Movement Disorders
CLINICAL PRACTICE

REVIEW

A Reflection on Motor Overflow, Mirror Phenomena, Synkinesia and Entrainment

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Abstract: In patients with movement disorders, voluntary movements can sometimes be accompanied by unintentional muscle contractions in other body regions. In this review, we discuss clinical and pathophysiological aspects of several motor phenomena including mirror movements, dystonic overflow, synkinesia, entrainment and mirror dystonia, focusing on their similarities and differences. These phenomena share some common clinical and pathophysiological features, which often leads to confusion in their definition. However, they differ in several aspects, such as the body part showing the undesired movement, the type of this movement (identical or not to the intentional movement), the underlying neurological condition, and the role of primary motor areas, descending pathways and inhibitory circuits involved, suggesting that these are distinct phenomena. We summarize the main features of these fascinating clinical signs aiming to improve the clinical recognition and standardize the terminology in research studies. We also suggest that the term "mirror dystonia" may be not appropriate to describe this peculiar phenomenon which may be closer to dystonic overflow rather than to the classical mirror movements.

There has been a growing recognition that voluntary movements can sometimes be accompanied by unintentional muscle contractions in other body regions, in a number of neurological conditions.[1–4] Several terms have been used to describe these phenomena, including overflow, synkinesia (or synkinesis) and mirror movements (MM). However, there is often nosological inexactitude, meaning that these terms are often inappropriately used as synonyms. Motor overflow and synkinesia are often used in the literature as broad terms to describe any unintentional activation of muscles not directly involved in the motor task, accompanying a movement.[2,4] While a more a more precise definition of synkinesia is lacking, a formal definition of motor overflow has been developed in the specific context of dystonia, as "an unintentional muscle contraction which accompanies, but is anatomically distinct from the primary dystonic movement, commonly occurring at the peak of dystonic movements".[5] On the other hand, MM are defined as unintentional movements of one side of the body that "mirror" intentional movements on the opposite side.[6]

In this review, we discuss each of these distinct phenomena from clinical and pathophysiological perspectives, aiming to both standardize their definition and classification, and delineate the clinical and pathological significance of each entity.

Motor Overflow

Motor overflow can be at times observed in healthy adults under effortful and fatiguing conditions, where it may be due to effort-related facilitation or fatigue-induced disinhibition.[7] The effort applies not only to the strength of the contraction but also to the difficulty of the action; in fact, motor overflow becomes more pronounced if the task is demanding, but its magnitude can be reduced with training (ie, learning a complex manual task).

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Motor overflow is typically observed in dystonia, a hyperkinetic disorder characterized by sustained or intermittent muscle contraction causing abnormal movements and or postures.[5,8] In such situations, dystonic movements often "overflow" toward apparently unaffected body segments.[8–10] From the clinical perspective, the presence of motor overflow may be a useful clue for movement disorder specialists in distinguishing organic from functional limb dystonia, since this latter condition usually presents as a fixed abnormal posture associated with pain in the same region, and does not present motor overflow phenomenon.[11]

In contrast to motor overflow observed in healthy individuals, dystonic overflow occurs during routine tasks (ie, simple hand movements, finger tapping or writing; Video 1) which do not necessitate strenuous physical or cognitive input. This might suggest that though underpinned by similar pathophysiological mechanisms in both cases, the threshold for its appearance is lower in dystonia, likely due to a loss of inhibition of sensorimotor circuits, which typifies dystonia at a neurophysiologic level.[12,13] Under normal conditions, the execution of a precise motor task requires the suppression of excitatory motor signals in an area surrounding the activated neural network, to sharpen the motor command and inhibit undesired movements (Fig. 1A).[12–17] This "surround inhibition" is reduced in dystonia, predisposing to inappropriate and excessive recruitment of muscles not involved in the voluntary movement, and thus causing motor overflow (Fig. 1B).[12,13] This hypothesis fits well with the typical observation in patients with focal hand dystonia (FHD), where movements of a single finger in the dystonic hand produces also movements of adjacent fingers of the same hand or the contiguous arm. Indeed, motor overflow in dystonia usually involves muscles anatomically contiguous to the dystonic region (ipsilateral overflow), due to loss of surround inhibition of bordering motor programs.[12]

More debated is the concept of motor overflow involving body regions noncontiguous or contralateral to the dystonic limb. A couple of studies[9,10] reported a contralateral overflow in some patients with FHD and defined it as "an involuntary movement or dystonic posture *in the normal, contralateral limb* during dystonic movements of the hand primarily affected by FHD". Another study[18] found EMG activation in the extensor digitorum communis and trapezius muscles of the unaffected limb in patients with FHD during a writing task performed with the dystonic hand. Some authors also reported contralateral overflow in patients with Huntington's chorea, correlating with disease severity.[19] This contralateral overflow phenomenon might be explained by the existence of a broad lack of inhibition in dystonia, involving both cerebral hemispheres even when the clinical symptoms involve only one body region.[1,12,13] No study, however, directly investigated the pathophysiological bases of contralateral overflow in dystonic patients.

Video 1. Segment 1: a patient with right focal hand dystonia showing motor overflow characterized by ipsilateral shoulder elevation during a writing task performed with the dystonic hand. Segment 2: a patient with right focal hand dystonia showing *mirror dystonia* characterized by thumb extension in the right (dystonic) hand while performing a writing task with the contralateral hand. The movement does not "mirror" the writing task. Segment 3: a patient with congenital mirror movements (MM), showing bilateral MM in the fingers occurring during different motor tasks. Segment 4: a patient with "vascular" corticobasal syndrome showing MM in the right (most affected) hand while performing motor tasks with the contralateral hand. Segment 5: a patient with Parkinson's disease and a patient with segmental dystonia showing ocular-jaw synkinesia, characterized by a jaw deviation ipsilateral to the horizontal ocular saccadic movement. Segment 6: a patient with functional palatal tremor showing entrainment phenomenon (tremor frequency changes to match that of the tapping task).
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13798

Mirror Movements

MM are unintentional movements of one side of the body that mirror intentional movements on the opposite side (Video 1).[6,20–22] They have been described in several congenital and acquired neurological disorders[20–22] and mainly involve the fingers, sometimes making activities such as typing on a keyboard or using cutlery difficult.[1,6,20–22] Mild bilateral MM can be observed in children due to the natural tendency of the brain to produce symmetrical mirror motions with both hands, but MM usually disappear before the age of 7–10 years because of morphological and functional maturation of circuits mediating interhemispheric interactions between the motor areas; overt MM occurring during routine tasks persisting after this age may be considered pathological.[20–22] Mild MM can be occasionally seen in normal adults only under effortful conditions and fatiguing voluntary contractions, but not during common manual tasks.[4,6] Congenital MM persisting throughout adulthood in individuals who have no other symptoms are usually due to monoallelic variants in the *DCC*,[22–24] *NTN1*,[25] or *RAD51*[26] genes, but MM can also be observed in patients with Klippel-Feil syndrome, X-linked Kallmann syndrome due to *KAL1* gene variants, and a variable percentage of patients with hemiplegic cerebral palsy.[20–22,27–29] Regarding acquired neurological diseases, MM have been described mainly in pyramidal syndromes (in amyotrophic lateral sclerosis and in non-paretic limbs of patients with hemiplegic stroke), in parkinsonian syndromes, in essential tremor and in Huntington's disease.[20,21] In Parkinson's disease (PD) patients,

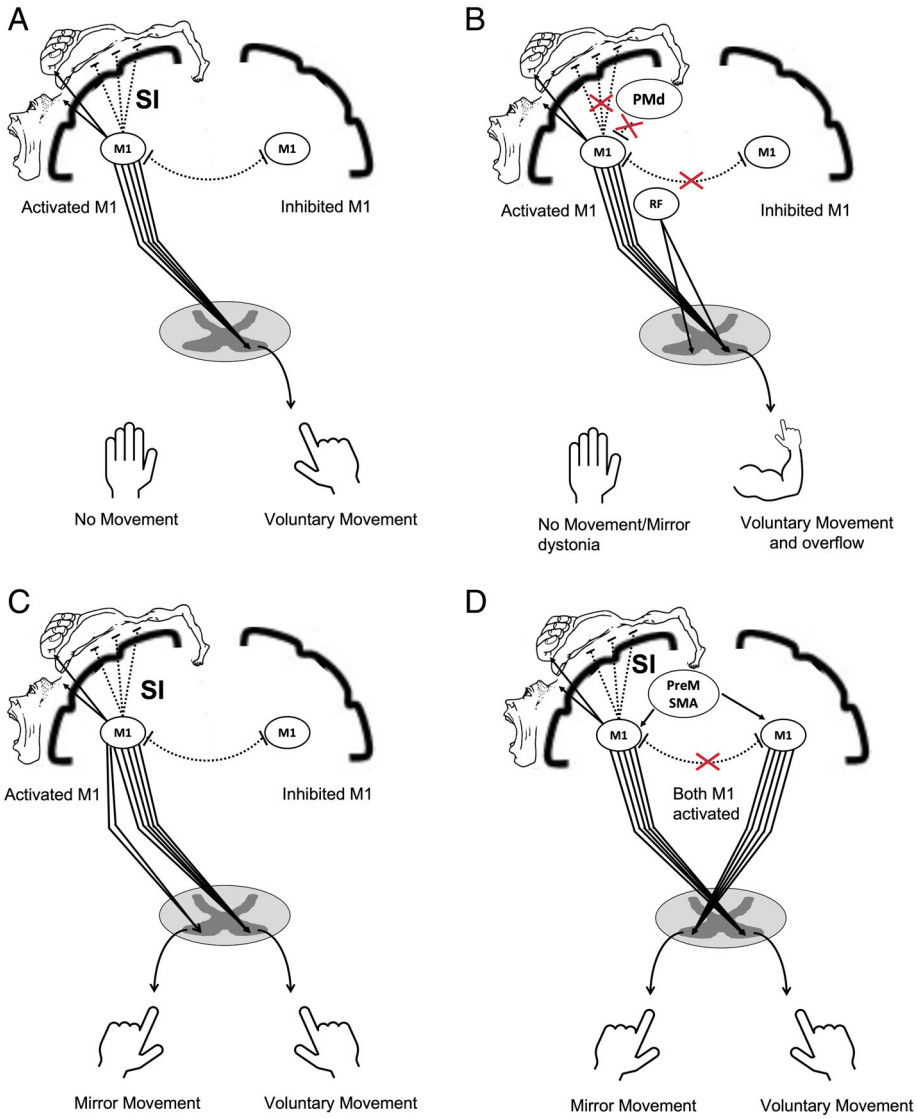

FIG. 1. (A) Unilateral manual task under normal conditions: the figure shows inhibitory mechanisms including surround inhibition (SI) and transcallosal inhibition. (B) Dystonic overflow/mirror dystonia, characterized by reduced SI, reduced PMd inhibitory control over the ipsilateral M1, abnormal interhemispheric connection and possible involvement of the reticulospinal tract. (C) Mirror movements, mechanism 1: abnormal ipsilateral corticospinal projections. (D) Mirror movements, mechanism 2: abnormal activation of both M1s and transmission of the command along both corticospinal tracts. M1, primary motor cortex; PMd, dorsal premotor cortex; PreM, pre-motor areas; RF, reticular formation; SMA, supplementary motor area.

MM typically involve the less affected hand during voluntary movements of the more affected hand, especially in the ON state.[30–33] They are usually observed in the early stage of the disease and fade as the disease progress, possibly due to the increase in bradykinesia/hypokinesia.[34–37] Differently from PD, in cortico-basal syndrome (CBS) patients, MM have been usually described in the most affected hand.[20,21] There is not a definitive explanation for the different hand involvement in these two parkinsonian syndromes. Some authors hypothesized that MM might be more evident in the less affected side in PD patients due to the lower degree of rigidity and bradykinesia[34]; however, this explanation would not fit the case of CBS patients. Another possibility is that the dorsal premotor cortex activity, which may play a role in suppressing MM, is reduced in the less affected side in PD (see below). The reason why MM usually occur in the most affected hand in CBS patients has not a solid explanation yet, but it has been hypothesized that mirror movements may be part of the clinical spectrum of alien hand phenomenon,[38] which also include motor interference or disruption of movements performed with the contralateral limb, and typically involve the most affected hand.

From a physiological point of view, the ability to perform unilateral finger/hand movements requires the activation of contralateral primary motor cortex (M1) motor neurons coupled with a transient inhibition of ipsilateral neurons innervating muscles on the other side.[15–17,27] In fact, the activation of the motor cortex on one side leads to a transcallosal (or interhemispheric) inhibition (TCI or IHI) of the M1 in the other hemisphere. The aim of TCI is to restrict motor output to the contralateral primary motor cortex, thus allowing to perform a unilateral motor task suppressing symmetrical contralateral movements.[15–17,27] If the cortical activation continues to increase in strength, TCI is replaced by facilitation and this may explain why MM can rarely be seen in adults under effortful conditions and fatiguing voluntary contractions.[4,6] In addition to TCI, other inhibitory mechanisms may also be involved in preventing mirroring, such as intra-hemispheric inhibition of the ipsilateral hemisphere (a process depending on the motor task performed and mediated through premotor areas).[39]

Two mechanisms have been proposed so far to explain the pathophysiology of MM in neurological disorders.[14,20–22,24,26] One is the presence of abnormal ipsilateral corticospinal projections. In this case, a motor command from M1 proceeds to the contralateral hand through the normally crossed corticospinal tract but also to the ipsilateral hand through abnormally uncrossed fibers (Fig. 1C).[20–22,26–29] The presence of a significant number of ipsilateral corticospinal fibers has been demonstrated in patients with congenital MM using diffusion tensor imaging and corticospinal tractography MRI[25,26] and evaluating ipsilateral motor-evoked potentials in the distal muscles of the hands.[24,25,27,40] The second mechanism is the abnormal activation of both motor areas, due to spread of the motor plan from supplementary motor areas to both M1s,[16,22,26,41] and to a reduced interhemispheric inhibition from the active M1 to the contralateral M1 via transcallosal pathways (Fig. 1D).[16,20,22,26,42] This evidence is supported by functional neuroimaging studies showing activation of bilateral brain structures during MM[26,43] and abnormal connectivity between both M1s,[24] and by transcranial magnetic stimulation (TMS) studies reporting reduced IHI in patients with MM.[24,40,42,44] Both these mechanisms play a role in congenital MM, with abnormal ipsilateral corticospinal projections probably providing the major contribution.[22,25–27] On the contrary, there is no evidence of uncrossed corticospinal fibers in patients with MM in acquired disorders such as parkinsonian syndromes,[34,45] and MM in these patients seem due mainly to the abnormal bilateral M1 activation.[20–22,34,35,45,46] Among acquired disorders showing MM, PD is by far the most studied. An important role in the pathophysiology of MM in PD seems to be played by the reduced activation of the dorsal premotor cortex and supplementary motor area (SMA), which normally contribute to unimanual tasks suppressing contralateral movements.[34,35,37] An fMRI study demonstrated reduced activation of these structures during unimanual tasks, especially in the less affected hemisphere, which might explain why MM are usually observed in the less affected hand in PD patients.[37] Another study suggested a role of basal ganglia involvement, showing that the reduced output from basal ganglia to cortical regions in PD leads to a reduced lateralization of brain activity during unilateral movements, which may also contribute to MM.[35] Finally, a further possible hypothesis to explain MM in PD patients is that the greater effort needed to produce a quick movement compared to normal volunteers leads to "compensatory" overactivation of the motor cortical areas and consequently to a transcallosal facilitation (TCF) of the contralateral M1, as it physiologically happens during complex and effortful motor tasks in healthy people.[46–49] This hypothesis fits well with the presence of MM mainly in the less affected clinical side in PD patients during motor tasks performed with the most affected side, and the reduction of these compensatory movements with disease progression may explain the lower prevalence of MM in advanced PD patients.[35–37] One study,[34] however, found reduced IHI and normal TCF in PD patients with MM, pointing against this hypothesis and suggesting that the reduced inhibition rather than increased facilitation may be mainly responsible for the overactivity of the ipsilateral M1. Further studies are needed to establish the possible role of TCF in determining MM in PD patients.

In patients with stroke, some authors showed that MM in the non-paretic limb are caused by overactivation of the contralesional sensorimotor cortex.[21,46,48] On the contrary, one recent study in 53 patients with stroke showed lack of cortical overactivation and suggested a subcortical origin for MM in stroke patients.[49]

Mirror Dystonia

In dystonia, classic MM have not been widely reported, and the most common mirroring phenomenon is termed "mirror dystonia." It is defined as a unilateral posture or movement similar to a dystonic feature that can be elicited, usually *in the most severely affected side*, when contralateral movements or actions are performed.[5,8–10] The term "mirror" implies an analogy between the two motor phenomena. However, in MM the extra movements *mirror* the intentional ones, while in "mirror" dystonia the two movements are different (Video 1).[9,10,20] This might suggest an inappropriate use of the term "mirror" as in fact, no "mirroring" is taking place[9,10]; a different hypothesis might be considering mirror dystonia as a triggered, non-contiguous dystonic overflow. In addition, since mirror dystonia is commonly elicited with a writing task, there may be some confusion with "mirror writing," which is a distinct phenomenon rarely observed in children or after left hemisphere lesions, characterized by the writing running in the opposite direction compared to normal, with individual letters reversed, so that it can be easily read using a mirror.[50]

Mirror dystonia is observed in 40–50% of FHD patients[51,52] and is commonly elicited during a writing task, but also with finger tapping or finger-nose task performed with the unaffected contralateral hand.[8–10] Some authors suggested that mirror dystonia may be useful to guide selection of muscles for botulinum toxin injections in FHD, because the phenomenon allows one to

observe the "natural" dystonic posture of the affected hand, in the absence of secondary compensatory movements.[53]

From a pathophysiological point of view, the available evidence suggests that mirror dystonia may be related to abnormal interhemispheric communication between the two primary motor cortices, coupled with the deficient intra-cortical inhibition in the dystonic hemisphere, which is a well-known feature of FHD.[54,55] Nevertheless, the miscommunication between the two hemispheres might be driven by different mechanisms compared to those observed in MM (see discussion). In addition, voluntary motor tasks performed by unaffected body parts can trigger or exacerbate the dystonic abnormal postures/movements, as commonly observed in cervical dystonia while walking,[3] thus another hypothesis is that mirror dystonia might be an exacerbation of the dystonic posture due to a voluntary motor task performed with another limb. From this point of view, this phenomenon might share some similarities with the increase of rigidity commonly observed in PD patients while performing voluntary motor tasks with the unaffected or less affected limbs (Froment's maneuver).[3,56,57]

Synkinesia

The term "synkinesia" (or synkinesis) includes different forms of extra movements occurring simultaneously to voluntary muscle contraction. The most common form of synkinesia is the facial synkinesia, commonly occurring after Bell's palsy[58] and clinically characterized by contraction of additional facial mimetic musculature (ie, eye closing) accompanying volitional facial movements such as smiling or chewing; however, other types of synkinesia have also been described. These include the ocular-jaw synkinesia (observed in PD, characterized by jaw movements ipsilateral to the horizontal gaze deviation),[59] the respiratory synkinesia (also called "breathing arm," characterized by contraction of one or multiple upper limb muscles together with the diaphragm muscle; usually reported in the context of an upper limb injury)[60] and arm-leg synkinesia (sporadically reported in patients with frontoparietal or thalamic stroke,[61,62] prion disease,[63] or parkinsonian conditions such as PD and corticobasal syndrome).[64] In this latter case, voluntary hand movement may be accompanied by similar movements in the ipsilateral leg, or vice versa.[1,65] Although some authors consider MM a form of synkinesis, these two motor phenomena can be clinically distinguished because synkinetic movements often involve another region on the same side of the body rather than "mirroring" the voluntary movement in the contralateral hand.[61–67] The arm-leg synkinesia may also be distinguished from the ipsilateral overflow seen in dystonia, because they usually occur in a different limb rather than involving muscles contiguous to those activated during the motor task.

From a pathophysiological point of view, the facial synkinesia may be due to aberrant growth of regenerating neurons after injuries, with aberrant neurons also projecting to other facial muscles.[1,2,58,66] Less straightforward is the explanation of limb synkinesia. A sort of physiological hand-foot synchrony has been described voluntary movements of flexo-extension of the hand are naturally coupled with similar movements of the foot, while significant attention is required to move the two segments in opposite directions.[68] However, hands and feet are non-contiguous body segments, thus the theory of aberrant growth of regenerating neurons does not apply in this context; in addition, there are no significant connections between hand and foot motor cortex. One fMRI study in patients with hand–foot synkinesia showed activation of the SMA during these movments.[67] While a motor task performed with the hand was associated with activation of hand motor cortex in control subjects, the additional activation of foot motor cortex and of the ipsilateral SMA was also evident in patients in whom this hand motor task determined similar movements in the ipsilateral foot (hand–foot synkinesia).[67] On these basis, the main hypothesis regarding the development of arm-leg synkinesia is related to the dysfunction of secondary motor areas, such as the premotor cortex, SMA, cingulate cortex, and their connections to the primary motor cortex.[1,64] Indeed, the arm and leg regions overlap considerably in the secondary motor cortical areas, thus it is possible that synchronous motor neuron activation in the arm and leg areas within the primary motor cortex may be maintained by the common input from the secondary motor areas rather than an increased horizontal connectivity within the M1 area.[63]

Entrainment

Another phenomenon related to the bimanual motor control is the entrainment. Broadly speaking, entrainment can be defined as the integration or harmonization of different oscillators.[69] In healthy subjects, entrainment can be observed, for example, when a subject is performing a unimanual rhythmic tapping task and at some point initiates a movement with the contralateral hand while maintaining the base movement.[69] In physiological conditions there is strong temporal coupling during rhythmic movements performed with both hands at the same time, meaning that these movements generally have the same frequency and phase.[69,70] Thus, in the previous example, the second movement generally starts in phase with the base rhythm of the other arm (phase entrainment).[69] This occurs because it is extremely difficult to generate and voluntarily maintain two independent rapid rhythms at the same time[71]; this can be observed in trained musicians and is coupled with extensive SMA activation.[70] From a pathophysiological point of view, entrainment likely results from the transcallosal interactions between the two hemispheres, as demonstrated by the lack of phase entrainment at the initiation of the second rhythmic movement and the lower temporal coupling observed in patients with agenesia of the corpus callosum or callosectomy.[69] However, the physiological bases of this phenomenon remain largely unexplored.

Interestingly, the entrainment phenomenon is commonly used by movement disorders specialists in the evaluation of tremor syndromes.[71] A tremor is defined "entrainable" when it changes

TABLE 1 *Clinical and pathophysiological features of the different motor phenomena*

Motor phenomenon	Involved body region	Phenomenology	Pathophysiological mechanisms	Condition
Mirror movements	Body regions contralateral to those performing the voluntary task; typically the fingers.	Involuntary movements of one side of the body identical to the intentional movements on the opposite side.	• Abnormal ipsilateral corticospinal projections • Abnormal activation of both M1s and transmission of the command along both corticospinal tracts	• Physiological in children. • Genetic conditions (DCC, NTN1, or RAD51 genes) • Klippel-Feil syndrome • X-Linked Kallmann syndrome • Hemiplegic cerebral palsy • Pyramidal syndromes • Parkinson's disease • Cortico-basal syndrome • Essential tremor • Huntington's disease • CJD
Dystonic overflow*	Body parts often contiguous to the dystonic regions; ipsilateral to the voluntary movement	Involuntary muscle contraction which accompanies the dystonic movement	Reduced surround inhibition; possible involvement of reticulospinal tract	Dystonia
Mirror dystonia	Hand affected by focal dystonia; contralateral to the voluntary movement	A dystonic posture or twisting movement elicited by a contralateral motor task (ie, writing)	Reduced cortical inhibition; reduced PMd inhibitory control over the M1; abnormal interhemispheric connection	Focal Hand Dystonia
Synkinesia	Face (facial synkinesia; ocular-jaw synkinesia) and limbs (arm-leg synkinesia); usually ipsilateral to the voluntary movement	Involuntary movements occurring during voluntary actions involving another region usually on the same side of the body (ie, voluntary hand movements coupled with synkinetic movements of the ipsilateral leg, or vice versa)	• Aberrant growth of regenerating neurons after injuries • Dysfunction in the secondary motor areas, (premotor cortex, SMA, cingulate cortex) and their connections to the primary motor cortex	• Bell's palsy (facial synkinesia) • Stroke (arm-leg synkinesia) • Parkinson's disease • Cortico-basal syndrome • CJD
Entrainment	Limb with tremor; usually contralateral to the voluntary movement	Shift of the tremor frequency to match the frequency of a repetitive task performed by another limb (ie, a contralateral finger tap)	Largely unexplored; related to the transcallosal interactions between the two hemispheres	Functional tremor

Abbreviations: CJD, Creutzfeldt-Jakob disease; M1, primary motor area; PMd, dorsal premotor cortex; SMA, Supplementary motor area.

*Since "motor overflow" is often used as a broad term including a bunch of different phenomena, we focused in the table on the overflow occurring in dystonia which is defined as "an unintentional muscle contraction which accompanies, but is anatomically distinct from the primary dystonic movement, commonly occurring at the peak of dystonic movements."

its original frequency to match the frequency of a requested repetitive task performed by another limb, such as a contralateral finger tapping task.[70,72] The lack of entrainment points toward an "organic" tremor, where the central oscillator maintains its frequency despite the rhythmic voluntary task.[73] On the contrary, entrainment is commonly observed in patients with functional tremor, where the physiological tendency of the nervous system to generate only one temporal pattern when moving different parts of the body makes the tremor frequency change to resemble that of the tapping task. In addition to the clinical evaluation, the presence of entrainment can also be investigated with electrophysiological tremor analysis (with accelerometers or surface electromyography),[73] and the evaluation of entrainment or shift of tremor frequency during a contralateral tapping task is included in validated electrophysiological criteria to support the diagnosis of psychogenic/functional tremor.[73,74]

Discussion

Mirror dystonia, dystonic overflow, synkinesia and MM are distinct phenomena which, although visually similar, exhibit important differences both from a clinical and pathophysiological perspective (Table 1). Clinically, all of them represent extra movements occurring in a body segment other than that engaged in a particular action. On the other hand, they formally differ regarding: (a) the body part showing the undesired movement (affected or not affected limb; ipsilateral or contralateral to the voluntary movement, muscles continuous or not to those involved in the voluntary task), (b) the type of the observed movement (identical or not to the intentional movement) and (c) their pathological significance and the underlying condition (congenital syndromes, PD, stroke, dystonia). Indeed, while mirror dystonia and dystonic overflow are related to dystonia, MM are mostly observed in congenital and parkinsonian disorders, and entrainment is a physiological phenomenon. This is not only a matter of classification, but it can help to understand and speculate on the possible underpinning mechanisms. From the pathophysiological perspective, mirror phenomena, overflow and synkinesia seem to share some common bases, including abnormal activation of a neural network involving premotor cortex, SMA, cingulate cortex and their connections to the primary motor cortex, which normally suppresses additional movements during a specific motor task. However, these phenomena differ regarding the role of M1 areas and corticospinal tracts, the type of cortical inhibition (surrounding vs. interhemispheric inhibition) and the specific time when inhibition occurs during motor preparation.

MM typically occur distally in the limbs (usually in the hands and fingers) during fine motor actions, sometimes leading to inability to perform tasks requiring skilled bimanual coordination.[20,21] All these features imply the involvement of the corticospinal tract in the pathophysiology of MM.[20,21,45–47] In congenital MM, the presence of abnormal ipsilateral corticospinal projections makes a motor command proceed from M1 to both hands.[20–28] On the other hand, MM in the context of parkinsonism are due to the abnormal activity of bilateral M1s and consequent transmission of cortical motor output along both corticospinal tracts, causing bilateral spinal motoneuron discharges.[21,45–47] The bilateral activation of M1 area seems to be due to reduced activation of a neural network including secondary motor areas such as premotor cortex, SMA, cingulate cortex, and their connections to the primary motor cortex, operating the "non-mirror transformation" which consists in transforming bilateral to lateralized motor activity.[46] The primary role of M1 in the pathophysiology of MM is supported by several lines of evidence. First, it is well-known that fine manual coordination is specifically controlled by M1 and that cortico-motoneuronal system provides the control of small muscle groups in a highly selective manner, a relevant feature of skilled voluntary movements.[15] Second, several experiments in MM patients, using different TMS techniques and cross-correlation analysis of the EMG spikes recorded from bilaterally contracting homologous hand muscles, have highlighted the synchronous activation of ipsilaterally and contralaterally projecting corticospinal neurons and a contribution of both M1s to the motor output during intended unimanual movements.[46]

Very different is the case of mirror dystonia and dystonic overflow, which are phenomenologically characterized by twisting movements or abnormal postures of muscles nearby (dystonic overflow) or distant (mirror dystonia) to the voluntary action.[5,8] Also at the neural level, some differences may occur between MM (where the M1 and corticospinal tracts play a major role) and these latter dystonic phenomena (where the premotor cortex and the reticulospinal tract may be involved; see below). One of the main pathophysiological mechanisms in dystonia is the lack of inhibition at different levels of the central nervous system.[75] At the cortical level, reduced excitability of inhibitory circuits has been largely demonstrated in the sensorimotor cortex,[76] but also as reduced excitability of dorsal premotor cortex (PMd)-M1 connections.[77] The PMd plays an important role in the selection of movement execution, mediated by facilitatory and inhibitory effect onto the contralateral M1; a mechanism independent from M1 circuits. Brain imaging and TMS studies have proposed a role of PMd in the pathophysiology of dystonia,[77,78] showing reduced inhibitory control over M1 through inhibitory PMd-M1 connections, contributing to a failure in suppressing unwanted movement patterns.[79] Another explanation for overflow contraction of adjacent muscles in dystonia is the deficient surround inhibition.[12,13] The inhibitory effects of PMd over the ipsilateral M1 may also contribute to the lack of surround inhibition in dystonia.[80] It is also possible that motor overflow may involve other descending pathways rather the corticalspinal tract involved in MM, such as the reticulospinal tract. The reticulospinal tract innervates axial and appendicular muscles bilaterally, and the postsynaptic connections are highly divergent and innervate many motor unit pools, allowing for the coordination of multiple muscle groups related to gross motor function.[81] These neuroanatomical features explain why the reticulospinal tract is implicated in the execution of forceful movements, in comparison to the fine motor tasks mediated primarily by the

corticospinal tract.[82] Although the reticulospinal tract is poorly studied in humans due to its deep location in the brainstem, we might assume, considering its anatomical connections and function, that it has a relevant role in the motor overflow/mirror dystonia.

The mechanisms described so far may clarify the pathophysiological bases of motor overflow phenomenon but cannot fully explain the abnormal spread of activation to the contralateral muscles (contralateral overflow and mirror dystonia). Although clinically different (mirror dystonia is an exacerbation of the abnormal posture/movements in the dystonic limb, while the contralateral overflow is usually observed in the unaffected limb), these two phenomena have in common the crossover between both hemispheres. However, whether this is driven by the affected or unaffected hemisphere, or by their abnormal connection remains unclear. In FHD, despite the unilaterality of the symptoms, most of the cortical inhibitory abnormalities have been observed even in the "non-dystonic" hemisphere, suggesting that both hemispheres are part of a primary deficit that interacts with other factors to produce overt symptoms. Is it therefore possible that contralateral overflow and mirror dystonia are both caused by loss of inhibition in non-contiguous/interhemispheric areas? The simple answer is yes, and we are inclined to believe that this could be mediated by insufficient inhibition through callosal fibers (interhemispheric or transcallosal inhibition). If this is the case, what differentiates this from the abnormal interhemispheric connectivity observed in MM? The excitability of inhibitory interhemispheric connections between M1s can be measured with a TMS paired-pulse technique termed IHI. MM patients have lower IHI between homologous M1 hand areas, in both directions, during intended unimanual movement compared with healthy controls; a finding that explains the clinical phenomenology observed in this disorder.[26] Unsurprisingly, in mirror dystonia the evidence is different. One study showed reduced IHI in patients with FHD and mirror dystonia between the homologs surrounding but not active muscles and only in the premotor phase (50 ms before EMG onset) compared to FHD without mirror dystonia, suggesting that mirror dystonia is associated with time-specific lack of IHI not in the target muscle (ie, the muscle performing the task), but in the adjacent muscles not involved in the task.[54] Considering that the interhemispheric interaction starts 80–100 ms before the EMG onset, these results suggest a deficit in movement selection during movement initiation at the cortical level, very likely resulting in unwanted movement causing mirror dystonia. There are no data on the contralateral overflow in dystonia, but by analogy we might assume that similar mechanisms may occur. Mirror dystonia and overflow may share some common pathophysiologic mechanisms based on the loss of inhibitory mechanisms of motor control, which may involve close areas in ipsilateral overflow and (non)contiguous areas in contralateral overflow and mirror dystonia. Future clinical studies in patients with mirror dystonia are needed to better characterize this fascinating phenomenon. Regarding terminology, the term "mirror dystonia" may be not appropriate to describe this peculiar phenomenon which may be closer to dystonic overflow rather than to the classical mirror movements. We thus propose to abandon the term "mirror dystonia" to avoid confusion, as previously suggested also by other authors.[9,10]

In conclusion, despite the general similarities and partial overlap between MM, mirror dystonia, overflow, synkinesis and entrainment which lead to confusion in the terminology, these are distinct fascinating motor phenomena which can be observed in different neurological conditions and can give important clues as to underlying disease-specific pathophysiological differences.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

A. Q.: 1A, 3A, 3B
A. L.: 1A, 3A, 3B
M. K.: 3B
F. M.: 3B
E. M.: 3B
R. J. N.: 3B
J. C. R.: 3B
K. P. B.: 1A, 3B

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this work. Written informed consent was obtained from all patients involved in the study. All authors have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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