after anterior and posterior callosotomy. The ideal patterns are shown on the left and refer to a drawing with the same (top) and different (bottom) orientations. The pairs of shapes were presented for 150 ms while the patient fixated a central cross. In the pre-operative condition and after anterior callosotomy, shapes with the same orientation are drawn successfully, whereas shapes with different orientations give directional interference. The direction of one hand is attracted to that of the other. After posterior callosotomy, shapes with the same orientation deteriorate, becoming less similar, whereas the shapes with different orientations are now produced more successfully, free of directional interference. Reproduced with permission from REF. 39 © 1999 Springer-Verlag.

body are compatible with each other in that they do not cause interference when performed simultaneously (FIG. 3). However, when combining limb movements along radial and non-radial axes, interference arises, becoming maximal when a radial and orthogonal-to-radial movement orientation has to be produced⁴⁷ (FIG. 3). As these incompatible limb combinations involve different patterns of muscle activity, one might speculate that the interference arises predominantly from crosstalk between muscle-activation patterns. However, when changing these patterns through spring loading while preserving the kinematics, interference is largely preserved and can therefore be dissociated from muscle activation⁴⁸. These findings have two implications. First, assuming that the observed behavioural patterns provide an indirect window into neural function, the findings indicate that movement encoding occurs

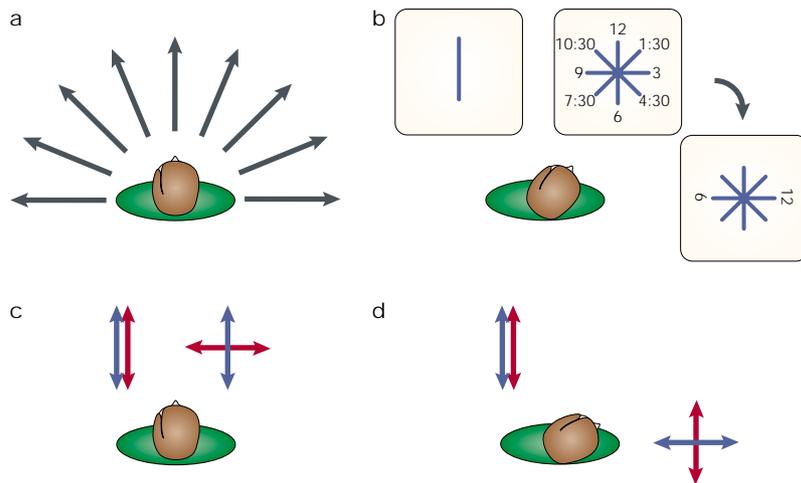


Figure 3 | Patterns of directional interference within egocentric workspace. **a** | The radial egocentric reference frame. **b** | Bimanual task set-up in which both limbs perform cyclical bimanual line drawings with different orientation requirements. The left limb continuously produces vertical line drawings. Using the right limb, the subject starts with five vertical lines, after which orientation is shifted by 45° in a clockwise manner until all orientations are completed. Subjects have to maintain the vertical line drawing with the left limb while performing the orientational shifts with the right limb. Can bimanual spatial interference be understood more parsimoniously within an egocentric or an allocentric reference frame? **c** | In the parallel board configuration, the combination of vertical line orientations (blue) causes no interference, whereas a combination of vertical and horizontal orientations (red) causes maximal interference. **d** | In the orthogonal board configuration, the combination of vertical and horizontal line orientations (blue) causes no interference, whereas the parallel line orientations (red) now cause maximal spatial interference. The findings favour an egocentric reference frame, in which line combinations along radial orientations cause minimal interference, whereas a combination of radial and orthogonal-to-radial orientations cause maximal interference. Modified with permission from REF. 47 © 2002 Massachusetts Institute of Technology.

within an intrinsic or egocentric reference frame. Second, directional coding is abstract, as the pattern of directional interference seems to be dissociable from the specific patterns of muscle activation⁴⁸. In general, these observations are consistent with evidence from neurophysiological studies showing that direction is an important parameter of movement and is coded in the central nervous system by a population of neurons^{49–51}.

Temporal constraints have been investigated much more intensively than spatial constraints. With respect to finger tapping, a distinction is often made between simple rhythms in which one frequency is an integer multiple of the other (such as 1:1, 2:1 or 3:1), and polyrhythms in which this condition is not met (such as 3:2 or 5:3). The latter patterns are more difficult to produce than the former, and show higher variability^{52–57}. Moreover, higher-order ratios (ratios that are composed of large numerators and denominators, such as 5:4 or 4:3) are less stable than lower-order ratios (3:2, 2:1 or 1:1), often resulting in transitions to lower-order ratios when the system is stressed by increasing tapping frequency^{57,58}.

The production of such multi-frequency tasks is also associated with an asymmetrical coupling effect in which the fast hand, which receives focal attention, has a larger influence on the slow hand than vice versa^{55,56,59–61}. Musically trained subjects are more accurate than non-musicians in the performance of polyrhythms, because they show less stringent interlimb interactions⁵⁶. A prominent theoretical account of these observations

involves a central timekeeper that generates pulses at regular intervals, thereby providing the time basis for the temporal patterning of movements (top-down approach)⁶². It is commonly assumed that the timing of the two hands is not independent (parallel organization), but subsumed under a single, integrated, hierarchical, temporal structure (integrated organization)^{53,56,60}. The fast hand usually forms the time frame into which slow-hand responses are inserted. An alternative framework is DPT (BOX 1), in which multi-frequency tasks are modelled as coupled nonlinear oscillators. Here, the focus is on stability and on loss of stability that is associated with transition routes from one tapping pattern to another during manipulations of tapping frequency (bottom-up approach)^{10,29,58}.

Plasticity: overcoming constraints by learning I argued in the previous section that the basic constraints that are inherent in the control of coordination patterns become most clearly apparent when different movements have to be performed simultaneously with the limbs. The errors that become evident are informative of the limitations of the central nervous system in dealing with multiple tasks, and also provide a starting point to look for plastic changes that are associated with skill learning. The basic tenet is that the acquisition of new coordination patterns should be considered against the background of the previously described default coordination modes^{10,32,63–66}. This is not a trivial matter, because the difficulties that arise when learning new coordination patterns can often be accounted for by the intruding nature of the pre-existing preferred patterns (see above), and the associated tendency towards phase and frequency synchronization. Stated differently, learning does not start from a *tabula rasa*, but evolves against the background of pre-existing coordination tendencies. Accordingly, it is not sufficient to ask how new patterns of neural excitation can be built up — we also need to ask how the pre-existing patterns can be suppressed. The stronger the pre-existing, or default, wiring patterns between neural assemblies, the more difficult it might be to shape new ones. This can be illustrated with the example of learning to perform a 2:1 frequency ratio with the limbs. Previously, higher connection strength has been suggested between homologous than between non-homologous limbs, and this could be the basis of the higher coupling accuracy during 1:1 frequency locking in the former case, as compared with the latter. However, overcoming 1:1 coordination to adopt the 2:1 frequency ratio is more difficult for homologous than non-homologous limbs, because the default pathways of neural coupling constrain the formation of new ones^{25,26}. Examples of multi-frequency patterns between the upper and lower limbs can be readily observed in swimming the crawl stroke. Cycling frequencies of the legs exceed those of the arms by up to a factor of five when swimming quickly. When using flippers, the frequency ratio decreases to 2:1 or 1:1. Frequency locking between limb girdles is prominent under all of these conditions¹². This indicates that different frequency ratios can be flexibly adopted during coordination of the

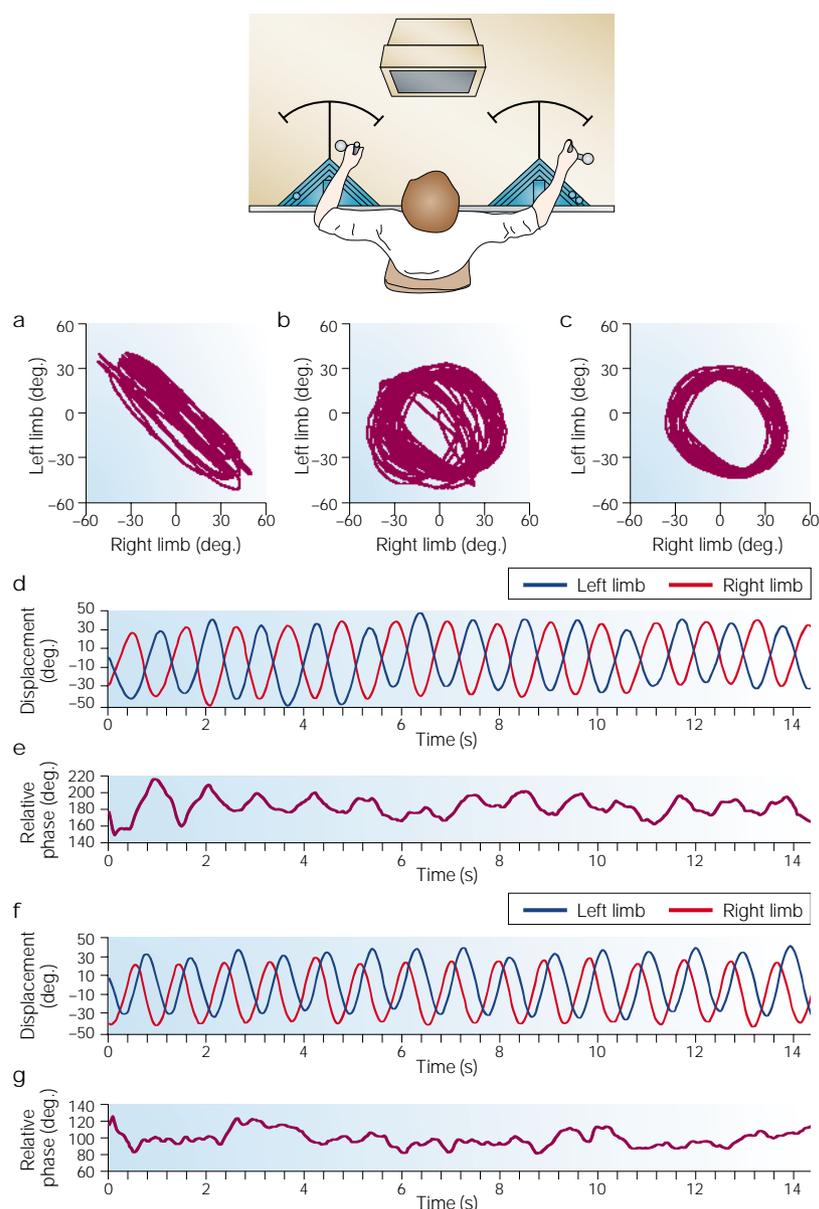


Figure 4 | Performance of the 90° out-of-phase task during 1:1 frequency locking.
a–g | Evolution of performance of the 90° out-of-phase mode in adolescents during 1:1 frequency locking across two days of practising a cyclical bimanual forearm task in the horizontal plane. The displacements of the right and left limb are plotted against each other (**a–c**). Successful performance with a relative phase (Φ) of 90° is characterized by a circle configuration. At the start of practice, the performer is attracted to the anti-phase coordination mode (**a**). The resulting left and right limb movements are shown as a function of time (**d**). Relative phase hovers periodically around $\Phi = 180^\circ$ (**e**). At the end of the first practice day (**b**), the required circular configuration roughly appears, even though tendencies towards anti-phase remain evident. By the end of practice, the circular configuration has become highly consistent and the effect of the preferred coordination modes has waned (**c**). The kinematics now show a phase difference between both limbs (**f**) that is centred on $\Phi = 90^\circ$ (**g**). Modified with permission from REF. 65 © 1998 Psychology Press Ltd, Hove, UK.

CENTRAL PATTERN GENERATOR
 A neural circuit that produces self-sustaining patterns of behaviour independently of sensory input.

upper and lower limbs, and that mechanical constraints can determine the adopted frequency ratio.

Besides the study of the acquisition of multi-frequency tasks, the ability of the performer to coordinate the limbs according to less familiar phase relationships is also an example of plasticity that has been championed

by DPT. This refers to relative-phase modes that are located between the previously discussed in-phase and anti-phase modes. It normally takes substantial practice to perform successfully in a bimanual coordination mode with a 90° phase difference ($\Phi = 90^\circ$)^{32,63,66,67} (FIG. 4). This is because the in-phase and/or anti-phase modes intrude into attempts to perform in the new mode. Practice results in overcoming elementary phase and frequency synchronization to develop differentiated patterns of activity in which each limb goes its own way, seemingly moving independently of the other. However, true independence within a highly linked inter-hemispheric medium is rather unlikely. Learning complex coordination skills can therefore be considered as a two-component process, consisting of de-integration of basic action patterns on the microscopic temporal scale to defy default coupling and re-integration on the macroscopic scale. The degree of efficiency in the formation of these new neural connections depends on various extrinsic and intrinsic conditions. On the one hand, differences between performers in their ability to build new coordination modes are very apparent and could reflect a genetic predisposition for neural plasticity. On the other hand, instructional techniques can boost the learning process, particularly when the action goal is conceptualized as a familiar symbol or entity⁶⁸, or when feedback techniques integrate information from the respective limbs in a meaningful way^{63,65,67,69}. Such conceptualization phenomena or goal-oriented action rules might help to overcome the innate rules and enslave the sensorimotor networks in new patterns of coordination.

The network involved in coordination
 Since the pioneering work of Sherrington, neuroscientists have focused primarily on the nervous control of locomotion as the prototype of interlimb coordination. This field of research has been dominated by the idea of connections between CENTRAL PATTERN GENERATORS (CPGs), which are defined as relatively autonomous spinal networks that orchestrate the locomotor coordination of single limbs^{70,71}. The CPG is composed of a group of cells that undergo oscillations of their membrane potential. Animals still show coordinated behaviour when their spinal cord is isolated from the higher neural centres⁷². The spinal modules can be flexibly combined to produce a wide range of behaviours⁷³. Earlier studies by von Holst⁷⁴ had already shown a rich variety of inter-fin interactions in isolated fish preparations. Indirect evidence for the existence of a CPG in humans has also been advanced, but has proved to be more difficult to establish experimentally^{28,75,76}.

In addition, interlimb coordination depends on interlimb reflexes that are regulated by afferent input²⁸. These reflexes also serve to regulate locomotion during unexpected perturbations. They subserve the common goals of minimizing instability and securing progression. The patterns of reflex modulation are task dependent, but also depend on the phase of the movement cycle. For example, when the ipsilateral swing phase is prolonged by electrical stimulation or mechanical perturbation, the contralateral stance phase is also

prolonged. Although interlimb reflexes have been shown most convincingly in leg movements, they are also evident in arm movements⁷⁷. Across-girdle interactions have also been established during human walking, an observation that is indicative of neuronal coupling between the upper and lower limbs, which could reflect a remnant of CPG interconnections that are involved in quadrupedal locomotion⁷⁵. Research on the neural mechanisms that underlie locomotion is very extensive, but is beyond the scope of the present review (for reviews, see REFS 28,78).

Even though interlimb coordination is presumably assured through propriospinal pathways, supraspinal structures are also crucial⁷². At the highest level, cortical regions also come into play to supervise and modulate the basic spinal coordination networks. Recent work using NEAR-INFRARED SPECTROSCOPY attests to the fact that sensory cortex and primary and secondary motor cortical areas are active during locomotion⁷⁹. Moreover, evolution towards bipedal locomotion has promoted highly refined bimanual coordination patterns in primates and humans that are associated with increased cortical mass and dedicated networks for their control. Much less attention has been devoted to unravelling the neural basis of these sophisticated coordinative functions. Initial experimental work on primates was based on the assumption that bimanual coordination can be assigned to a single medial frontal brain locus — the supplementary motor area (SMA) — and this idea was supported by anatomical, electrophysiological and lesion data^{80–82}. Although this viewpoint has dominated thinking in this field for a long time, several lines of evidence have forced a shift in focus from a single dedicated area to a more distributed brain network that is involved in various forms of interlimb coordination^{83–87}. First, lesion and reversible inactivation studies have shown that goal invariance is preserved during a bimanual reach-and-grasp task, indicating that the SMA does not represent the bimanual command structure^{88–90}. Second, neurophysiological techniques have shown that neuronal activity not only in the SMA, but also in the primary motor cortex (M1)^{91,92} and in other brain areas⁸⁹, is associated with bimanual movements. Third, the SMA is also involved in coordination between arm and leg segments, and is modulated as a function of coordinative complexity⁸⁷. Establishing a unique role for the SMA in bimanual coordination is further complicated by the fact that this brain area is involved in many unilateral tasks, particularly those involving movement sequencing and internal pacing.

Although there is converging evidence about the involvement of various brain areas in coordination tasks, there is much less agreement as to whether these areas make a specific contribution to coordination. There are various ways to explore this issue; for example, by showing distinct patterns of activation of single neurons or neuronal groups, or increased blood flow in association with the production of coordination patterns. The brain areas identified in these ways are favourite candidates for a more pervasive involvement in the control of coordination patterns. These candidate

areas are the SMA, the primary motor and sensory cortices (M1, S1), the premotor cortex (PM), the cingulate motor area (CMA) and, depending on task complexity and degree of familiarity, the posterior parietal cortex (PPC)^{84–86,93–98}. A similar distributed network that is composed of SMA, S1, M1, PM, CMA and cerebellum has also been identified during coordination of the ipsilateral right wrist and foot, indicating that the proposed network might not be confined to bimanual coordination⁸⁷. With respect to the SMA, coordination-related activity has been observed predominantly in the SMA proper (caudal), rather than in the pre-SMA (rostral); the latter is generally more involved in planning more complex and/or less familiar tasks^{99,100}, task switching¹⁰¹ and working memory¹⁰². In coordination tasks, activity of the SMA proper is often associated with activity in the CMA, to which it is strongly connected. Because the sulcal anatomy of medial regions is highly variable, it is sometimes difficult to dissociate SMA from cingulate activations⁹⁴. It also remains to be explored how the contribution of the medial areas differs from that of the lateral premotor areas. With respect to motor skill tasks in general, SMA activations are prominent when performance is guided by internal cues, whereas PM is more involved in movements that are dependent on external information. It remains to be investigated whether this dissociation applies equally to interlimb coordination tasks or whether PM has a specific involvement in bimanual coordination.

Recent studies have addressed the distinction between variants of symmetrical (in-phase) and parallel (anti-phase) bimanual movements using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) (FIG. 1a). This comparison has resulted in higher activation levels in the SMA^{85,86,94–98,103}, S1, M1⁹⁸, CMA^{85,94} and PM^{85,94,96} during parallel, as compared with symmetrical, bimanual coordination. Comparison of isodirectional versus non-isodirectional ipsilateral coordination patterns (FIG. 1b) has also revealed differential activation levels in the medial frontal areas (SMA, CMA)⁸⁷. Increased medial frontal activation has also been observed during 3:2 as compared with 2:2 finger tapping in electroencephalographic (EEG) studies¹⁰⁴. The fact that there is no complete agreement with respect to the distribution of brain-activation patterns as a function of different coordination modes or as a function of two- versus single-limb comparisons should not come as a surprise. The techniques that are used to compare activation levels across experimental conditions, as well as the statistical power, differ between studies. Furthermore, the studied tasks differ in their degree of complexity and familiarity. Compared with the preferred coordination modes, less familiar modes will show more widespread activations across the brain, and these activations might change with learning (F. Debaere *et al.*, unpublished data). Accordingly, it no longer seems fruitful to ask whether there are specific areas for (bimanual) coordination; instead, we should ask which parameters define activation-related coordinative complexity and how brain-activation networks are modulated as a function of practice.

NEAR-INFRARED SPECTROSCOPY
A form of optical imaging that uses arrays of lasers and detectors to measure changes in the absorption of near-infrared light caused by neural activation.

In view of the distributed nature of the cerebral control of interlimb coordination, it is no surprise that patients who suffer from various lesions or from neurodegenerative disorders show deficits in interlimb, particularly bimanual, coordination. Evidence for such deficits has been found in patients with lesions in the cerebellum^{105–108}, the SMA and/or cingulate cortex^{85,86,109–111}, the corpus callosum^{44–46,112} and the parietal areas^{113,114}. Similarly, deficits are seen in patients with **Parkinson's disease**^{115–120}, **Huntington's disease**^{105,121} and **TOURETTE'S SYNDROME**¹²². Lesions of the left hemisphere affect bimanual coordination more profoundly than right-hemisphere lesions¹²³, in agreement with fMRI evidence for a greater involvement of the left hemisphere during bimanual coordination¹⁰³. Anti-phase coordination is usually more affected than in-phase coordination and, because the in-phase mode is not easily disrupted by lesions outside M1, is therefore a better candidate for clinical assessment of the degree of deficit¹²⁴. The observation that coordination is also disrupted in neurodegenerative disorders of the basal ganglia might seem surprising, because this structure has previously not been listed as a principal candidate for the distributed coordination network for basic patterns. However, the basal ganglia project to primary and secondary motor cortical areas through thalamic relay nuclei¹²⁵, and the latter have been shown to participate in coordination. Accordingly, linking function and structure should be done with great care, considering the prominent interconnections between brain areas and the patient's ability to develop compensatory control strategies to bypass the deficient default networks.

An area that has largely been neglected in functional imaging studies of coordination-related activity is the cerebellum (for exceptions, see REFS 87,126). This is unfortunate, because there are long-standing associations between the cerebellum and coordination^{106,107}. Holmes' historical work on patients with cerebellar lesions pointed to deficits in intralimb (inter-muscular) as well as interlimb coordination. But the presence of unimanual deficits complicates interpretations about the putative involvement of a brain area in bimanual coordination. More conclusive evidence about the role of the cerebellum has been found in recent work on eye–hand coupling, which can be considered as a special case of inter-effector coordination¹²⁷. During eye and hand tracking tasks, the cerebellum was the only area that showed a parametric relationship with the degree of eye–hand coordination. More specifically, cerebellar activity was more pronounced during both optimal coordination (synchronization with a small phase lag between eye and hand) and lack of coordination. This was presumed to reflect cerebellar involvement in the comparison between predicted and actual movement outcomes — a role that is assigned to forward models with predictive control¹²⁷. A forward model uses **EFFERENCE-COPY** signals that are produced together with the generation of motor commands to predict the sensory consequences of the motor act. Future work should establish whether the results on eye–hand coordination can be generalized to interlimb coordination that involves various phase relationships.

The distributed network for interlimb coordination that I discussed previously pertains mainly to relatively simple patterns that generally belong to the intrinsic repertoire of normal individuals. When new patterns of coordination are performed, such as those involving multi-frequency ratios or less familiar relative-phasing patterns, the previously identified network expands to prefrontal, parietal and subcortical brain areas, the involvement of which changes with increasing automaticity (F. Debaere *et al.*, unpublished data). More specifically, the rostral parts of the SMA (pre-SMA), the anterior parts of the cingulate cortex (caudal part of the anterior cingulate cortex (ACC), which is distinct from the CMA) and other prefrontal areas become involved to cope with increased working-memory load and attentional requirements, as well as with movement selection processes¹²⁸. In this respect, the lateral prefrontal cortex might cooperate with the ACC (with which it is connected) to suppress competing or unwanted response tendencies, such as phase and frequency synchronization, and to select appropriate movement combinations. Pianists show activity in the pre-SMA and SMA when playing unfamiliar pieces, whereas SMA activity prevails during highly automated ones^{129,130}. In addition, pianists show lower degrees of activation in primary and secondary motor areas (M1, SMA proper, pre-SMA, CMA) than non-musicians¹³¹. As initial learning is also associated with more elaborate sensory monitoring of afferent information from different limbs and their comparison with predicted sensory information, the parietal cortex and cerebellum are likely to show increased involvement during the acquisition of new coordination patterns (F. Debaere *et al.*, unpublished data).

With respect to the previously discussed pre-SMA activations, it is important to bear in mind that this brain area is involved not only in acquiring new patterns of simultaneous movements, as required during interlimb coordination, but also in the elaboration of successive elements in a sequential task with motor or non-motor components^{132,133}. Similarly, the role of the ACC goes beyond motor control, as it is also involved in cognitive and emotional processes^{128,134}. As such, it serves as an important interface between cognition and action. In summary, functional imaging studies point to the involvement of many brain areas during interlimb coordination, but this involvement is shared largely with the control of other types of task. Accordingly, a 'process' approach seems more fruitful than a 'task' approach to guide future research on the cerebral control of interlimb coordination.

Although brain-imaging studies have provided insights into the brain areas that might be involved in interlimb coordination, they do not tell us much about the specific nature of the interactions between these distributed areas on shorter timescales. Similarly, they tell us little about the neuronal encoding patterns that are required for coordination. Stated differently, if interlimb coordination is best understood as a distributed network, how is integration of neural assemblies within and across the brain areas accomplished? Recent studies using techniques with higher temporal resolution, such as

TOURETTE'S SYNDROME

A rare disorder that is thought to be caused by abnormalities of the basal ganglia. It is characterized by facial and vocal tics, and less frequently by verbal profanities.

EFFERENCE COPY

A copy of the motor command that is sent back to the central nervous system to inform it of the executed movement.

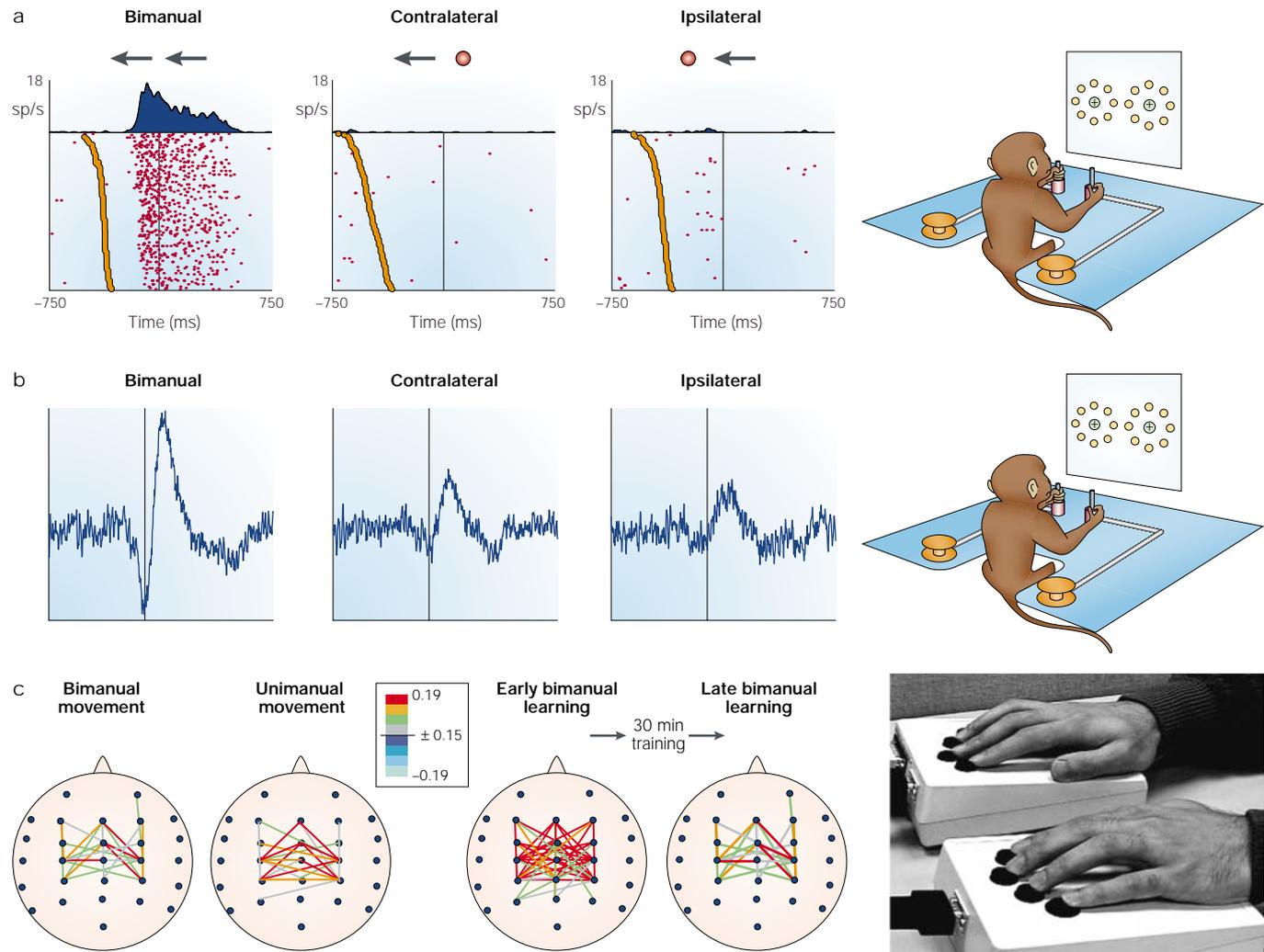


Figure 5 | Techniques that are used to study the neural basis of interlimb coordination. **a** | Example of a supplementary motor area (SMA) cell in a monkey, showing bimanual-related activity during parallel arm movements. Each plot contains peristimulus time histograms and raster displays that show cell activity (sp/s, spikes s^{-1}). The cell shows strong activation during bimanual movement (left column), but not during contralateral (middle column) or ipsilateral movement (right column). Similar bimanual-related activity patterns are also shown in cells of the primary motor cortex (M1). Reproduced with permission from *Nature* (REF. 91) © 1998 Macmillan Magazines Ltd. **b** | Example of mean motor-evoked potential, as recorded in M1, in which the size of the local field potential is higher during bimanual than during unimanual left (contralateral) or right (ipsilateral) movements (bimanual-related effect). Reproduced with permission from REF. 135 © 2001 Springer-Verlag. **c** | Multichannel surface electroencephalographic (EEG) recording of cortical sensorimotor areas made with scalp electrodes in humans during the production of unimanual and coordinated bimanual finger movement sequences. Task-related coherence (TRCoh) is used as a measure of inter-regional functional coupling and is shown as colour-coded link plots, which reflect the magnitude and spatial patterns of the TRCoh. The TRCoh does not differ between unimanual movement production and bimanual movement production after learning, indicating that functional coupling between hemispheres is important not only for bimanual movements, but also for performing complex unimanual sequences. Furthermore, bimanual practice is associated with a reduction in TRCoh. The highest interhemispheric TRCoh values are observed in the early bimanual learning phase, after which the values regress towards unimanual control values. This indicates a modulation of degree of interhemispheric coupling of sensorimotor cortices during bimanual learning. Reproduced with permission from REF. 137 © 1999 Oxford University Press.

LOCAL FIELD POTENTIAL
The summated electrical current in the vicinity of the recording electrode — current that is generated by a large population of neurons.

single-cell recording and EEG, have provided preliminary insights, ranging from the level of single neurons to that of neuronal groups (FIG. 5). In this respect, associations have been observed between coupling modes at the behavioural (kinematic) and neuronal level. Neurons in SMA and M1 have shown activity levels during bimanual movements that differ from their unimanual counterparts (FIG. 5a). The study of LOCAL FIELD POTENTIALS (LFP) has revealed that the size of movement-evoked potentials in both SMA and M1 is larger during bimanual than during unimanual movements¹³⁵ (FIG. 5b). Moreover, LFP

correlations between interhemispheric motor cortical pairs are consistently associated with the type of bimanual movement; bimanual symmetric movements show stronger increases than bimanual asymmetric and unimanual movements¹³⁶. These inter-hemispheric correlations could provide the neural basis of crosstalk between limbs, as observed at the behavioural level. Not only are firing rates or the amplitudes of evoked potentials related to the particular mode of coordination, so too are the dynamic interactions between neuronal populations. These observations, which might extend beyond SMA

and M1, indicate that bimanual movements have a distinct neuronal representation that is not generated by simply combining the activity patterns associated with unimanual movements.

On a larger spatial scale, EEG recordings have shown that the degree of task-related coherence between the left and right central cortices is similar during unimanual and bimanual finger movements, except at the start of bimanual practice when task-related coherence is elevated. This indicates that interhemispheric functional coupling between human premotor and sensorimotor areas might initially be enhanced during the acquisition of a new bimanual finger sequence task, and subsequently decreases¹³⁷ (FIG. 5c). These observations provide examples of processes of neuronal group interaction on multiple scales in association with modes of interlimb coupling at the behavioural level. The correlated oscillatory activity seems to be a basic property of cortico-cortical networks and forms the basis of coherent coordination patterns by which movements of each limb are merged into a unified action plan.

Although studies on neural integration have focused primarily on bimanual coordination, in which the communication between both hemispheres is established through the corpus callosum, similar processes of neural integration could occur within a hemisphere when the coordinating limbs are on the same side of the body. As behavioural coupling between non-homologous limb segments is usually weaker than between homologous segments^{23,25,26}, the default connection strength of limb-related motor-cortical areas within a hemisphere might be weaker than between hemispheres, despite the shorter physical distance of intrahemispheric connections. The behavioural consequence is that performing different movements simultaneously will be easier with hand and foot than with left- and right-hand combinations.

Summary

This is an exciting time for the study of motor control, because the merging of information from different approaches and technologies on multiple scales of neural functioning is truly unsurpassed. The emerging message is that the control of interlimb coordination should not be assigned to a single locus; rather, it seems to involve a distributed network in which interactive processes between many neural assemblies at spinal and supra-spinal levels take place to secure efferent organization and sensory integration. Cortical control becomes more prominent when the default coordination patterns that are provided by spinal assemblies have to be overcome. However, many questions still remain unresolved. One of the main problems is the identification of the specific roles of the different brain areas that constitute the network, as well as their mode of communication and the encoding properties of the neurons that are involved in coordination. This also relates to the balance between processes of excitation and inhibition. The processes of neural integration between distributed areas do not only imply basic synchronization processes at different systems levels. As discussed earlier, the acquisition of new skills is often hampered by the emergence of preferred coupling modes that need to be suppressed to develop differentiated patterns of activity between the limbs. As such, large-scale integration of neural assemblies might also depend on the recruitment of inhibitory networks; however, current imaging techniques do not distinguish between inhibition and excitation. The study of human movement coordination provides an ideal system to unravel multiple-task management and task integration by the central nervous system in general, and interactions between distributed neural assemblies in particular, because the consequences of these neural processes can be traced at the behavioural level with high kinematic resolution.

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