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REVIEW

Congenital facial palsy and emotion processing: The case of Moebius syndrome

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According to the Darwinian perspective, facial expressions of emotions evolved to quickly communicate emotional states and would serve adaptive functions that promote social interactions. Embodied cognition theories suggest that we understand others' emotions by reproducing the perceived expression in our own facial musculature (facial mimicry) and the mere observation of a facial expression can evoke the corresponding emotion in the perceivers. Consequently, the inability to form facial expressions would affect the experience of emotional understanding. In this review, we aimed at providing account on the link between the lack of emotion production and the mechanisms of emotion processing. We address this issue by taking into account Moebius syndrome, a rare neurological disorder that primarily affects the muscles controlling facial expressions. Individuals with Moebius syndrome are born with facial paralysis and inability to form facial expressions. This makes them the ideal population to study whether facial mimicry is necessary for emotion understanding. Here, we discuss behavioral ambiguous/mixed results on emotion recognition deficits in Moebius syndrome suggesting the need to investigate further aspects of emotional processing such as the physiological responses associated with the emotional experience during developmental age.

KEYWORDS

autonomic nervous system, congenital facial palsy, embodied simulation theories, emotion understanding, emotional processing, facial expressions, facial mimicry, mirror neuron system, Moebius syndrome, recognition of emotions

1 | INTRODUCTION

Darwin's contribution to our comprehension of the evolutionary roots of emotions is included in his seminal work *The Expression of the Emotions in Man and Animals* published in 1872.[1] Beyond the concept of the universality of emotions and the idea that they are discrete entities, Darwin was particularly interested in the way they are expressed through the face and how they dynamically change in the configuration and intensity. One central idea was that the same principles in which emotions are expressed in humans can be applied to other animals, thus helping our interpretation on their functional meaning. Despite most of Darwin's ideas have been challenged by modern research, nevertheless the foundations of its theory still hold the test of time and have been validated in some notions concerning the evolutionary continuum between animals and humans in the expression of emotions.[2]

A central focus of Darwin research on emotions, so well-documented with photographs and drawings, was the face. The face carries key information on how we express our emotions and the study of the patterns movement activity of the face muscles may be interpreted as signature of a specific emotion and of its communicative value.[3] Subsequent comparative studies in nonhuman primates have adopted such approach to better understand the evolutionary origins of specific facial expressions and their possible function.[4–6]

Recent models on how facial expressions of emotion are controlled have undoubtedly benefitted from research in neuroscience.[7,8] Neuroanatomical dissection of the patterns of facial movements and

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their innervation, together with the knowledge of the neural control under normal and pathological conditions, have provided information not only on the neurobiology of facial expression and its communicative value, but also on how the motor control of emotions is strictly connected with the capacity to perceive and understand emotions. A wealth of literature argues that a potential mechanism that allows humans to recognize[7] and share emotions is automatic mimicry,[9,10] defined as the unconscious or automatic imitation of speech and movements, gestures, and in particular facial expressions. Specifically, the tendency to automatically mimic and synchronize facial movements with those of another person has been proposed to be central in daily interactions, starting from the very early form of communication between the mother and their infants.[11,12]

Here we discuss the role of facial mimicry in emotional processing reviewing results in individuals with congenital facial paralysis. We believe that this population, especially during developmental age, could represent an optimal model to better understand the role of facial mimicry in emotional processing. In the first section, we will describe a form of congenital and not progressive facial paralysis that implies the control loss of movement of the sixth and seventh facial cranial nerves (CNs). Such congenital disease, named Moebius syndrome (MBS),[13] is still very poorly understood from a genetic point of view and from a psychological perspective. In the second section, we will provide an account of the role of sensorimotor processes in emotion recognition. Viewing another person's facial expression has been proposed to activate the same neural processes involved in producing the expression. Specifically, through an action-perception matching mechanism,[14] perceptual processes underlying the visual recognition of a facial expression would activate somatosensory and motor cortical areas overlapping with those that normally underlie the production of the same facial expression, as well as brain regions that control and integrate visceral responses associated to emotions[7,8] such as the insula and the anterior cingulate cortex.[15–17] Through this sensorimotor simulation mechanism, the perceiver can access to the internal emotional state of the person who produced the facial expression, and to its meaning.[7]

In the third section, we will discuss the role of facial mimicry in emotion recognition and describe the possible consequences when facial expressions are blocked. We will review current studies on the explicit recognition of emotions in MBS patients and discuss preliminary results related to modifications of autonomic response during the observation of emotional stimuli in MBS patients and healthy controls, emphasizing the need to investigate not only the explicit recognition of others' emotions but also the physiological responses associated to them. In the last section, we will propose future experimental protocols to fill the gap in our understanding of the cognitive and physiological mechanisms involved in emotional processing.

2 | MOEBIUS SYNDROME: MAIN CLINICAL CHARACTERISTICS AND GENETIC ASPECTS

MBS, originally described in the 1880s by Moebius[18] and von Graefe,[19] is a rare congenital disorder which presents altered development of facial (VII) and abducens (VI) CNs, resulting in "uni- or bilateral, nonprogressive facial weakness and limited abduction of the eye(s)".[20–29] It can also be associated with other CN palsies (affecting XII, X, IX, III, VIII, V, IV and XI CN in order of decreasing frequency),[30–32] orofacial malformations (epicanthic folds, micrognathia), limb defects (such as club feet and missing or underdeveloped fingers or hands), musculoskeletal abnormalities and hypoglossia (weakness or malformation of the tongue).[27,32–36] Functional anomalies of face and mouth implicate lack of facial expression, difficulties in speaking, eating, sucking and swallowing.[32] Some MBS individuals retain residual lower facial muscle activity, possibly because of aberrant innervation from other CNs.[36] A few radiologic and neuroimaging studies also showed brainstem and cerebellum abnormalities in Moebius subjects.[37–39] Cerebellar anomalies could not only contribute to the motor deficits of MBS patients, but also to nonmotor functional deficits such as executive function, linguistic processing and emotional processes, in particular emotional memory consolidation.[40,41]

The prevalence of MBS is estimated to be 1 in 50 000 to 1 in 500 000 live births[42] with equal incidence in both sexes.[30,43] Because of facial and eye movement restriction, rates of autism and other mental disorders in people with MBS were previously overstated in the literature.[44,45] Most patients present normal intelligence, while rare cases of autistic-like behaviors (0%-5%) and mild mental retardation (9%-15%) have been reported.[44,46,47] The syndrome is also referred to as Moebius "sequence," term which defines a cascade of secondary events after an initial insult during the embryonic development,[13,48] as well as a possible genetic etiology[49] (see Box 1).

The main characteristic of this syndrome is the absence of facial expressions: MBS patients cannot smile or frown since birth. Because of their facial paralysis, although they usually have normal intelligence, they are sometimes wrongly perceived as unintelligent or less likely to interact with each other probably because they cannot display emotions as readily as other individuals.[74–77]

Considering how the face predominates our social relations,[1,11,78–84] difficulties in social interactions have been reported in MBS patients, especially during developmental age, probably becoming a risk factor leading to individuals' social and psychological difficulties later in adulthood.[85–87]

For this reason, to enhance speech and oral competence and improve their quality of life, many intervention programs have been proposed, such as respiration control, neuromuscular training, massage, meditation-relaxation,[88,89] as well as psychological and communication strategies interventions.[46,90] In these years it has been developed a series of surgical strategies that overcome one of the most important and psychologically devastating deficits for MBS subjects, namely the lack of facial animation[91] (see Box 2). The surgical procedure consists in restoring the facial muscular function that leads to lack of expression and speech problems.[92,93] In particular, the *smile surgery*, recommended for individuals of at least 6 years old, consists in a micro-neurovascular transfer of a muscle (usually the Gracilis) that is grafted from the leg to the corners of the mouth and innervated by the masseteric nerve.[22,25,33,91–93] Thus, after a rehabilitation period (Figure 1), *smile surgery* can help individuals recovering the ability to voluntary smile, improving also their general competence related to mouth movements.[92,93]

BOX 1

GENETIC ASPECTS OF MOEBIUS SYNDROME

Although MBS etiology is still unknown or unclear, theories of the underlying intrauterine environmental factors and genetic causes have been considered. Nongenetic causes are thought to involve vascular events with interruption of blood supply during the initial development of the embryo, causing damage to the CNs centers and parts of the fetus' developing brain.[26,50,51] During the fourth and fifth week of development, cephalic neural crest cells begin to differentiate, starting from the CN nuclei.[21,52] The proximity between facial nerve fibers and the abducens nucleus at the cerebellopontine angle is a potential trigger of concurrent palsies.[26] During the sixth week of gestation, the blood supply to the nascent hindbrain changes from the basilar to the vertebral artery and specific timing is crucial to guarantee adequate blood supply to the CN nuclei.[26,50] In support of this hypothesis, findings from radiological imaging, including ultrasonography, computed tomography and magnetic resonance imaging in individuals with MBS showed calcifications and hypoplasia of the brainstem.[32,53] However, given that not all MBS patients show signs of CN nuclei hypoplasia,[54] this seems a poor demonstration to endorse the vascular event.

According to available studies, infection, hyperthermia, hypoxia and vasculitis seem to interfere with blood flow.[26] In addition, the vascular disruption could be caused by teratogens acting on the embryo during the first trimester, such as abuse of benzodiazepines[55] and misoprostol (an abortifacient drug),[56,57] thalidomide[58] and alcohol[59] or cocaine[56] exposure during pregnancy. As an example, case reports and reports data showed a strong association between MBS and prenatal use of misoprostol and thalidomide by mothers; drug exposure during the first 2 months of pregnancy could have caused an ischemic event in the embryonic brainstem, resulting in MBS.[58,60,61] It has to be pointed out that the expression of genes involved in the brain can be influenced by gene-environment interactions as well; drugs such as ethanol, thalidomide and misoprostol are able to modulate the expression of many genes involved in mechanisms like proliferation, apoptosis, neuronal differentiation and migration, synaptogenesis and synaptic activity.[62] Fetal exposure to teratogens, for example, has been shown to be associated with an increased incidence of autism.[63] In line with these results, epigenetic mechanisms could have a role in triggering MBS as well.

The genetics underlying MBS remains unclear. Even if most Moebius cases are sporadic, some familial trends have been seen with both autosomal dominant and recessive patterns.[64–68] In particular, the risk of hereditariness is as low as 2% when MBS is linked to musculoskeletal anomalies, but it increases to 25% to 30% with clinical features suggesting a genetic etiology such as isolated facial palsy, deafness, ophthalmoplegia and digital contractures.[69]

Genetic studies have mainly focused on potential chromosomal loci, selecting candidate genes and analyzing the genomes of MBS individuals for mutations in those specific genes. These studies are particularly difficult because of the syndrome's genetic heterogeneity. The most implicated loci include 1p22, 3q21-q22, 10q21.3-q22.1 and 13q12.2-1345. Some of them have been defined as MBS1 at 13q12.2-q13 identified by Slee et al,[70] MBS2 or HCFP1 (hereditary congenital facial paresis 1) at 3q21-q22 as reported by Kremer et al,[71] and MBS3 or HCFP2 (hereditary congenital facial paresis 2) at 10q21.3-q22.1 from a report by Verzijl et al[64] of dominant MBS in a Dutch family. These loci are linked to particular homeobox genes (including HOXA1, HOXB1 and SOX14), necessary for spatial and temporal development of the brain. Mutations in homeobox genes may also influence other genes, therefore determining the varying phenotypes characterizing the syndrome. Further candidate genes, which are crucial for neuronal development and possibly involved with the syndrome are PLEXIN-A1, GATA2, EGR2, BASP1 and TUBB3.[29,72] Interestingly, the gene FLT1/VEGFR1, which is linked to an aberrant vascular growth, is probably implicated in the syndrome, thus sustaining the previously mentioned intrauterine vascular event.[73] Recently, Tomas-Roca et al[49] reported de novo mutations affecting two genes, PLXND1 and REV3L, in six MBS individuals. The neuropathological deficiencies found in MBS individuals correlated with those found in mutant mice models. In this regard, analysis of PLXND1 and REV3L in knock-out mice[49] demonstrated that mutations in these genes were responsible for a defect in the facial branchiomotor neuron migration and craniofacial bone abnormalities/vertebral defects both in knock-out mice and in MBS individuals therefore supporting these genes as causative for a proportion of MBS cases. Summing up, these results are of general interest, because the outcome that PLXND1 and REV3L mutations are responsible for MBS symptoms shows that genetic mechanisms can be considered a significant leading cause of MBS.[49]

However, in order to intervene and improve the social skills of these individuals, it is necessary to understand how the lack of facial expressions impacts emotional processing and socio-communicative capacities. As previously mentioned, emotional facial expressions are a powerful channel of communicating information about one's affective states and, during development to adulthood, we increase our ability to process facial expressions faster and more accurately. Individuals can extract information about emotional meaning within few hundred milliseconds.[80,97] However, emotions are not always expressed with the same intensity, in a prototypical manner, making them sometimes more difficult to distinguish and to categorize. In addition, there are interindividual and cultural differences in the way they are expressed. Nevertheless, since very early in life we are capable effortlessly to recognize emotions from others and to respond appropriately. One of the most typical responses to facial emotional signal is the reproduction of the perceived expressions. These

BOX 2

SMILE SURGERY AND POSTOPERATIVE NEUROREHABILITATIVE TREATMENT FOR BILATERAL CONGENITAL FACIAL PALSY

The paralysis of the VII CN leads to facial paralysis. Patients with congenital unilateral or bilateral facial palsy show a reduced or absent expressivity, they either cannot smile (such as bilateral paralysis) or find it very difficult to smile (unilateral paralysis), grimace or close their eyes. Because of the lack of strength in their lip muscles, they also have articulatory difficulties with chewing, swallowing and speaking. Thus, the deficiency is both functional and esthetic. The surgical intervention aims at reducing the symptoms and restores some movements of the face.[22,92] To reanimate the face, a surgical procedure (*smile surgery*) is performed transplanting a segment of the gracilis muscle (free muscle transfer).[91] The gracilis, a muscle located in the medial area between the pubis and the medial knee area, is considered the best choice for the free muscle transfer procedure, because it is easily accessible and its withdrawal does not determine any functional deficit.[22,92] In patients with congenital facial paralysis such as MBS, the complete bilateral facial paralysis requires a muscle transplantation to both the right and left sides of the face.[22,92] The microneuromuscular transfer surgical technique consists in transplanting the gracilis muscle to the face and innervating it by a donor nerve, usually the masseteric nerve (V CN) that is responsible for chewing movements.[22,92]

About 3 to 6 months after *smile surgery*,[94] the first contraction of the transplanted muscle appears, but the use of the masseteric nerve results in a not completely emotional smile. In fact, the trigeminal nerve is a nerve responsible for sensation in the face and motor functions such as biting and chewing, and it cannot replace volitional movement and emotional animation. As a consequence, patients are very far from achieving a capacity to smile without asymmetries, and they spend many months in exercising. Unfortunately, no consensus guidelines for the rehabilitative protocol are available so far. Nevertheless, a new neurorehabilitation treatment (FIT-SAT, Figure 1) that exploits the properties of the MNS (in particular, the action observation therapy[95]) and the synergies between the hand and the mouth[96] seems to be effective in facilitating the activation of the motor programs involved in the control of the transplanted muscle, permitting the achievement of a spontaneous and naturalistic smile.[94] Although these preliminary data are encouraging, it will be needed to include a greater number of patients to confirm the efficacy of the FIT-SAT treatment. It is clear that MBS is a complex syndrome that requires the synergistic activity of different specialists (speech therapists, surgeons, etc.). The strict cooperation among clinicians would permit to intervene as possible on functional and esthetic symptoms with the aim to improve the quality of life of these patients.

spontaneous facial reactions, called *facial mimicry*, occur very rapidly, and often are nonconscious responses.[80,97] Such phenomenon is widely distributed in several primate species,[98–100] suggesting a common evolutionary origin and shared functions. Facial mimicry is expressed during social play or during mother-infant affective interactions thus playing an important role for regulating social emotional exchanges and for supporting the recognition of others' emotional states. In the following section, we will review the work linking the facial mimicry phenomenon with the processes of sensorimotor simulation as one of the key neural mechanisms, which support the recognition of others' emotions. Based on the few studies available, and more recent investigations, we will consider the hypothesis that if facial mimicry is somehow blocked, as in the case of MBS, the process of emotion recognition could be compromised or impaired.

3 | ROLE OF MOTOR SYSTEM AND SIMULATION MECHANISMS IN EMOTION PROCESSING

> The movements of expression in the face and body, whatever their origin may have been, are in themselves of much importance for our welfare. They serve as the first means of communication between the mother and her infant; she smiles approval, and thus encourages her child on the right path, or frowns disapproval […]. The movements of expression give vividness and energy to our spoken words. They reveal the thoughts and intentions of others more truly than do words. (Darwin, 1872)[1]

Darwin[1] was one of the earliest researchers to scientifically study emotions and to address their origins from an evolutionary perspective. He suggested that emotional facial expressions play a central role in individuals' survival, giving clear information about how to respond in a particular situation. He also observed that the motor component of the expression of emotions affects the subjective experience of it: "The free expression by outward signs of an emotion intensifies it. On the other hand, the repression, as far as this is possible, of all outward signs softens our emotions." In his concluding remarks of the seminal book *The Expression of the Emotions in Man and Animals*[1] he acknowledged a potential theoretical gap between the instinctive origins of the expression of emotions and the capacity to recognize them. In doing so, he had an intuition on how we recognize emotions, which indeed echoes with some current simulation theories. Darwin argued that the experience of an emotion may be key for the recognition of it, and this emerges very early in development: "[…] when a child cries or laughs, he knows in a general manner what he is doing and what he feels; so that a very small exertion of reason would tell him what crying or laughing meant in others." Describing his own child smiling, he further observed: "[…] I was convinced that he understood a smile and received pleasure from seeing one, answering it by another, at much too early an age to have learnt anything by experience." Such unique and anecdotal observations must have been stuck in Darwin's mind to include them in the conclusions of his volume on emotions. It is also

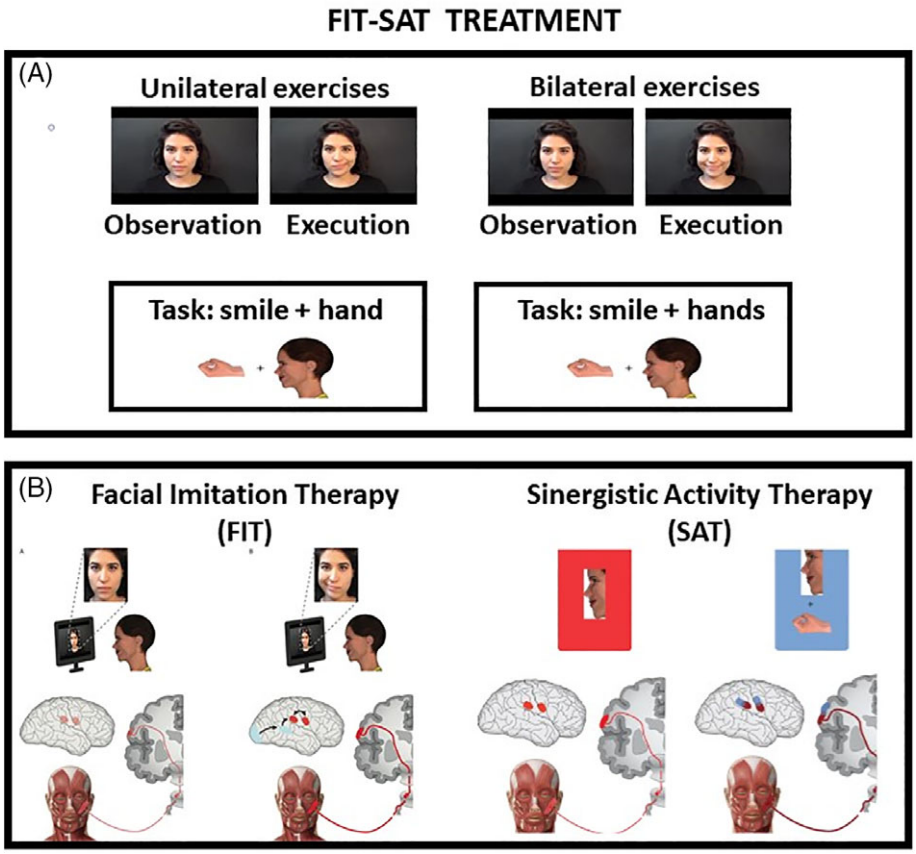

FIGURE 1 (A) FIT-SAT treatment. Each session starts with a video-clip in which an actor remains still for 3 seconds and vocal instruction are given to the patients. Then the actor performs a smile either unilaterally (left or right side) or bilaterally. The patients are instructed to observe the video-clip and simultaneously imitate the actor's smile. While they are smiling, the patients simultaneously clench their fist. Patients start the daily treatment with three sets of five repetitions. Progressively, further repetitions are gradually included until the patient is able to perform at least 10 successive repetitions and to maintain the smile posture for at least 3 seconds. (B) FIT combined action observation with the direct effects of action execution suggesting that the activation of motor areas by action observation becomes reinforced by the concomitant active execution of the observed actions[94]; SAT refers to the synergistic activity of hand closing while smiling should facilitate the activation of the cortical areas connected to the mouth. The hand contraction facilitates the recruitment of the Gracilis muscle as consequence of the activity of mouth motor neurons in motor cortical areas[94]

notable in these observations that he was aware of the infant's capacity of mimicking facial gestures without much experience and of the implications this phenomenon implied for the emotion recognition process.

Nowadays, we have accumulated evidence that the mimicking of facial expressions is a universal common feature in our daily social interactions and is shared among other primate species.[98,100] However, the issue that we are addressing here is: which mechanism can trigger its expression and how much the properties of the motor system, involved during such sensory-motor transformation, are contributing to other cognitive processes such as emotion recognition.

According to the reverse simulation model, individuals recognize facial expressions by mimicking the observed expressions.[8] Facial muscle activity would provide proprioceptive information that generate the corresponding emotional experience within the observer, permitting the recognition of others' internal states. Evidence in support to the reverse simulation model came from a number of studies that used electromyography (EMG) to measure facial muscle activity during facial expressions observation.[80–82,101] When viewing emotional expressions, people tend to react with congruent facial expressions and activate the corresponding facial muscles (ie, we smile to a smile[101]). This phenomenon, called "*facial mimicry*," describes the automatic[80] and unintentional imitation of emotional expressions in human faces. For example, it is possible to observe an enhanced EMG activity of the *zygomaticus major muscle* (the muscle responsible for smiling) when a person sees a happy expression and an increase in *corrugator supercilii muscle* activity (the muscle involved in frowning) in response to an angry face. Such facial mimicry reactions occur spontaneously and rapidly (already after 300-400 ms[80,97]). Such phenomenon has also been described in nonhuman primates within the context of friendly and playful interactions.[102] When individuals observe the facial expression of another person, they would mimic that facial expression (through a subthreshold facial muscles activation) and this initial process would be at the basis of emotion recognition.[80,103] Consequently, reverse simulation model sustains a causal role for facial mimicry in emotion recognition and this assumption is grounded in facial feedback theory.

The reverse simulation model is not the only model that provides an account to explain how our own emotions experience is involved in reading and inferring somebody else's emotions. On the basis of the

existent literature, at least four models of simulation mechanisms can be taken into account for recognition of facial expressions.[8] All simulation models of emotion recognition propose that at least part of the mechanism by which we recognize others' emotional states relies on internally simulating the same emotional state in ourselves, emphasizing the utilization of body representations in both perception and imitation.[104] Nevertheless, the role that these models attributed to facial mimicry is not always considered to be critical.[8] If reverse simulation model emphasizes the centrality of facial mimicry, the generate-and-test model postulates that when observers see an emotional face (such as a happy face), they would infer about its corresponding emotion (happiness). Specifically, people unconsciously express the inferred emotion by micromovements, invisible to the eye, and compare their visual representation with the feedback from their own faces.[8]

A further approach, the reverse simulation "as if" loop[105] assumes that, after observers have seen an emotional face, they mimic it, which in turn leads to emotion recognition (as if the observer was experiencing that emotion). In other terms, after observing others' facial expressions people directly activate their somatosensory representations, which determine the activity of the corresponding emotional states. Crucial to this model is the fact that observers can directly produce the emotional state that corresponds to the facial expression they observe bypassing the facial musculature. Finally, the unmediated resonance model suggests that the mere observation of a facial expression directly triggers a subthreshold activation of the same neural substrate associated with the observed emotion.[8] This view is grounded on an action-perception mechanism named the "mirror neuron system" (MNS),[84,106,107] supporting for the role of specific neural structures in both recognition and emotional experience. Mirror neurons (MNs) are neurons which were first described in the monkey and discharge both when the monkey performs specific hand actions and when it observes another individual performing similar actions.[108] MNs were firstly discovered during single cell recordings of the premotor cortex (F5) in macaques[108–110] and subsequently in the inferior parietal lobule.[111] Using different methodologies (ie, Transcranial Magnetic Stimulation; Functional Magnetic Resonance Imaging and Positron Emission Tomography), an homologous mechanism has been found in humans.[14,112] It has been proposed that this mechanism may support several functions such as action recognition,[14,113,114] imitation,[115,116] language[117–119] and the development of social interactions, including empathy and facial emotion processing.[120–124]

The discovery of MNs responding to facial expressions[120] and the presence of a similar mechanism for emotions in humans have prompted the idea that the MNS contributes to the perception and decoding of emotions. In particular, MNs have been argued to support simulation theories of action understanding and mind reading,[125,126] a theoretical position that has been defined as the "direct-matching hypothesis" or "embodied simulation" (an action is understood when its observation causes the motor system of the observer to "resonate"[115]). Specifically, Gallese et al[126] proposed that emotional understanding is driven by a mirror matching mechanism which allows a direct first person experience of an observed emotion mediated by motor and visceromotor activations. Consequently, simulation would occur in a wider network than the one classically associated to the MNS. Notably, neuroimaging studies in humans have shown that the observation and performance of facial expressions of emotions activate not only motor regions, typically activated during the observation of hand actions, but also regions of the limbic system, such as the anterior cingulate cortex, the amygdala and the anterior insula.[15,16,127] Thus, in addition to the classic mirror circuits, emotional brain regions also seem to be vicariously activated while participants perceive the emotional states of others.[128] Together, these findings provide a new picture on how MNs operate within a larger network (now called "Extended Mirror Neuron Network"),[128,129] with clear implications on the multiple functions to which they might contribute. This is consistent with recent neuroanatomical meta-analyses in the monkey in which the authors reported connections between the mouth region of the ventral premotor cortex (F5) and brain regions involved in emotion processing, such as the basolateral amygdala, the anterior cingulate cortex and the anterior insula.[128] These functional connections between the motor/premotor regions and limbic system would be considered a core neural system for emotion processing which, through a sensorimotor matching mechanism, provides to the observer a direct understanding of others' emotional experience.

The amygdala is known to play an important role in the response to facial expressions that convey fear,[130] although its involvement in emotion processing is broader and not specific for negative emotions only.[131] Interestingly, more recent studies in the monkey showed that the amygdala can process complex stimuli, especially during social interactions related to both positive and negative experiences.[132] Several studies also showed, for example, that the central nucleus of the amygdala likely represents the interface between the motor brain regions controlling specific emotional responses and autonomic/endocrine responses.[133–135]

Vicarious insula activity has been evidenced during both experience and observation of disgust.[127] This demonstrates that similar networks of brain areas are activated by the perception of facial expressions depicting emotions and the overt expression of the same emotions.[15,127] Considering the rich connections of insula with parietal, premotor and frontal areas involved in the organization of arm and face movements in the monkey,[128,136–138] some authors suggest that this sector of the insula could be part of the Extended Mirror Neuron Network.[128,139] Neurophysiological and electrical stimulation studies in the monkey further support the notion of the insula involvement in emotion processing, because this area receives not only nociceptive and other somatosensory inputs but also information from the main subcortical nodes of the emotional network.[140,141] Interestingly, electrical stimulation of insula[142] elicits disgusted facial expressions and affiliative gestures characterized by specific facial motor and vegetative responses, thus highlighting the functional role of this regions of the brain in coordinating motor and autonomic responses in relation to emotional stimuli.

Neuroimaging studies have also shown a shared neural activation for observing and experiencing pain that includes the bilateral anterior insula, dorsal anterior cingulate, and sensorimotor cortices.[143] These findings support the existence of shared neural circuits between self and other, and that is probably central for the generation of empathic responses based on affective sharing.[144,145]

From a functional and theoretical perspective, which are the implications of these findings on our comprehension of how we decode emotions in others? People can identify what type of emotion an individual is experiencing making use of sensorimotor simulation, in which they re-enact in themselves the same motor programs of the perceived emotions (ie, facial expressions).[8,83,84,146,147] Through an embodied simulation mechanism, individuals implicitly and automatically (ie, not mediated by inferential or metalizing processes) can access to the meaning of others' emotions in terms of somatomotor experience and of the bodily changes (eg, heart rate activity, pupil dilation and other visceral responses) typically associated to a specific emotion. Given the complexity that such simulation process entails, it is not surprising that the neural networks involved in perceiving others' facial expressions would be distributed across several cortical and subcortical networks.[128,148]

4 | FACIAL MIMICRY AND THE DECODING OF OTHERS' EMOTIONS

The controversial role of facial mimicry in emotional processing can be better evaluated by studying what happens when the muscles of the face are experimentally blocked or impaired. If facial mimicry plays a causal role in understanding other people's emotions, blocking or reducing facial movements should make emotion recognition more difficult, for example, by reducing the accuracy of the detection of facial expressions.[149,150]

Clinical evidence found a lower face recognition performance in Parkinson's disease patients than in matched healthy controls.[151,152] However, it should be noted that neurological diseases presenting facial amimia (such as Parkinsonism or Huntington disease) could present other symptoms such as impaired movement initiation, rigidity, tremors, postural instability and, in particular, reduced expressivity not only in the face but also in the body and voice.[151] Furthermore, comorbid disorders such as depression may have a confounding effect on the decoding of facial affect.[151] Consequently, these clinical populations do not allow to clarify the effect of the lack of facial mimicry on emotional processing.

Other studies have attempted to artificially inhibit participants' facial movements. They found a reduced ability to recognize emotions[103,149] supporting the hypothesis that being able to freely express facial mimicry facilitates the emotion recognition process.[153,154] Notably, in Oberman et al's study,[149] the authors compared recognition rates for different facial expressions (happiness, disgust, fear and sadness) in a condition where participants' facial mimicry was prevented. Participants were requested to hold a pen between the lips, thus forcing a specific mouth configuration and strongly limiting other facial movements. This experimental condition created a constant muscular activity, which interfered with facial mimicry. Results showed a reduced recognition of disgust and happiness probably caused from hindering the observer's facial mimicry, compared to a condition where no facial movement manipulation was performed.

In this perspective, the recognition of emotional facial expressions would be the result of the activation of the facial musculature and the blocking of the facial feedback to neural systems would determine impairment in emotion recognition.

However, some issues still remain controversial in the scientific debate. First, some theoretical positions assign to the blocking of facial mimicry only an interfering role.[7] During the observation of a facial expression, the block of the mimicry would represent an incongruent feedback with the efference copies reaching somatosensory areas during the internal simulation of the observed facial expression.[7] Consequently, an absence of facial mimicry may not necessarily imply the lack of sensorimotor simulation processes. Second, studies measuring the electromyographic activity of the *zygomaticus major* and *supercilior corrugator* muscles can focus only on a restricted number of emotions (happiness, anger and sadness, for a review see Reference [155]). These muscles are not emotion-specific because they are also activated during the expressions of other emotions, for example, the *supercilior corrugator* muscle during surprise or, in general, in negative valence emotions.[156] Third, the facial mimicry could be an effect of the ongoing motor simulation (crossing the threshold and producing muscle activity) rather than a process that is necessary to understand the facial expressions of others.[7]

The study on individuals with peripheral facial palsy probably represents an interesting and more appropriate approach to assess to what extent the lack of facial mimicry interferes with the emotion processing. In particular, MBS is the most interesting form of facial palsy because it is a neurological condition present since birth and it mainly affects people of normal intelligence and cognitive development.[20–29,94]

Unfortunately, only few studies on MBS individuals' emotions recognition ability are currently present in the literature and their results are ambiguous and not conclusive (Table 1).

Giannini et al's study,[157] for example, examined facial expressions processing in a single MBS patient, a 36-year-old woman. The participant was presented with a series of gambling task video-clips and she had to interpret the facial expressions of slot machine players in relation to prizes. The authors found the inability of the patient to perform the task. The authors compared the individuals' results with approximately 300 control participants. The authors suggested that the deficit in emotion recognition was related to MBS participant's inability to process cues.

Calder et al[158] provided evidence that three adult people with bilateral MBS (mean age: 28.7 years) were considerably better at recognizing facial expressions than the person tested by Giannini et al.[157] They were able to recognize basic facial expressions, despite some difficulties in a more complex task. In particular, they showed a relatively mild deficit affecting the recognition of morphed facial expressions.

Bogart and Matsumoto[159] carried out an online assessment of facial expression recognition in 37 individuals with MBS. The authors used a facial expression recognition task selecting a set of 42 validated photographs representing seven emotions (anger, contempt, disgust, fear, happiness, sadness and surprise). Participants were asked to identify each stimulus by selecting the correct response from a list of possible response choices. Results showed that MBS individuals' accuracy did not differ from the performance of the control group. Their findings suggested that facial mimicry and in general sensorimotor simulation are not necessary for facial expression recognition.

TABLE 1 Previous studies on emotion recognition in MBS

Study	Sample (MBS) participants and control group (CG)	MBS and CG mean age and SD	MBS individuals' sampling/assessment	Stimuli	Task	Emotion recognition deficits
Giannini et al (1984)[157]	MBS: 1; CG: Normative data taken from literature covering about 300 subjects which performed the same task	MBS: 36 years	Short clinical description including social difficulties. Report of IQ assessment. Absence of coordination and sensory deficits.	Video-clips	To interpret the right facial expressions of slot machine players in relation to prizes	Yes
Calder et al (2000)[158a]	MBS: 3; CG: Exp. 1: 40, Exp. 2: 40	MBS: 28.7 years ±6.6; CG: Exp. 1: 21-59 years, Exp. 2: 20-59 years	Absence of intellectual impairment. Assessment of clinical features	Exp. 1: Static basic facial expressions	Exp. 1: To label basic facial expressions by choosing the answer among happiness, sadness, anger, fear, disgust and surprise	No
				Exp. 2: Ambiguous morphed facial expressions	Exp. 2: To choose the label that best described the ambiguous (morphed) facial expression displayed	Mild deficits
Bogart and Matsumoto (2010)[159]	MBS: 37; CG: 23 females and 14 male. Selected from a larger dataset of 249 individuals	MBS: 37.53 years ±13.84; CG: 35.19 years ±12.62	USA-based Moebius syndrome foundation (MSF) newsletter and MSF website. 31 participants recruited based on self-report diagnosis. No formal diagnosis on six patients. No report on IQ assessment	Seven static facial expressions	To identify facial expressions by observing as long as necessary the stimuli presented on a screen	No
Bate et al (2013)[189a]	MBS: 6; CG: Each MBS participant's performance was compared to that of one of three age-, gender- and IQ-matched CG: First: 8 (4 males, 4 females) Second: 8 males Third: 8 males	MBS: 42.8 years ±11 First: 48.5 years ±4.8 Second: 56.3 years ±8.3 Third: 21.4 years ±3.49	Clinical diagnosis of MBS; brief description of the clinical features; estimated IQ	Exp. 1a: Static basic facial expressions	Exp. 1a: To observe static basic facial expressions (5 seconds per face) and identify them (no time limit to make the response)	Exp. 1 (a, b, c): Five of six MBS participants, YES or mild deficit
				Exp. 1b: Morphed ambiguous facial expressions	Exp. 1b: To observe ambiguous facial expressions (5 seconds per face) and identify them (no time limit to make the response)	
				Exp. 1c: Photograph of the eye region of the face	Exp. 1c: To decide which adjective best describes the emotional state of the model already observed	
				Exp. 2: Facial expressions imagery	Exp. 2: To imagine a face depicting emotional expressions and answer eight yes/no questions about the physical characteristics of each expression	One of six, Yes
Nicolini et al (2018)[182]	MBS: 9 children (5 males); CG: 15 children (9 males)	MBS: 5.7 years ±1.78); CG: 6.6 year ±1.79	Clinical diagnosis of MBS; brief description of the clinical features; estimated IQ	Emotional cartoon video stimuli representing three main emotions, namely happiness, sadness, fear. In total: 6 different video-clips (2 happy, 2 sad, 2 scaring situations clips)	Test of emotion comprehension. Autonomic activity was monitored by means of functional infrared thermal imaging technique	Yes MBS showed weaker temperature changes compared to controls while watching emotional stimuli, suggesting an impaired autonomic activity

[a] Of these studies here we reported only the stimuli, procedure and main results concerning the emotion recognition tasks.

The studies discussed so far on explicit facial expression recognition in MBS are clearly not conclusive; nevertheless, they offer the opportunity to critically evaluate the discrepancies in their results. For example, MBS participants were all adults who never experienced or mimicked others' facial expressions for their entire lives. However, it is likely that they have developed alternative cognitive strategies for emotion recognition. The simulation mechanism is not the only one that can be used for facial expressions recognition. Individuals often can do use of facial available information to interpret others' emotional states. For example, for recognizing an emotional facial expression an observer could analyze specific face configurations (eyebrow, retractions of the lips corners of the mouth, etc.) and match these facial configurations with prior knowledge.[160] This cognitive strategy could be particularly effective when the display is represented by a prototypical emotion.

From a neuroconstructivist approach,[161] MBS patients' physical constraints (ie, the block of facial muscles) may lead them to adapt their strategies to detect others' emotions by integrating different elements related to both bodily and contextual aspects. Thus, they may associate a specific facial configuration (such as a face expressing disgust) to its cognitive and social meaning (an unpleasant state). The guiding principle behind these considerations is context dependence.[161] In fact, emotional facial expressions are social cues that inform us about others' intentions to approach or avoid us. For example, the smile is a signal of approaching intentions whereas the frown is a signal of negative intentions.

Moreover, although facial mimicry plays an important role in facial expressions recognition, people may also use other expressive channels to communicate emotions such as gestures, posture, proximity[162,163] or the voice (eg, prosody, language)[164] and these channels may further support the process of emotion understanding and social interactions.[165–167]

Over the years, these individuals may likely have compensated for their facial paralysis by learning, for example, which contextual bodily cues are used in association with specific face configurations. Interestingly, a recent study[168] showed that very early in development, infants are capable to discriminate emotions from body postures. Thus, under more ecological situations the possibility to infer others' emotions could occur even when the processing of facial expressions is relatively compromised.

Important differences in the developmental pattern of the recognition of emotions in childhood have been documented showing how the ability to recognize emotions from facial expressions increases with age.[169–172] Thus, facial expressions of happiness, anger and sadness are generally recognized at an earlier age than those of fear, surprise and disgust.[173] With respect to these considerations, it would be very informative to compare the recognition of emotions between MBS children and adults. Given the amount of literature on emotions development in childhood, it would not be surprising to find MBS children's impaired performance in the recognition of emotions in comparison to an age-matched control group.

Another important issue to be concerned is that previous studies on MBS patients focused only on explicit recognition of emotions. An emotion can be defined as a subjectively experienced affect, which can be accompanied by cognitive processes, behavioral expressions (eg, mimic expression) and physiological changes. These latter can be directly measured during the ongoing emotional processing, whereas the cognitive responses (such as the labeling of an emotion) can only be explored indirectly by questionnaires or questions, which are typically administered at the end of task when the decoding of the emotion had already occurred. For example, in Bogart and Matsumoto's study[159] the authors used static images that were presented without a time limit, possibly facilitating the association between a facial expression and the corresponding verbal labeling. In such a case, any interference in the simulation process, such as a less intense physiological response, could be masked. For these reasons, it would be highly informative to investigate the concurrent physiological responses during the presentation of emotional stimuli.

Among the physiological parameters, the autonomic nervous system (ANS) represents the principal regulatory route of internal bodily functions and its involvement in emotion processing has been demonstrated in a large body of researches.[174] It is possible that the congenital absence of facial mimicry that implies the inability to simulate the facial expressions of others has determined alterations in the visceral responses associated with emotions. The link between motor simulation and ANS reactivity is supported by several neuroimaging studies demonstrating motor pathways activation[15] and brain structures (eg, amygdala, insula)[127,175,176] regarded as part of the extended MNS[128,129] both during execution and observation of emotional facial expressions. Thus, it would be interesting to explore whether people with MBS show reduced autonomic responses such as skin conductance response, finger temperature and heart rate,[174] pupil diameter[177–179] or hormonal levels.[180,181] We recently addressed these issues by investigating the autonomic response to emotional stimuli in MBS children through functional Infrared Thermal Imaging (fITI).[182] During the experiment, children were presented with a series of cartoon video-clips with different emotional contents (happiness, sadness, fear) and their faces were video-recorded with both a digital video camera and a thermal camera. Nasal facial temperature assessed through thermal imaging has been shown to reflect the autonomic response of an individual to the emotional stimuli.[183–185] These findings highlighted a significant weaker thermal response in MBS children compared with age-matched controls and a parallel difficulty to recognize emotions (ie, we used an adapted version of Test of Emotion Comprehension[186]). Although these results are still preliminary, nevertheless they show some impairment of MBS individuals in processing emotions and also highlight the necessity to further investigate the physiological responses associated to emotion processing. For example, without the benefit of a fast, spontaneous mechanism, such as facial mimicry, the identification of a facial expression could be the result of a matching between the visual perception of the changes in facial configuration and the memorized characteristics, which have been associated to specific emotional expressions through learning (ie, in the case of smiling, differences can be searched in the contraction of the muscle around the eyes or the retractions of the lips with an exposure of the teeth). This could lead MBS children to look for the presence of these specific characteristics when performing emotional perception tasks making them less accurate in labeling emotions.

5 | CONCLUDING REMARKS AND FUTURE PERSPECTIVES

The ability to detect and recognize facial expressions may confer adaptive advantages so that a critical social signal can be decoded more efficiently and rapidly in order to prepare an adaptive response. Studies on individuals with MBS, who are impaired in expressing emotions through the face since birth, reported that their inability to form facial expressions can affect their social interactions,[85,86,187] and therefore their quality of life.

From the perspective of embodied simulation theories, the simulation of other people's facial configuration would trigger matched affective states that permit emotion recognition.[188] The motor system is therefore fundamental to operate such simulation and to translate the perception of an emotion into the corresponding motor representation. In support to this model, we reviewed several EMG experiments showing that any interference with the simulation process, such as blocking facial muscles, could affect others' emotions recognition.[149,150] Given such theoretical perspective, in the current review we addressed the following questions: what happens when individuals have motor deficits in the use of facial muscles, which prevent them from mimicking the facial expressions of others? Do these deficits impact the process of the recognition of others' emotions? How do MBS individuals process emotions? The few studies on MBS patients were based on specific assessments where they had to match a label to a facial expression, and the findings have been so far ambiguous. Some authors did not find significant differences in emotions recognition tasks when comparing individuals with MBS and controls.[159] Other studies have highlighted some difficulties in facial expression recognition.[158,189] In general, emotions recognition deficits, when present, are not dramatic and do not prevent individuals to conduct, as adults, a rich affective life. Indeed, during the developmental period, the difficulties in social interactions may impact the quality of social life in MBS children with experiences of social rejection, feelings of anger, externalizing problems and reduced social networks.[187] Our comprehension of the early social problems of MBS children is far from being understood. Early difficulties might emerge as difficulties in emotional regulation, emotional recognition, or as the consequence of being more exposed to bullying and active rejections from peers, that ultimately affect the frequency and quality of social interactions.[87]

Here, we analyzed the aspects of emotion processing in MBS, and pointed out some limitations of previous studies; for example, the evaluation of emotional skills focused only on verbal labeling of emotional expressions. Moreover, MBS adult participants were allowed to examine the emotional stimuli as long as necessary before providing a response. These experimental biases may not reflect the demands and processes involved while recognizing expressions in natural settings. In a recent study by Nicolini et al,[182] authors presented to children aged 5 years, dynamic emotional stimuli and measured the physiological responses associated to them. In particular, they used fITI that allows measuring the autonomic responses normally associated to emotional stimuli[190] without interfering with the natural emotional processing. Results showed that during the observation of emotional stimuli, children with MBS presented a lower facial skin temperature variation (related to emotional changes[191]) than controls. These results are very interesting especially because this study is unique in addressing the development of emotion processing in children with MBS. Given that, in typically developing individuals, the ability to recognize emotions continues to develop since birth till adulthood,[192] we highlighted the necessity to investigate more in deep the autonomic reactions of MBS individuals to emotional stimuli at various developmental stages.

To further understand the specific deficits in emotion processing in MBS patients, we recommend, in future studies, to implement protocols by using more ecological emotional stimuli (such as dynamic morphed facial expressions). For example, morphing technique creates stimuli in which the face changes from neutral to a peak expression with different degrees of intermediate stages.[148,193] The processing of morphed facial expressions may point out the contribution of temporal information that could be impaired in MBS individuals, who cannot benefit of peripheral facial feedback to detect facial expressions.

Finally, a crucial aspect concerns the effects of *smile surgery* (see Box 2) on individuals' emotional processing. After *smile surgery*, facial mimicry of MBS patients is restored (although limited to the smile) so that they can implement a new motor smile circuit. Investigating emotional recognition before and after the *smile surgery* will highlight the importance of facial mimicry in understanding other people's emotions. In particular, it will be of great importance to explore with neurophysiological and neuroimaging techniques the cascade of events involved in emotional processing that are the result of the restoration of smile cortical circuitry following to the *smile surgery*.

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