

Mirror Movements in Movement Disorders: A Review

Benjamin C. Cox¹, Massimo Cincotta² & Alberto J. Espay^{1*}

¹University of Cincinnati Neuroscience Institute, Department of Neurology, Gardner Family Center for Parkinson's Disease and Movement Disorders, University of Cincinnati, Cincinnati, Ohio, United States of America, ²Unit of Neurology, Florence Health Authority, Florence, Italy

Abstract

Background: Mirror movements (MM) are involuntary movements of homologous muscles during voluntary movements of contralateral body regions. While subtle mirroring can be present in otherwise healthy adults, overt MM may be common in many movement disorders. Examining these collective findings may further our understanding of MM and help define their usefulness as a clinical sign.

Methods: We sought to review English language research articles examining the presence, clinical significance, and/or pathophysiology of MM in Parkinson's disease (PD), corticobasal syndrome (CBS), essential tremor (ET), focal hand dystonia, Creutzfeldt-Jakob's disease (CJD), and Huntington's disease. When available, MM in these disorders were compared with those of healthy age-matched controls and congenital disorders such as Klippel-Feil syndrome and X-linked Kallman's syndrome.

Results: Clinical presentation of MM is common in asymmetric parkinsonian disorders (early PD, CBS) and manifests differently depending on the side affected (less affected hand in PD, more affected hand in CBS, either hand in ET, and both hands in healthy adults and congenital disorders), stage of disease (early, asymmetric PD and CJD), and presence of concomitant mirror-like overflow phenomena (focal dystonia and CBS-associated alien hand). In general, uncrossed descending corticospinal projections (congenital MM) and/or abnormal activation of the motor cortex ipsilateral to the voluntary task (most acquired MM), i.e., activation of the normal crossed corticospinal pathway, are required for the generation of MM.

Discussion: MM are common motor phenomena and present differently in several acquired (mostly neurodegenerative) and congenital movement disorders. Future studies on MM will enhance the clinical diagnosis of selected movement disorders and contribute to our understanding of the normal physiology of bimanual coordination.

Keywords: Mirror movements, Parkinson's disease, essential tremor, corticobasal degeneration, focal hand dystonia

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*To whom correspondence should be addressed. E-mail: alberto.espay@uc.edu

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Introduction

Mirror movements (MM) refer to the involuntary movements on one side of the body, which mimic voluntary movements of the opposite side of the body through the activation of homologous muscles that approach the performance (i.e., mirror) of a specific task. They may be considered a subset of motor overflow – the unintentional muscle contractions, which accompany, but are distinct from, dystonic limb movement. Overflow includes movements induced by involuntary movement or that do not perfectly mirror voluntary action.¹ MM may be present in all limbs, but are most common in the upper limbs, especially the hands.

MM may interfere with bimanual coordination, causing difficulty in tasks that require each hand to act independently.^{2,3} While patients can sometime suppress or minimize MM through the activation of antagonistic muscles, MM are often debilitating. They may interfere with tasks such as tying shoe-laces, cutting vegetables, or buttoning shirts. Regli et al.² reported an 11-year-old boy who was admitted to the hospital for injuries caused by an inability to climb vertical bars in gym class — releasing one hand caused him to release the other. Cincotta et al.⁴ reported another case of a 15-year-old girl with strong and sustained congenital MM affecting both hands and forearms, who complained about a painful contraction of

left shoulder muscles when she wrote with her right hand. This contraction, which subsided when MM were greatly reduced after a successful rehabilitative training, was thought to be due to a motor strategy the patient had adopted to counteract MM in the left hand during writing.

Physiological MM may appear during infancy of healthy children, persisting until around 10 years of age.⁵ This may be the result of immaturity of the central nervous system.⁶ Subtle physiological mirroring (sometimes only observable with electromyogram [EMG]) may be seen in normal adults, and is known to increase with fatigue, more demanding motor tasks, and/or age.⁷ Nevertheless, the persistence of MM into adulthood is abnormal. Persistent congenital MM also continue into adulthood, but may be differentiated from physiological MM by their prominence. While persistent congenital MM may occur sporadically, they are often inherited autosomal dominantly.^{2,7,8} MM may present as part of larger congenital disorders such as Klippel-Feil syndrome,^{9,10} X-linked Kallman's syndrome,¹¹ or hemiplegic cerebral palsy.^{3,12,13} Overt MM may also be acquired later in life as a result of either a neurodegenerative disease, such as amyotrophic lateral sclerosis,¹³ or an acute lesion such as in hemiplegic stroke.¹⁴

Two general mechanisms have been proposed to explain the occurrence of MM. First, MM may stem from the same hemisphere as their voluntary counterpart by an uncrossed fast-conducting corticospinal tract that descends from the hand area of one primary motor cortex (M1) to the ipsilateral side of the spinal cord. This abnormal ipsilateral projection could depend on either a branching of crossed corticospinal fibers or a separate ipsilateral corticospinal projection (Figure 1A or 1B). Alternatively or complementarily, MM may result from an abnormal activation of both hemispheres during intended unimanual movement. This could be due to dysfunction of the neural circuits that focus the generation of motor activity in the M1 contralateral to the voluntary movement (Figure 1C or 1D). These mechanisms are not mutually exclusive and more than one may contribute to the generation of MM.

There appears to be a difference in the pathophysiological mechanisms of congenital MM and acquired MM. An ipsilateral corticospinal pathway is the main neural substrate of congenital MM, as demonstrated by the presence of motor evoked potentials (MEP) in the resting hand muscles following transcranial magnetic stimulation (TMS) of the ipsilateral M1.^{8,9,16,17} Moreover, focal disruption of M1 activity by TMS indicates that an unintended motor output from the M1 contralateral to the mirror hand may coexist in patients with congenital MM.¹⁸

Acquired MM, by contrast, appear to stem primarily from an abnormal activation of the hemisphere contralateral to MM, however, these mechanisms will be explored further in the present article.

Herein we review the current understanding of MM as described in selected movement disorders, examining both their clinical presentation and the underlying pathophysiology that produces them.

Parkinson's disease

Description and demographics

While there have been numerous studies of MM in Parkinson's disease (PD), the literature on this topic is often nuanced. MM were first observed in hemiparkinsonism by Kinnier Wilson in 1928,¹⁹ but were relatively underappreciated in PD until fairly recently. In 1999, using biomechanical analysis of rhythmic movements, a case-control study by van den Berg et al.²⁰ described coordination disorders in PD and noted the presence of MM in all 11 of their PD patients. These patients exhibited MM of significantly greater amplitude than those exhibited by age-matched controls (greater amplitude was determined by a ratio of MM amplitude to amplitude of the voluntary arm).

Despite these findings, there have been conflicting reports regarding the prominence of MM in PD. Several studies in small cohorts have confirmed a greater prevalence of MM in PD patients compared to age-matched controls.^{20,21,22,23} In contrast to these findings, a large study aimed at ascertaining the frequency of MM in PD and healthy controls reported a lower prevalence in PD than in the normal age-matched population.²⁴ These findings may be more generalizable given the sample size (274 PD patients and 100 healthy controls). Prior studies included relatively small cohorts: Espay et al.²¹ examined 24 patients with recent onset asymmetric PD; Vidal et al.²² studied 21 patients with hemiparkinsonism; and, Cincotta et al.²⁵ studied 12 patients without clinical evidence of mirroring. Comparability between studies, however, may be limited by virtue of differences in the measurement instruments. Ottaviani and colleagues²⁶ evaluated MM using the Woods Teuber scale, the most common scale for evaluating MM, whereas other studies have used a study-specific scoring system based on amplitude, severity and distribution of the Unified Parkinson's Disease Rating Scale (UPDRS) tasks 23–26.^{21,27} The studies converge in defining a greater prevalence of MM in the early and middle stages of PD compared to late stages.²¹ Perhaps the lower prevalence of MM among late-stage PD patients contributed to the overall lower prevalence of MM in PD compared to healthy controls found in the larger study by Ottaviani and colleagues. Furthermore, the same pathophysiological mechanisms that lead to deficient activation of cortical motor areas during voluntary movements may reduce the subtle, normal physiological mirroring in PD patients, resulting in the lower overall frequency of MM in PD with respect to healthy individuals. By contrast, the increased MM seen in selected PD patients could be due to a prominent dysfunction of the neural mechanisms underlying voluntary movement lateralization.

Nevertheless, several key features of MM in PD may be isolated. As with the general population, PD patients most frequently exhibit mirroring of the upper extremities, particularly the hands and fingers, although MM have been observed in the legs and feet.²¹ Unlike MM in congenital disorders such as Klippel Feil syndrome¹⁰ and X-linked Kallman's syndrome,¹² MM in PD are typically unilateral and observed in the less affected hand during voluntary movement of the more affected hand.^{21,22,24,29,27,28} MM in the more affected hand are

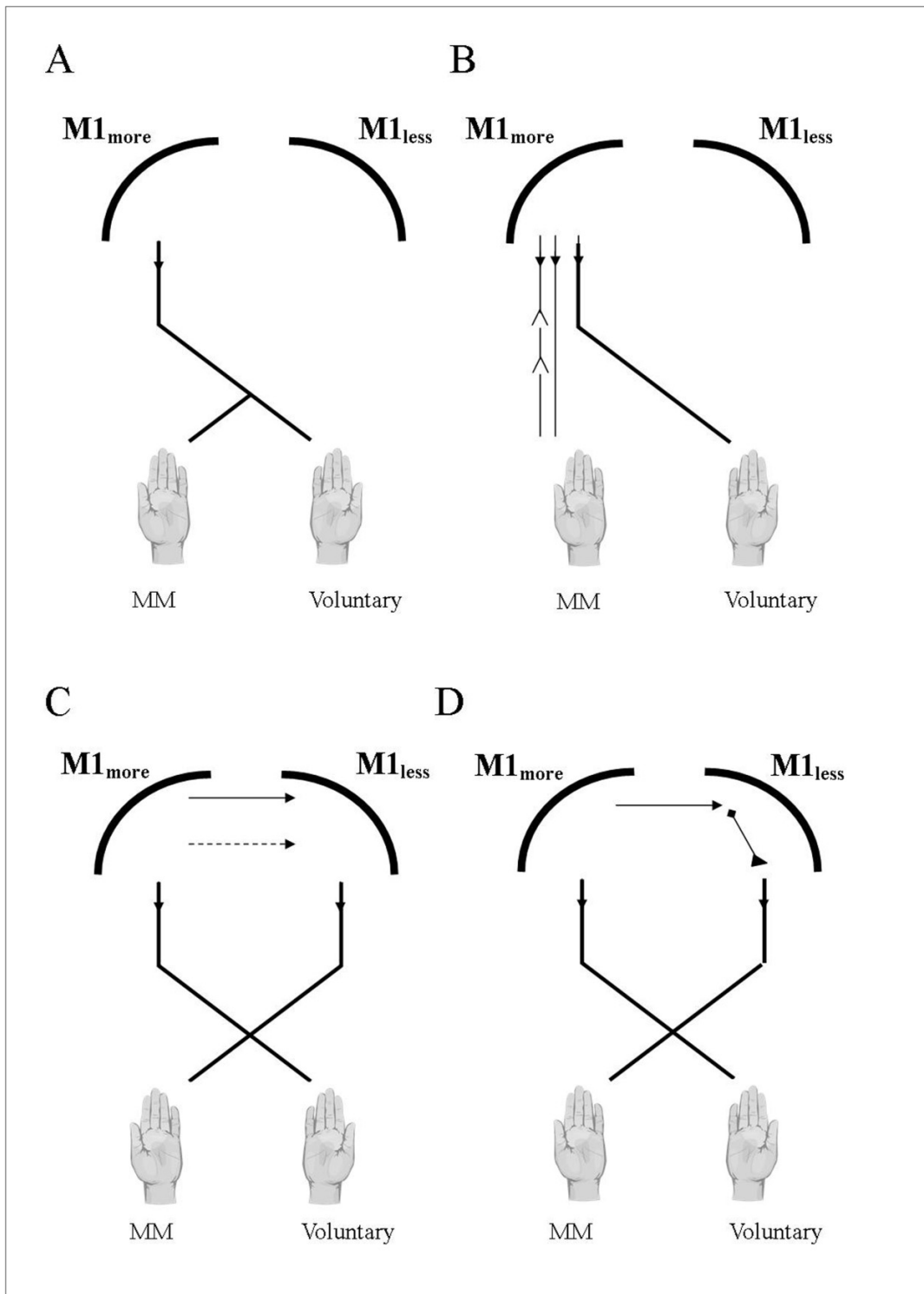


Figure 1. Possible Mechanisms for MM. A. MM caused by a common drive to bilateral homologous motoneuron pools. B. Abnormal uncrossed ipsilateral corticospinal tracts. C. Decreased transcallosal inhibition (dotted line) or increased facilitation (solid line) of the M1 contralateral to the MM hand. D. Altered interhemispheric inhibition of intracortical facilitation in the M1 contralateral to MM. Any combination of these mechanisms may be involved in the generation of MM. M1_{more}= more affected cortex; M1_{less}= less affected cortex (modified from Li et al., 2007.²⁹)

usually not associated with classic PD but may be found in corticobasal degeneration.²⁵

While the vast majority of PD patients with MM acquire the phenomenon in the early phases of their disease, congenital MM may also coexist. Borgheresi et al.²³ described two PD patients with congenital MM whose MM may be clinically distinguished from acquired MM. Firstly, whereas acquired MM in PD are only present on the less-affected side, congenital MM are seen contralateral to the movements of either upper limb. Secondly, both of these patients had bilateral onset of parkinsonian symptoms. Since congenital MM begin well before the onset of PD, the two disorders are probably unrelated, although vulnerability to both may be pathophysiologically shared.

Course and relationship with dopaminergic therapy

MM have been observed in early, asymmetric PD, and have been shown to persist at least 5 years into the progression of the disease.²⁷ In general, MM are typically seen in patients who are less severely affected; PD patients with severe, bilateral motor deficits, tend to exhibit little or no MM.²¹ Vidal et al.²² reported a correlation between occurrence of MM and UPDRS score, which predicted MM in the presence of greater motor impairment. This study, however, was limited in that it examined patients with hemiparkinsonism. The correlation observed could have been due to either an increase in the total UPDRS score, as posited, or an increase in the lateral difference. Both of these relationships would look the same in a population of hemiparkinsonian patients. Espay et al.²¹ examined patients with asymmetric but not unilateral PD. This study found a strong correlation between MM and lateralized, but not total UPDRS score. In PD patients, mirroring appears to be related to the levodopa response. First, MM appear to be more prominent in patients whose response to levodopa is greatest.²⁷ Second, from the “off” to “on” medication state, patients with a large improvement in UPDRS score exhibited greater mirroring, while patients with a small UPDRS improvement exhibited less mirroring. The increase of mirroring in patients with the greatest response to dopaminergic drugs may have been due to the lessening of symptoms such as bradykinesia and rigidity in the less affected arm, facilitating greater mirroring. The lessening of mirroring in patients with a small response to levodopa may be due to the fact that these small motor improvements were typically greater in the more affected hand, which decreased the disease asymmetry. The effect of dopaminergic drugs has also been studied in patients without overt MM, using surface electromyography of right and left abductor pollicis brevis contractions.³⁰ In this study, there was no significant difference in magnitude of EMG-detected mirroring in the “off” compared to the “on” state. Since mirroring was not clinically overt, it is possible that levodopa had correspondingly little effect on MM.

Pathophysiology

In PD patients with MM, electrophysiological evidence strongly supports an abnormal activation of the hemisphere contralateral to MM. Focal TMS of each M1 elicited normal MEP in the contralateral

hand muscles, while failing to produce any response in the ipsilateral hand.^{27,30} This ruled out an unmasking of uncrossed corticospinal tracts as the mechanism for MM in these patients, as had been demonstrated in patients with congenital MM. Accordingly, the cross-correlation analysis of surface EMG signals did not reveal a common motor drive to homologous hand muscles during intended unilateral movements, as would have been expected if MM were due to the synchronous activation of uncrossed and crossed corticospinal neurons originating from the same M1.^{27,30} During both mirror and voluntary movements of one hand, TMS of the contralateral M1 produced a similar, long-lasting pattern of disruption of the movement-related EMG activity, but TMS of the ipsilateral M1 produced much less disruption during both movements.³⁰ This finding was observed with both tonic and phasic muscle activity. Accordingly, during mirror contraction of a hand muscle, focal paired-pulse stimulation of the contralateral M1 revealed a down regulation of the neural mechanisms responsible for short-interval intracortical inhibition (SICI), similar to the physiological SICI suppression observed during voluntary contraction of the same muscle.³⁰ In conclusion, strong and sustained MM in PD are due to unwanted motor output from the M1 ipsilateral to the voluntary movements, through crossed corticospinal pathways and, therefore, represent an abnormal enhancement of physiological mirroring.

The reason why, in PD patients, the ability to focus the motor output in the M1 contralateral to the voluntary movement may be reduced is still a matter of investigation. In healthy individuals, voluntary movement lateralization depends on a partly known, distributed cortical network (for a detailed review, see Cincotta and Ziemann, 2008⁷).¹⁶ Data from lesioned monkeys³¹ and human patients³² suggest that this network probably includes the supplementary motor area and the cingulate gyrus. In healthy humans, neuroimaging findings³³ and TMS data^{34,35,36} suggest that the dorsal premotor cortex is also involved. Although these findings indicate that the neural processes underlying movement lateralization mainly occur upstream of the M1 contralateral to the voluntary task (i.e., in the premotor cortical areas), a number of TMS data in healthy subjects support the existence of a last-stage inhibition from the active M1 to the contralateral M1, via transcallosal pathways.^{37,38,39,40,41,42} Nevertheless, callosal damage alone is usually not associated with MM.¹⁷ In PD patients with MM, it is reasonable to hypothesize that a failure of basal ganglia output to energize the neural network that enables the corticospinal system to execute unilateral movements is responsible for these MM.²⁸ Recent TMS data in 13 PD patients with MM, seven without, and 15 normal controls, suggest that one of the targets of this failure may be transcallosal inhibitory circuits.²² Namely, PD patients with unilateral MM had a decreased ipsilateral silent period in the hand affected by MM, compared to the unaffected hand and to controls (ipsilateral silent period is a TMS measure of inhibition between M1, likely due to transcallosal inhibitory circuits). Moreover, interhemispheric inhibition of the MEP tested by paired-pulse TMS at long interstimulus intervals (20–50 milliseconds) was more pronounced

in PD patients without MM than in PD patients with MM and healthy individuals. Further studies are needed to clarify these intriguing issues.

The case study of a PD patient with congenital MM demonstrated that TMS of either M1 elicits an ipsilateral MEP, which confirms an ipsilateral corticospinal pathway descending from each M1.²³ Interestingly, suprathreshold repetitive TMS of either M1 during intended unilateral repetitive thumb-to-index tapping failed to completely disrupt EMG activity in both voluntary and mirror hands. By contrast, using the same experimental paradigm in PD patients with acquired MM, Cincotta and co-workers³⁰ found a marked disruption of both mirror and voluntary tapping of the target muscle with rTMS of the contralateral M1, whereas the effects of rTMS of the ipsilateral M1 were much less during both tasks. This suggests that, in PD patients with congenital MM, *both* M1 are involved in motor output during voluntary unilateral movement.

Corticobasal syndrome

MM are a common finding in corticobasal syndrome (CBS) and are considered a standard component of the clinical diagnosis.⁴³ Although MM can occur independently in CBS,⁴³ they are frequently reported in conjunction with other involuntary movements such as the alien hand phenomenon, a class of movement disorder in which the patient's affected limb acts independently of the patient's will,^{44,45} and with which MM and synkinetic movements may be confused. The alien hand phenomenon also manifests as intermanual conflict and failure to recognize one's limb as one's own.⁴⁶ In contrast to PD, CBS-associated MM occur predominantly in the *more* affected side, which, interestingly, tends to be the left.⁴⁶ Despite these findings, however, little is known about the relevance of MM as a sign of CBS.

Although no studies have focused on the pathophysiology of MM in CBS, thinning of the corpus callosum and subsequent impairment of transcallosal inhibition documented in these patients could also play a role in MM in CBS.^{43,47,48,49}

Essential tremor

Louis et al.⁵⁰ first reported an association between MM and essential tremor (ET).

In this extensive study of 107 ET cases, 32.7% exhibited MM compared to 23.7% in the control population. ET cases demonstrated MM that were roughly twice as strong as control MM and three times as prevalent in the hands, compared with other body regions. MM occurred in ET patients with and without rest tremor, but were more common and severe in those with rest tremor. Unlike PD, there was no apparent correlation between tremor asymmetry and total MM score, or between tremor asymmetry and lateralized MM score. There was also no correlation between the presence, or absence, of MM and age, gender, tremor severity, or tremor duration. The relatively high frequency of MM in ET patients with resting tremor prompted the authors to question whether these cases may represent early, undiagnosed PD, given that some cases of ET may go on to develop PD.^{51,52} The lack of correlation between MM and tremor asymmetry is, however, atypical of MM in PD and these patients also have other

parkinsonian signs such as bradykinesia. Moreover, even if the cases with rest tremor were excluded, there would still remain a significantly greater prevalence and severity of MM in ET compared to controls.

The pathophysiology of MM in ET remains unexamined. Studies have shown that the cortical networks generating unilateral movement within one hemisphere are disrupted in ET, which could be a possible pathway for these MM.⁵³

Focal hand dystonia

Motor overflow is an intrinsic phenomenon of focal hand dystonia (FHD). As true MM are not a typical feature of FHD, mirror dystonia represents a frequent expression of motor overflow in FHD patients.^{54,55,56,57} This peculiar motor phenomenon is defined as the appearance of dystonic movement or posture in the homologous muscle of the affected (usually dominant) upper limb induced by a specific task performed by the unaffected hand when the contralateral hand is engaged in a specific task.⁵⁴ Often, mirror dystonia presents in the affected hand of patients who attempt to learn to write with their non-dominant hand,⁵⁷ although Merello et al.⁵⁸ described a patient with MM of both hands. The motor overflow of FHD (and in particular mirror dystonia) may be useful in differentiating between dystonic and secondary compensatory movements, which serves to increase accuracy during therapeutic botulinum toxin injections into dystonic forearm muscles.^{59,60}

Pathophysiology

In a study comparing two FHD patients, with and without mirror dystonia (namely mirror writing), functional magnetic resonance imaging (fMRI) revealed bilateral cortical activation in the patient with mirror writing.⁵⁸ The authors hypothesized that these findings may have been due to altered interhemispheric inhibition, which was later confirmed by Beck and colleagues.⁶¹ These investigators corroborated the previous findings of bilateral cortical activation and used TMS to demonstrate decreased interhemispheric inhibition of the dystonic M1 cortex during the premotor phase of movement, which was not seen in FHD patients without mirror dystonia. Other authors, however, recently reported that interhemispheric inhibition at rest was also decreased in a group of FHD patients without mirror dystonia.⁶² Notwithstanding these partly conflicting findings, it appears that interhemispheric transfer may be altered in FHD *per se*,⁶² and direct comparison of FHD patients with and without mirror dystonia supports the view that mirror dystonia may be associated with greater dysfunction of interhemispheric inhibition.⁶¹

Creutzfeldt-Jakob disease

MM are not a well established finding in Creutzfeldt-Jakob disease (CJD) and there have only been a few isolated reports. MacGowen et al.⁶³ described two patients who presented with both the alien hand phenomenon and MM. Both of these symptoms were present in the left side, as is typical of CBS. Unlike CBS, in which these manifestations take an average of one year to develop,⁶³ MM were the first signs seen in these patients. Park et al.⁶⁴ described one CJD

patient with MM in the right (more affected) hand during voluntary left hand movement. The patient also had ipsilateral motor overflow from each arm to the corresponding leg and vice versa. To date, there have been no electrophysiological studies of MM in CJD and the abnormal pathway(s) remains largely unknown.

Huntington's disease

Manifestations of motor overflow such as MM are common findings in Huntington's disease (HD) and positively correlate with overall United Huntington's Disease Rating Scale (UHDRS) motor scores.⁶⁵ A study by Hashimoto et al.⁶⁶ demonstrated greater mirroring in HD (measured as a percentage of voluntary muscle EMG) than in akinetic parkinsonism, spinocerebellar degeneration, or control patients. This study also suggested that MM are more common in conjunction with chorea; however, other studies have shown a weaker correlation between these two phenomena.⁶⁵ Interestingly, these MM seem to decrease with increased voluntary force, which is in contrast to MM of the general population in which MM tend to increase in response to increased effort and attention.^{67,68} There have been no studies to uncover the pathophysiology of MM in HD.

Discussion

MM are common in a variety of movement disorders. Their clinical presentation may vary among them and their presence, along with other symptoms, can serve in the diagnostic process. In PD and CJD, MM appear in the early stages of the disease, whereas in other disorders, stage and severity of disease have no correlation with MM. MM appear in the less affected hand in PD and the more affected hand in CBS and CJD, while mirroring has no relation to symptom asymmetry in ET. Other motor-overflow manifestations such as the alien hand phenomenon in CBS and CJD or "mirror dystonia" in FHD may accompany MM in these disorders. Further clinical studies are needed to understand the relevance of MM in these disorders. Also, in determining the prevalence of MM in any given disorder, a number of investigators have noted the lack of data regarding their prevalence in the general population.^{24,49} A study of MM in a large healthy population would be useful in order to compare their significance in the various disease states in which it has been described.

Clinically, MM may be useful in distinguishing a number of different movement disorders. The presence of MM in the less affected hand helps to differentiate PD from other movement disorders such as ET, in which no such distinction is present, or CBD and CJD in which the more affected hand exhibits MM. Furthermore, CJD may be distinguished from CBD based on the early presence of MM, although more research is needed to corroborate this. While MM in HD remain poorly understood, findings suggest that these MM decrease with more concerted effort, which may be a useful diagnostic clue. While proper MM have not been well described in FHD, related mirror dystonia is helpful in targeting botulinum toxin injections; by activating various muscles in the unaffected hand one can identify, by the resulting dystonic posture, optimal injection targets.

There currently exists a great diversity of research methods for MM, which makes it difficult to compare results from different studies. While the UPDRS and UHDRS may be useful for evaluating MM within PD and HD respectively, the Woods Teuber scale remains the accepted universal standard for evaluating MM across a broad spectrum of disorders. TMS and electric muscle stimulation (EMS) studies may be useful tools to supplement Woods Teuber classification, helping to specify the location and strength of mirror muscle contractions. There have been a wide variety of muscle groups used to measure MM; contraction of hand muscles such as first dorsal interosseous muscles (FDI) is useful to study, since this muscle is active in finger tapping, a typical test for MM. Greater homogeneity of research methods would facilitate better discussion of MM and hopefully lead to a richer understanding of this phenomenon.

Two main mechanisms have been identified for the generation of MM. Congenital MM are driven by abnormal uncrossed corticospinal tracts descending from the M1 ipsilateral to MM (Figure 1B), however, in congenital MM not associated with severe congenital palsy, motor output from the M1 contralateral to MM may coexist. On the other hand, MM in PD and CBS depend on bilateral cortical activation (Figure 1C and 1D), likely due to a deficiency of the neural mechanisms that focus the motor output in the M1 contralateral to the voluntary task. Imaging and electrophysiological studies are needed to determine the pathway for MM in ET, CJD, and HD. Future studies on MM will not only aid in clinical diagnosis of selected movement disorders, but will also contribute to our understanding of the normal physiology of bimanual coordination.

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