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1 **Sensory-motor integration in focal dystonia**

2

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17

18 **Keywords:** focal dystonia; sensory-motor integration; proprioception; transcranial magnetic  
19 stimulation

20

21 **Abbreviations:**

22 CNS= central nervous system; fMRI = functional magnetic resonance imaging; LAI = long-latency  
23 afferent inhibition; M1 = primary motor cortex; MEP = motor evoked potential; PET = positron  
24 emission tomography; PMd = dorsal premotor cortex; PMv = ventral premotor cortex; PPC =  
25 posterior parietal cortex; ppTMS = paired pulse transcranial magnetic stimulation; rCBF = regional  
26 cerebral blood flow; rTMS = repetitive transcranial magnetic stimulation; SAI = short-latency

27 afferent inhibition; SI= primary somatosensory cortex; SII= secondary somatosensory cortex; SDT  
28 = spatial discrimination threshold; SMA = supplementary motor area; TDT = temporal  
29 discrimination threshold; TMS = transcranial magnetic stimulation; TVR = tonic vibration reflex;  
30 VBM = voxel-based morphometry.  
31

32 **Abstract**

33 Traditional definitions of focal dystonia point to its motor component, mainly affecting  
34 planning and execution of voluntary movements. However, focal dystonia is tightly linked also to  
35 sensory dysfunction. Accurate motor control requires an optimal processing of afferent inputs from  
36 different sensory systems, in particular visual and somatosensory (e.g., touch and proprioception).  
37 Several experimental studies indicate that sensory-motor integration –the process through which  
38 sensory information is used to plan, execute, and monitor movements– is impaired in focal  
39 dystonia. The neural degenerations associated with these alterations affect not only the basal  
40 ganglia-thalamic-frontal cortex loop, but also the parietal cortex and cerebellum. The present review  
41 outlines the experimental studies describing impaired sensory-motor integration in focal dystonia,  
42 establishes their relationship with changes in specific neural mechanisms, and provides new insight  
43 towards the implementation of novel intervention protocols. Based on the reviewed state-of-the-art  
44 evidence, the theoretical framework summarized in the present article will not only result in a better  
45 understanding of the pathophysiology of dystonia, but it will also lead to the development of new  
46 rehabilitation strategies.

47

## 48 **1. Introduction**

49 Dystonia is a syndrome characterized by prolonged muscle contractions causing involuntary  
50 repetitive twisting movements and abnormal postures. In focal dystonia, the dystonic pattern can  
51 involve single body parts in isolation and may occur at rest or during the performance of intended  
52 movements (Fahn, Bressman, & Marsden, 1998). Cervical and hand dystonia are the most common  
53 forms of late-onset primary focal dystonia (Jankovic, 2009), but little is known about their  
54 etiopathogenesis and treatment. Historically, dystonia has been considered a disorder of the basal  
55 ganglia, mainly affecting planning and execution of voluntary movements. This notion comes from  
56 the observation that most lesions responsible for secondary dystonia involve the basal ganglia  
57 (Bhatia & Marsden, 1994). However, recent research highlights that dystonia is linked to the  
58 dysfunction of a complex neural network comprising basal ganglia-thalamic-frontal regions, as well  
59 as the somatosensory cortex and cerebellum. Indeed, patients with dystonia display not only motor  
60 symptoms, but also a number of disturbances in the sensory domain (reviewed in: Avanzino &  
61 Fiorio, 2014; Konczak & Abbruzzese, 2013; Perruchoud, Murray, Lefebvre, & Ionta, 2014; Tinazzi,  
62 Fiorio, Fiaschi, Rothwell, & Bhatia, 2009) and in cognitive processing of movements, such as  
63 movement simulation and prediction (Avanzino, et al., 2013; Fiorio, Tinazzi, & Aglioti, 2006;  
64 Perruchoud, et al., 2014).

65 In this review, starting from the neurophysiological and the neuroanatomical aspects of  
66 sensory-motor integration processes, we will provide robust evidence consistent with the hypothesis  
67 that dystonia is a sensory and/or a sensory-motor rather than a motor disorder. To this aim first we  
68 will start by summarizing the available behavioral data on abnormalities in sensory functions,  
69 cognitive representation of movements, and sensory-motor integration in focal dystonia. Then, we  
70 will review the large amount of experimental evidence on the neural correlates of these aberrant  
71 functions. Furthermore, we will discuss novel therapeutic approaches aiming at promoting the  
72 reorganization of sensory-motor regions inspired by the reported findings. Finally, on the basis of  
73 the available data, we will strongly support the “network” hypothesis at the basis of the

74 pathophysiology of dystonia. In addition, some limitations to this hypothesis will be discussed, like  
75 the inability, so far, to establish which specific neural structure is primarily altered and which  
76 instead is altered for compensatory and not pathophysiological reasons.

77

## 78 **2. Sensory-motor integration: neurophysiological and neuroanatomical aspects**

79 Optimal movement execution requires accurate processing of sensory information from the  
80 environment and from the body. Different sensory systems contribute to motor control by encoding  
81 both such external and internal sources of information. For example, one of the most obvious  
82 interaction between senses and movements is visuo-motor integration, in which visual information  
83 about objects in the external world is converted from extrinsic/allocentric coordinates into  
84 intrinsic/egocentric coordinates (Pouget & Sejnowski, 1997). This transformation underlies the  
85 planning of goal-directed actions (Rizzolatti, Fogassi, & Gallese, 1997; Wolpert, Ghahramani, &  
86 Jordan, 1995; Wolpert, Goodbody, & Husain, 1998). Also the somatosensory systems, and in  
87 particular touch and proprioception, help movement execution. The interaction between the tactile  
88 and motor systems is revealed by the fact that the lack of afferent information (because of  
89 deafferentation or local anesthesia) strongly and selectively impairs motor control (Taub, 1976).  
90 Hence, even if the motor pathway is preserved, the absence of tactile information from the skin  
91 receptors undermines movement execution. In a similar vein, proprioception –the perception of the  
92 position and movements of our limbs and trunk– is strictly linked to motor control. Specialized  
93 receptors on the joints and muscle spindles signal the size and speed of muscle length changes  
94 (Goodwin, McCloskey, & Matthews, 1972; Matthews, 1972) and contribute to movement  
95 perception and processing (review in Proske & Gandevia, 2012). Yet, in 1996 Prochazka elegantly  
96 characterized the dependence of motor control mechanisms on sensory signals stating “*you can only*  
97 *control what you sense*” (Prochazka, 1996). This concept well explains the process of sensory-  
98 motor integration. It is worth noting that prior to sensory-motor integration, the brain operates a  
99 multisensory integration process, in which inputs from different sensory modalities are combined

100 together. Internal sources of information emanate from the body (e.g. somatosensory and vestibular  
101 input), whereas external sources are perceived by special senses (e.g. visual and auditory systems).  
102 Two multisensory integration processes proceed in parallel: the first dealing with body  
103 representation; the second with the representation of the external world. Both processes exploit the  
104 complementarities provided by multiple sensory modalities in order to produce i) body awareness  
105 and self-consciousness and ii) a coherent multimodal representation of the external world.

106 Finally, for action execution, the two processes need to be integrated (sensory-motor  
107 integration), i.e. sensory data are mapped onto volitional motor commands. In general, the term  
108 sensory-motor integration describes all the processes where sensory information is used to plan and  
109 execute volitional movement, as well as the sensory counterpart of each executed movement. It is  
110 worth noting that sensory-motor integration is requested even when movement processing is done  
111 in absence of sensory feedback (cognitive representation of movement). Indeed, movement  
112 processing, prediction, and planning involve the activation of higher order sensory areas and motor  
113 areas (Tin & Poon, 2005).

114 A complex cerebral network seems to be involved in sensory-motor integration, including the  
115 sensorimotor cerebral cortex, the basal ganglia and the cerebellum (Figure 1). Cortical frontal and  
116 parietal areas are strongly interconnected and function together for many aspects of action planning.  
117 Starting from sensory parietal areas, the primary somatosensory cortex (SI) consists of the  
118 postcentral gyrus of the parietal lobe, which corresponds to Brodmann areas 3a, 3b, 1, 2. Axons  
119 from the thalamic neurons receiving somatic sensations terminate in somatotopically corresponding  
120 regions of the primary somatosensory cortex. The primary somatosensory cortex projects to the  
121 secondary somatosensory cortex (SII), located on the superior border of the lateral fissure.

122 The posterior parietal cortex (PPC) is involved in spatial attention, spatial awareness, and  
123 multisensory integration (Colby & Goldberg, 1999). Furthermore, recent studies suggest that PPC  
124 plays also an important role in different action-related functions, including movement intention  
125 (together with frontal areas) (Andersen & Buneo, 2002). Thus, PPC is a crucial node for sensory-

126 motor integration, in that it integrates extrinsic (from the “external” world) and intrinsic (from the  
127 body) sensory inputs in order to create a cognitive representation of movement for motor planning  
128 and understanding.

129       Regarding frontal structures, the premotor area is of particular importance for the sensory  
130 guidance of movement. In humans, strong evidence has been provided for a dissociation between  
131 the role of the ventral premotor (PMv) and the dorsal premotor cortex (PMd) (Davare, Andres,  
132 Cosnard, Thonnard, & Olivier, 2006). PMv seems crucial when hand movements are selected to  
133 grasp objects according to their visuospatial properties, playing a key role in visuomotor  
134 transformations required to generate grasping. PMd instead provides signals related to the final goal  
135 of the movement rather than the intermediate steps (Hoshi & Tanji, 2007). For the final motor  
136 output, integrated signals from the premotor areas are sent to the primary motor cortex (M1), which  
137 consists of the precentral gyrus of the frontal lobe and corresponds to Brodmann area 4.

138       Not only the cerebral cortex, but also subcortical structures are involved in sensory-motor  
139 integration. The cerebellum plays a major role in modulating sensorimotor, premotor and posterior  
140 parietal areas for better fine-tuning motor control. In addition, it has been proposed that the  
141 cerebellum acts as a processor of sensory information, combining ascending input from the spino-  
142 cerebellar pathway and descending visual input from the parietal cortex in order to build up a  
143 forward model to predict the sensory consequences of an action (Wolpert, et al., 1998). Finally,  
144 although basal ganglia do not directly receive sensory information, processing of indirect  
145 information by the basal ganglia has a distinct effect on movement. Various models of the basal  
146 ganglia hint at two major roles in the generation and maintenance of movements: co-activation of  
147 agonist–antagonist muscles to maintain equilibrium and balance; and sequential activation of  
148 agonist and then antagonist muscles for implementation of fast movements (Hemami et al, 2013).  
149 Additionally, and perhaps more importantly, the basal ganglia enable the selection of specific  
150 movements and inhibit competing motor programs that could interfere with the intended voluntary  
151 movement (Mink et al., 2003). Several neurophysiological studies provide support for the emerging



152 idea that the basal ganglia serve as a gate-keeper for sensory inputs at various levels along the  
153 central nervous system (CNS), and that abnormal sensorimotor integration is a key feature in the  
154 pathogenesis of many movement disorders involving the basal ganglia (like focal dystonia)  
155 (Abbruzzese & Berardelli, 2003; Kaji & Murase 2001; Rajagopal et al., 2013). The role of the basal  
156 ganglia extends beyond motor control to include also cognitive, emotional, and sensorimotor  
157 functions, thanks to anatomically distinct loops that have reciprocal connections with the frontal,  
158 limbic, and sensory systems.

159 Based on all this evidence, it is clear that when sensory processing is impaired, also the motor  
160 output is deficient. Deficits of sensory-motor integration can be investigated at a pure sensory level,  
161 at a cognitive level (i.e., movement processing in the absence of sensory feedback), or at the  
162 intersection between the sensory inflow and the motor outflow (Figure 2).

163

### 164 **3. When behavior matters: sensory processing, cognitive representation of movement and** 165 **sensory-motor integration in focal dystonia**

166

#### 167 **3.1. Sensory processing**

168 The investigation of how the sensory systems work in focal dystonia helped to achieve a better  
169 understanding of its pathophysiology. The presence of somatosensory deficits in focal dystonia is  
170 now broadly recognized and consistently demonstrated. These deficits appear to be related to  
171 central rather than peripheral factors and are present for different somatosensory modalities,  
172 including touch and proprioception. The association between sensory deficits and motor symptoms,  
173 however, is not completely clear yet. On the one hand, sensory deficits in focal dystonia can address  
174 different body parts, affected and unaffected by motor symptoms, apparently contradicting the  
175 association between sensory dysfunctions and motor deficits. On the other hand, a strong link  
176 between somaesthetic factors and motor symptoms in focal hand dystonia is supported by the

177 effectiveness of sensory training, resulting in parallel improvements in tactile discrimination tasks  
178 (spatial acuity) and motor performance (Zeuner, et al., 2002).

179 Tactile perception in dystonia has been investigated by using psychophysical paradigms, such  
180 as the spatial discrimination threshold (SDT) and the temporal discrimination threshold (TDT)  
181 (Table1). SDT is the ability to perceive two stimuli as *spatially* separated, while TDT measures the  
182 ability to perceive two stimuli as *temporally* separated.

183 More precisely, SDT, measured with the two points discrimination task, represents the shortest  
184 perceivable spatial distance between two tactile stimuli applied to the fingertips. SDT can be  
185 measured also with the grating orientation task; in this case the threshold is the smallest width of  
186 parallel embossed gratings at which the subject recognizes the grating orientation. Higher SDT was  
187 found in both the dominant and non-dominant hand of patients with focal hand dystonia, cervical  
188 dystonia, and blepharospasm compared to healthy controls (Bara-Jimenez, Shelton, & Hallett, 2000;  
189 Molloy, Carr, Zeuner, Dambrosia, & Hallett, 2003; Sanger, Tarsy, & Pascual-Leone, 2001; Van  
190 Boven, 2001).

191 With regards to TDT, the threshold is the shortest perceivable temporal interval between two  
192 stimuli. Compared to healthy controls, increased tactile TDT was described in different types of  
193 focal dystonia, including focal hand dystonia, cervical dystonia, and blepharospasm (Bara-Jimenez,  
194 Shelton, Sanger, & Hallett, 2000; Tinazzi, et al., 2002; Tinazzi, et al., 2009; Tinazzi, et al., 1999).  
195 Interestingly, in focal hand dystonia tactile TDT abnormalities were observed not only for the  
196 affected hand, but also in the unaffected hand, again suggesting that tactile deficits are present  
197 independently of the clinical manifestations (Fiorio, Tinazzi, Bertolasi, & Aglioti, 2003). Moreover,  
198 in other types of dystonia, like cervical dystonia and blepharospasm, tactile TDT deficits are present  
199 even when the stimuli touch a symptom-free body part like the hand (Fiorio, Tinazzi, et al., 2008;  
200 Scontrini, et al., 2009; Tinazzi, Fiorio, Bertolasi, & Aglioti, 2004).

201 More recently, by applying the so-called Aristotle illusion paradigm, another type of sensory  
202 deficit has emerged in focal hand dystonia. In this illusion, one object is perceived as two if it is

203 placed in the contact point of crossed fingertips (Benedetti, 1985). In patients suffering from focal  
204 hand dystonia this illusion is preserved when the object contacts the affected fingers but it is  
205 reduced when the non-affected fingers of the affected hand are touched (Tinazzi, et al., 2013). The  
206 fact that the illusion is reduced in the non-affected fingers and preserved in the affected fingers hints  
207 at a dissociation between the abnormal processing of sensory signals and the presence of motor  
208 symptoms. Differently from other kinds of tactile deficits, this impairment is specific for focal hand  
209 dystonia, as it is not observed in blepharospasm and cervical dystonia (Tinazzi, et al., 2013).

210 The pervasive sensory deficits described in different forms of adult-onset focal dystonia and the  
211 fact that tactile deficits are present even in the absence of motor symptoms led to the hypothesis of a  
212 sensory endophenotype in focal dystonia (Bradley, et al., 2012; Fiorio, et al., 2003; Hutchinson, et  
213 al., 2013), that could be a useful biological marker of genetic status. This hypothesis is mainly  
214 supported by the observation that deficits in somatosensory SDT and TDT are present also in some  
215 patients' unaffected relatives, who could carry a mutated known (e.g. DYT1; Fiorio, Gambarin, et  
216 al., 2007) or unknown gene (Hutchinson, et al., 2013; Kimmich, et al., 2014; O'Dwyer, et al., 2005;  
217 Walsh, et al., 2007). In this regard, however, a distinction should be made between spatial and  
218 temporal discrimination abnormalities. For instance, treatment of cervical dystonia with botulinum  
219 toxin improves spatial discrimination (Walsh & Hutchinson, 2007), suggesting that spatial sensory  
220 abnormalities may represent an epiphenomenon of disease manifestation (Hutchinson, et al., 2013).  
221 Conversely, botulinum toxin injections and deep brain stimulation do not improve temporal  
222 discrimination (Sadnicka, et al., 2013; Scontrini, et al., 2011). Moreover, it is interesting to note that  
223 those unaffected relatives who had an increased tactile TDT also showed a bilateral increase in  
224 putaminal grey matter (Bradley, et al., 2009). Altogether, this evidence suggests that TDT (and not  
225 SDT) could be considered as a mediational endophenotype of dystonia (Hutchinson, et al., 2013).

226 Sensory dysfunctions in dystonia address not only the tactile modality but also proprioception  
227 (Table 1). Based on the proven tight association between proprioception and motor control (e.g.  
228 Ionta, Ferretti, Merla, Tartaro, & Romani, 2010), recently it has been proposed that proprioceptive

229 dysfunction could account for motor deficits in focal dystonia (Avanzino & Fiorio, 2014; Konczak  
230 & Abbruzzese, 2013). Different methods have been used to investigate proprioceptive function in  
231 dystonia. For instance, in focal hand and cervical dystonia vibration of the muscle belly or tendon at  
232 50-120 Hz results in a normal tonic vibration reflex (TVR), which represents the activation of  
233 muscle spindles and  $\gamma$ -motoneurons. Conversely, during the TVR the perception of real or illusory  
234 arm movements (for which a main contribution of group Ia afferents can be suggested) is abnormal  
235 (Bove, Bricchetto, Abbruzzese, Marchese, & Schieppati, 2004; Frima & Grunewald, 2005; Frima,  
236 Nasir, & Grunewald, 2008; Frima, Rome, & Grunewald, 2003; Grunewald, Yoneda, Shipman, &  
237 Sagar, 1997; Kaji, et al., 1995; Rome & Grunewald, 1999; Yoneda, Rome, Sagar, & Grunewald,  
238 2000). Despite an abnormal perception of movement, the sense of position (sub-served by group II  
239 afferents) appears to be preserved, as evidenced by the ability of patients with focal dystonia to  
240 perceive the temporal difference between two passive movements (Tinazzi, Fiorio, et al., 2006).

241 Further, it is becoming progressively clear that proprioception is not only involved in motor  
242 control, but also in higher order functions, such as the construction of the body schema and the  
243 sense of body ownership (Proske & Gandevia, 2012). Interestingly, the investigation of the sense of  
244 body ownership in patients suffering from focal hand dystonia by means of the so-called “rubber  
245 hand illusion” –the induction of the illusory sense of ownership of a fake hand thanks to  
246 synchronous visuo-tactile stimulation (Botvinick & Cohen, 1998)– revealed a dissociation between  
247 two sub-components of the illusion. In particular, the proprioceptive drift –i.e. the objectively  
248 measured illusory recalibration of the perceived location of one’s own hand– was reduced, while  
249 self-identification –the subjectively measured illusory feeling of ownership– was preserved (Fiorio,  
250 et al., 2011). In line with previous evidence pointing to the dissociation between objective and  
251 subjective measurements of the rubber hand illusion in healthy conditions (Ionta, Sforza, Funato, &  
252 Blanke, 2013; Rohde, Di Luca, & Ernst, 2011), the proprioceptive impairment shown by focal hand  
253 dystonia patients could be related to a failure in recalibrating the limb position according to the  
254 ongoing (visuo-tactile) multisensory stimulation (Fiorio, et al., 2011).

255

### 256 3.2. Cognitive representation of movement

257 Sensory information from the environment and from the body needs to be mapped into  
258 representations of intended movements in order to facilitate movement planning and execution  
259 (Perruchoud, et al., 2014). By excluding movement execution, it is still possible to investigate  
260 movement processing, prediction, and planning without the influence of (aberrant) sensory  
261 feedback, both in healthy subjects (Ionta & Blanke, 2009; Ionta, Fourkas, & Aglioti, 2010) and  
262 patients with focal hand dystonia (Fiorio, et al., 2006; Fiorio, Tinazzi, et al., 2007).

263 Different paradigms have been used to study cognitive representation of movement, such as  
264 explicit motor imagery (Delnooz, Helmich, Medendorp, Van de Warrenburg, & Toni, 2013;  
265 Delnooz, Helmich, Toni, & van de Warrenburg, 2012; Quartarone, Bagnato, et al., 2005; Tumas &  
266 Sakamoto, 2009), mental rotation of body parts (Fiorio, Garbarin, et al., 2008; Fiorio, et al., 2006;  
267 Fiorio, Tinazzi, et al., 2007) and temporal expectation of movements outcome (Avanzino, et al.,  
268 2013) (Table1).

269 With regards to explicit motor imagery, patients with focal hand dystonia appear to be slower  
270 than healthy controls during the imagination of writing and tapping movements (Tumas &  
271 Sakamoto, 2009).

272 Motor imagery, however, lacks from quantitative and objective measurements of subjects'  
273 performance. A useful and promising tool to quantify movement planning and prediction is mental  
274 rotation. In this task, subjects are asked to judge the laterality of body parts (or objects) presented  
275 on a computer screen in different postures and orientations. The task is carried out by implicitly  
276 simulating the movement of the same body part to be mentally rotated (Parsons, 1994) and therefore  
277 ongoing proprioceptive input can influence the performance. Patients suffering from focal hand  
278 dystonia display abnormalities in mental rotation of hands (both affected and unaffected) but not of  
279 feet (Fiorio, et al., 2006). Instead, patients with cervical dystonia show a more widespread slowness  
280 of mental rotation addressing several parts of the body, such as head, hand, and foot (Fiorio,

281 Tinazzi, et al., 2007). This different pattern between the two forms of dystonia could be related to a  
282 different pathophysiology, with local sensorimotor factors playing a more important role in focal  
283 hand dystonia and abnormalities of the vestibular system and neck proprioception in cervical  
284 dystonia (Dauer, Burke, Greene, & Fahn, 1998; Karnath, Konczak, & Dichgans, 2000).

285 Another cognitive function related to movement representation and processing is the ability to  
286 estimate the time course, speed, and end of a movement. This ability can be investigated by means  
287 of the temporal expectation task, in which participants are required to observe a movement in a  
288 video and to predict the end of the movement itself (Avanzino, et al., 2013). Crucially, some  
289 seconds after its onset, the video is occluded by a dark interval and therefore, the task can be  
290 performed only by extrapolating time-related features of the movement, such as its velocity, from  
291 the observed movement sequence. Compared to control subjects, patients with focal hand dystonia  
292 make more mistakes only when they have to predict the end of a movement performed by a human  
293 body segment (i.e., hand writing a sentence), whereas no differences are observed with regards to  
294 the movement of an inanimate object –hinting at a deficit of body movement representation  
295 (Avanzino, et al., 2013). In another study, the authors found the same dysfunction of temporal  
296 prediction in dystonic patients without hand involvement, i.e. cervical dystonia. This result further  
297 supported the hypothesis that the abnormal timing of visually perceived motion, assessed through a  
298 temporal expectation task, is selective for human body motion in patients with primary focal  
299 dystonia. Moreover, this abnormality is unlikely to be a direct expression of the motor symptoms,  
300 since it does not exclusively involve the movements strictly related to the manifestation of dystonia  
301 (Martino, et al., 2015). These studies further suggest that the cognitive representation of movements  
302 is impaired in focal dystonia.

303

### 304 **3.3. Sensory-motor integration in focal dystonia**

305 Behavioral tasks that require the integration of sensory information in order to plan and execute  
306 movements are suitable to study sensory-motor integration (Bleton, et al., 2014; Odergren, Iwasaki,

307 Borg, & Forssberg, 1996; Serrien, Burgunder, & Wiesendanger, 2000). For example, a force  
308 regulation task while performing a drawer-opening precision grip was applied in patients with  
309 writer's cramp (Serrien, et al., 2000) (Table 1). To focus on sensory-motor integration, grip-force  
310 changes during sensory perturbations (tactile/proprioceptive) were also assessed. First, writer's  
311 cramp patients showed increased grip force with respect to controls, with a stronger modulation in  
312 the symptomatic than in the asymptomatic hand. This result denotes a change in force scaling  
313 capabilities, especially for the hand preferentially used for manipulations. In addition, vibratory  
314 stimulation of the extrinsic hand/finger muscles resulted in an increased grip force for both patients'  
315 hands. Being absent in controls, this finding supports a bilateral dysfunction in sensory-motor  
316 integration resulting from focal dystonia. More recently, Bleton and colleagues (2014), examined  
317 grip-force adjustments according to visual and somatosensory (sense of effort) information in a  
318 group of patients affected by focal hand dystonia. The data revealed deficient grip force control in  
319 both the symptomatic and non-symptomatic hand. Since grip-force parameters changed as a  
320 function of sensory feedback, the inaccurate grip-force scaling can be interpreted as a manifestation  
321 of impaired sensory-motor integration. This result supports again a bilateral dysfunction in sensory-  
322 motor integration related to focal dystonia.

323 Another way to study sensory-motor integration is to ask participants to perform reaching  
324 movements with the upper limb towards a specific target. In absence of visual information, this task  
325 relies on proprioception. Impairments in reaching movements have been shown not only in patients  
326 with dystonia of the upper limb (Inzelberg, Flash, Schechtman, & Korczyn, 1995), but also in  
327 cervical dystonia (Pelosin, Bove, Marinelli, Abbruzzese, & Ghilardi, 2009), suggesting that focal  
328 dystonia is characterized by a widespread impairment of motor control. More precisely, hand  
329 trajectories were shorter, more curved and without overlapping of out- and back- strokes in cervical  
330 dystonia patients compared to controls. Moreover, temporal velocity profiles were asymmetrical  
331 and reversal lags between out- and back-strokes were longer in cervical dystonia patients. It was  
332 suggested that this deficit could be due to an error in the spatial representation of the hand location

333 or to a failure in integrating proprioceptive information with the motor output (Marinelli, et al.,  
334 2011).

335

#### 336 **4. Cerebral cortex, basal ganglia, and cerebellum: neurophysiological and neuro-** 337 **anatomical underpinnings of behavioral abnormalities**

338 Section 2 summarizes the CNS structures involved in sensory processing, cognitive movement  
339 representation, and sensory-motor integration. So far, we reported behavioral evidence of a  
340 dysfunction at all these levels of the sensory-motor integration process in patients with focal  
341 dystonia. By means of neurophysiological and neuro-imaging techniques, functional and anatomical  
342 correlates of these dysfunctions are elucidated here.

343

#### 344 **4.1 Cerebral cortex**

345 Following the “file rouge” adopted in Section 2, a large number of experimental data evidenced  
346 abnormalities in the parietal and frontal cortex and in the cortico-cortical pathways connecting  
347 sensory and motor areas and different motor areas between them (i.e., PM with M1).

348 The neural correlates of spatial sensory dysfunction (i.e., SDT), could be related to cortical  
349 disorganized digit representations in the parietal cortex (enlarged and overlapping receptive fields),  
350 as described in dystonic patients (Bara-Jimenez, Catalan, Hallett, & Gerloff, 1998; Butterworth, et  
351 al., 2003; Elbert, et al., 1998; Lenz & Byl, 1999; Lenz, et al., 1999; Meunier, et al., 2001; Vitek, et  
352 al., 1999) and non-human dystonic primates (Byl, Merzenich, & Jenkins, 1996; Topp & Byl, 1999).  
353 This explanation, however, does not appear to account for the other type of spatial sensory deficit  
354 presented above, i.e., the disturbed Aristotle illusion (Tinazzi, et al., 2013). The reduced illusory  
355 doubling perception in focal hand dystonia may not be related, indeed, to a disorganized digit  
356 representations, but rather to a different level of somatosensory activation of the unaffected digits  
357 (i.e., the fourth and the fifth), as evidenced in a functional neuroimaging study (Nelson, Blake, &  
358 Chen, 2009).



359 Abnormal connectivity between the sensory cortex and the frontal cortex seems to be  
360 responsible for higher order dysfunctions, like the ability to mentally construct a motor plan  
361 (Delnooz, et al., 2013; Delnooz, et al., 2012). Recent neuroimaging studies showed that patients  
362 with focal hand dystonia have not only an abnormal activation of the premotor areas during motor  
363 imagery of grasping for writing (Delnooz, et al., 2013), but also, and even more interestingly,  
364 reduced connectivity between the premotor cortex and the parietal cortex, that could represent the  
365 neuroanatomical correlate for the impairment to integrate sensory information (elaborated in the  
366 parietal cortex) with movement processing (elaborated in the premotor cortex) (Delnooz, et al.,  
367 2012). The same brain network involved in the integration of sensory input with motor actions is  
368 also activated by the mental rotation task (Bonda, Petrides, Frey, & Evans, 1995; Ganis, Keenan,  
369 Kosslyn, & Pascual-Leone, 2000; Kosslyn, DiGirolamo, Thompson, & Alpert, 1998) and an  
370 abnormal function in this network might be responsible also of behavioral deficits in this task.

371 Further, functional imaging studies during movement execution or during the application of  
372 sensory tricks (a maneuver in which touching the skin alleviates motor symptoms) confirmed that  
373 the premotor and parietal cortices are malfunctioning in the sensory-motor integration process.  
374 Aiming at identifying the neural underpinnings of abnormal motor behaviors in focal dystonia,  
375 several studies asked patients to perform actions triggering or not triggering the dystonic  
376 movements while brain activity was recorded. Following this procedure, focal dystonia has been  
377 associated with a widespread dysfunctional brain network, affecting both cortical and subcortical  
378 regions. The results, however, were sometimes contradictory showing either an increase or decrease  
379 of activation in certain brain regions during movement execution. A positron emission tomography  
380 (PET) study, for example, showed impaired activation of M1 and greater activation in frontal and  
381 parietal association areas in writer's cramp patients compared to controls during writing (Ceballos-  
382 Baumann, Sheean, Passingham, Marsden, & Brooks, 1997). In a study by Ibanez and colleagues  
383 (1999), patients with writer's cramp showed reduced regional cerebral blood flow (rCBF) in  
384 sensorimotor and premotor structures in different tasks compared to controls. For instance, patients

385 showed significantly less rCBF in the contralateral vs. ipsilateral primary sensorimotor cortex  
386 during sustained flexion or extension of the wrist. Furthermore, there was a significant decrease of  
387 rCBF in the left premotor cortex with writing, but there were no differences during tapping. Lerner  
388 et al. (2004) found a significant rCBF increase in the primary sensory cortex and in the right  
389 cerebellum and rCBF decrease in the supplementary motor area (SMA) in patients with writer's  
390 cramp during writing and tapping compared to controls. Increased blood flow of the primary  
391 sensory cortex might reflect more intense processing of the sensory information or possibly  
392 expanded cortical representation of the hand area. With regards to sensory tricks, in a seminal paper  
393 by Naumann and coworkers (Naumann, Magyar-Lehmann, Reiners, Erbguth, & Leenders, 2000)  
394 the effect of a sensory trick on cortical activation patterns in patients with cervical dystonia has  
395 been assessed by using H<sub>2</sub>(15)O PET. The application of the sensory trick stimulus, resulting in a  
396 near-neutral head position, led to an increased activation mainly of the superior and inferior parietal  
397 lobule (ipsilateral to the original head turn) and to a decreased activity of SMA and the primary  
398 sensorimotor cortex (contralateral to the head turn). The authors proposed that a perceptual  
399 disbalance induced by a sensory trick maneuver leads to a relative displacement of the egocentric  
400 midvertical reference to the opposite side and a decrease in motor cortex activity (Naumann, et al.,  
401 2000).

402 In accordance with all these functional data, structural imaging studies evidenced focal  
403 dystonia-related pathophysiological aberrancies at the cortical level. The analysis of voxel-based  
404 morphometry (VBM) is used to study human brain anatomy (Ashburner & Friston, 2000; May &  
405 Gaser, 2006). With VBM it is possible to detect and quantify differences in gray and white matter  
406 volume. Experimental data showed a bilateral increase of gray matter volume in the motor cortex in  
407 patients with cervical dystonia (Draganski, et al., 2003; Egger, et al., 2007), an increase in the gray  
408 matter volume of the premotor cortex but only contralateral to the affected hand (Delmaire, et al.,  
409 2007) in patients with focal hand dystonia, a bilateral increase in gray matter volume of the  
410 prefrontal cortex in patients with cervical dystonia and focal hand dystonia (Egger, et al., 2007) and

411 a decrease in gray matter of the left inferior parietal lobe in patients with blepharospasm (Etgen, et  
412 al., 2006). The increase of gray matter volume in premotor and prefrontal areas could hint at a  
413 compensatory mechanism to overcome deficits of sensory-motor processing.

414 Neurophysiological investigations helped to clarify whether, besides abnormal functions and  
415 structures, cortical regions presented also a lack of connectivity. More precisely, the communication  
416 between sensory and motor areas in humans can be studied at a cortical level by means of  
417 neurophysiological techniques, such as transcranial magnetic stimulation (TMS). By applying a  
418 conditioning electrical stimulus to a mixed nerve followed by a TMS stimulus over M1, inhibition  
419 of M1 excitability can be observed. These effects, more evident at inter-stimulus intervals of 20ms  
420 and 200ms, are described as short- (SAI) and long-latency afferent inhibition (LAI), respectively  
421 (Tokimura, et al., 2000). For the SAI, it is not clear yet if the effect is mediated directly through  
422 somatosensory projections to M1 or indirectly through S1. LAI probably involves other pathways,  
423 such as the basal ganglia or cortical association areas. LAI is defective in patients with focal hand  
424 dystonia (Abbruzzese, Marchese, Buccolieri, Gasparetto, & Trompetto, 2001), but SAI is normal  
425 (Avanzino, et al., 2008), indicating abnormal central processing of sensory inputs. Another option  
426 to study in vivo how a somatic stimulus interacts within M1 is to combine TMS with low amplitude  
427 muscle vibration. If the TMS pulse is delivered over M1 after 1 second of hand muscle vibration,  
428 M1 excitability is increased in the vibrated muscle and decreased in adjacent muscles (Rosenkranz  
429 & Rothwell, 2003). Further, the activity of the inhibitory interneurons targeting the vibrated muscle  
430 is reduced and the opposite changes occur in surrounding muscles (Rosenkranz & Rothwell, 2003).  
431 This pattern of sensory-motor interaction is abnormal in patients with focal hand dystonia, with a  
432 little effect of vibration on cortical excitability (Rosenkranz, et al., 2005).

433 Inter-regional interactions between M1 and other brain regions (i.e., premotor cortex, parietal  
434 cortex) can be assessed by evaluating how the amplitude of motor evoked potentials (MEPs),  
435 elicited by stimulation of M1, can be modulated by a preceding conditioning pulse delivered over  
436 the other areas. The connectivity between PPC and the ipsilateral M1 can be assessed by means of a

437 paired pulse TMS (ppTMS approach) (Koch & Rothwell, 2009). In healthy subjects, a conditioning  
438 TMS pulse applied over the right PPC is able to increase the excitability of the hand area of the  
439 right M1 (Koch, et al., 2007). The PPC-M1 interaction is crucial in preparation and planning of  
440 reaching and grasping movements toward visual targets (Figure 3) (Koch, Fernandez Del Olmo, et  
441 al., 2008; Van Der Werf, Jensen, Fries, & Medendorp, 2010), as well as in visuospatial mechanisms  
442 that affect temporal performance, accuracy and variability (Koch, et al., 2010; Vicario, Martino, &  
443 Koch, 2013). PPC-M1 connectivity was assessed in cervical dystonia patients, at rest, using this  
444 ppTMS protocol (Porcacchia, et al., 2014). The results showed that M1 facilitation induced by a  
445 conditioning stimulus on PPC is not present in dystonic patients (Figure 3). Further, reaction and  
446 movement times were significantly slower in patients than in controls and the relative strength of  
447 parieto-motor connectivity correlated with movement times in dystonic patients (Porcacchia, et al.,  
448 2014).

449 In healthy subjects, ppTMS studies have been used also to probe functional connectivity  
450 between PMd and M1 (Figure 3). A conditioning TMS pulse over PMd reduced the amplitude of  
451 MEPs evoked in hand muscles by a pulse over the contralateral M1 some 8 to 10ms later  
452 (Mochizuki, Huang, & Rothwell, 2004). The effectiveness of these interhemispheric connections  
453 changes prior to movement, suggesting that these connections play a role in motor preparation  
454 (Koch, et al., 2006). They may utilize either direct transcallosal connections between the  
455 contralateral PMd and M1 (Marconi, Genovesio, Giannetti, Molinari, & Caminiti, 2003), or take an  
456 indirect route through the contralateral and ipsilateral PMd and M1 (Dum & Strick, 2002, 2005). By  
457 applying this protocol in patients with focal hand dystonia, Koch and coworkers (Koch, Fernandez  
458 Del Olmo, et al., 2008) demonstrated that inhibitory interhemispheric interactions between left PMd  
459 and right M1 are less excitable compared to controls, possibly contributing to some of the problems  
460 in motor overflow that dystonic patients experience when they try to move. Namely, it is even  
461 possible that the reduced inhibition from PMd could contribute to abnormalities of synaptic

462 plasticity that have been described in M1 of dystonic patients (Figure 3) (Quartarone, et al., 2003;  
463 Quartarone, Rizzo, et al., 2005).

464 Involvement of PM in the pathophysiology of dystonia has been supported by repetitive  
465 transcranial magnetic stimulation (rTMS) studies. Siebner and colleagues (2003) and Murase and  
466 colleagues (2005) applied inhibitory rTMS over the premotor motor cortex in patients with focal  
467 hand dystonia. After one rTMS session there was an improvement in computerized measures of  
468 writing (e.g., pen pressure), and some participants reported an improvement in writing ability,  
469 which lasted up to a few hours (Murase, et al., 2005). This improvement was not seen in patients  
470 receiving the control sham stimulation. Furthermore, one session of rTMS over the PMd produced  
471 powerful and widespread changes in regional synaptic activity, as indexed by bilateral decreases in  
472 rCBF in prefrontal, premotor, and primary motor cortex (Siebner, et al., 2003). The possible  
473 therapeutic effects of premotor rTMS may involve indirect effects of PMd on inhibitory  
474 mechanisms in M1. Indeed, it was recently demonstrated that by applying an inhibitory rTMS on  
475 PMd, clinical improvement in writing speed and speed of maze completion was accompanied by the  
476 increased excitability of inhibitory circuits within M1, which were brought back towards the normal  
477 range (Huang, Rothwell, Lu, Wang, & Chen, 2010).

478 In summary, a number of cortical regions located in frontal, parietal and also prefrontal cortex  
479 presented an abnormal activation during sensory tasks, mental representation of movements, or  
480 when sensory information is used for motor output, as during sensory trick application or movement  
481 execution. In addition, structural imaging studies displayed focal dystonia-related  
482 pathophysiological aberrancies at the cortical level. To complete the scenario, TMS studies revealed  
483 that functional communication from sensory areas and premotor areas to M1 is abnormal in focal  
484 dystonia.

485

#### 486 **4.2. Cerebellum and Basal Ganglia**

487 Classically, dystonia has been considered a disorder of the basal ganglia, and in particular of  
488 the basal ganglia cortico-striatal-thalamo-cortical motor circuits (Bressman, et al., 1998). Support to  
489 this view derives from several lines of research. For instance, putaminal enlargement was found in  
490 patients with different types of dystonia (Draganski, et al., 2009; Etgen, Muhlau, Gaser, & Sander,  
491 2006; Granert, Peller, Jabusch, Altenmuller, & Siebner, 2011). Moreover, patients' unaffected  
492 relatives with abnormal TDT have larger putaminal volumes than relatives with normal TDT  
493 (Bradley, et al., 2009). This findings hint at an association between TDT and the function of the  
494 basal ganglia. Namely, it was suggested that temporal discrimination requires not only the cortex  
495 (i.e., primary sensory areas, pre-supplementary motor area, anterior cingulate cortex), but also sub-  
496 cortical structures, like the basal ganglia (Harrington, Haaland, & Knight, 1998; Lacruz, Artieda,  
497 Pastor, & Obeso, 1991; Pastor, Day, Macaluso, Friston, & Frackowiak, 2004). Furthermore, the  
498 basal ganglia play also a role in SDT and an fMRI study showed that in writer's cramp patients  
499 there subcortical structures are hyperactive during a tactile grating orientation task (Peller, et al.,  
500 2006).

501 This is in line with the evidence that (as already anticipated above) the basal ganglia play an  
502 important role not only in controlling and programming motor sequences, but also in non-motor  
503 cognitive functions (Bares & Rektor, 2001; Jahanshahi, et al., 2002; Koechlin, Danek, Burnod, &  
504 Grafman, 2002) particularly in sensory processing and multisensory integration (i.e. visual and  
505 tactile) (Graziano & Gross, 1993). Furthermore, the basal ganglia probably contribute to the  
506 integration of sensory information with motor actions, thus playing a role in movement  
507 representation and motor learning (de Lange, Hagoort, & Toni, 2005; Kuhn, et al., 2006).

508 Beyond this classical view, more recently research has started to investigate the role of the  
509 cerebellum in the pathophysiology of dystonia. Connectivity changes in the cerebello-thalamic tract  
510 have been associated with *DYT1* and *DYT6* dystonic mutations (Argyelan, et al., 2009). Mutation  
511 carriers exhibited reduced integrity of cerebello-thalamic fiber tracts, compared to non-mutated  
512 subjects, with non-manifesting carriers occupying an intermediate position between manifesting and

513 control subjects. Moreover, in this study the lower cerebellar connectivity was associated with  
514 greater activation in the sensorimotor and supplementary motor cortex, suggesting that  
515 abnormalities of cerebellar outflow pathways might contribute to loss of inhibition at the cortical  
516 level in dystonia. Structural MRI in non-hereditary primary dystonia also demonstrated white  
517 matter integrity abnormalities in the fiber tracts connecting the primary sensorimotor areas with  
518 subcortical structures (Colosimo, et al., 2005; Delmaire, et al., 2009).

519 Cerebello-cortical interaction can be tested with TMS by investigating how a conditioning  
520 stimulus over the cerebellum influences a subsequent stimulus over the contralateral M1. In normal  
521 subjects, when an inter-stimulus interval of 5-7 ms is used, a suppression of corticomotor  
522 excitability is detected (Figure 3) (Ugawa, Uesaka, Terao, Hanajima, & Kanazawa, 1995). It was  
523 shown that cerebellar output modulates the excitability of M1 via the projections to local  
524 GABAergic inhibitory interneurons (Daskalakis, et al., 2004; Koch, Mori, et al., 2008). In 2009,  
525 Brighina and coworkers showed a reduced cerebellar modulation of the motor cortex excitability in  
526 dystonia. Indeed, cerebellar conditioning stimulation had less of an effect on the motor cortex of  
527 dystonic patients (Figure 3), leaving conditioned MEPs and intracortical inhibition and facilitation  
528 unchanged (Brighina, et al., 2009). Reduced or absent cerebellar modulation has also been reported  
529 in patients with cerebellar ataxia –a disorder affecting movement coordination– of various origins  
530 (Ugawa, et al., 1997) or with lesions of the cerebellum or the dentate-thalamo-cortical pathways and  
531 in patients with focal cerebellar lesions and hemispherectomy (Di Lazzaro, et al., 1995). These  
532 findings suggest that dysfunctioning Purkinje cells in the cerebellar cortex might affect the  
533 inhibitory drive to the dentate-thalamo-cortical pathways. It has been proposed that the cerebello-  
534 thalamo-cortical network may contribute to the loss of inhibitory processes observed in dystonia  
535 (Hallett, 2006; Lin & Hallett, 2009), directly contributing to an abnormal sensory-motor integration  
536 process. Indeed, the cerebellum processes proprioceptive information, plays a key role in both  
537 temporal and spatial discrimination (Pastor, et al., 2004; Restuccia, et al., 2001) and contribute to  
538 movement simulation (Ionta, Ferretti, et al., 2010).

539 To complete the scenario, in a recent paper, Hubsch and coworkers (2013) examined whether  
540 putative cerebellar dysfunction in dystonia is linked to maladaptive plasticity in the sensorimotor  
541 cortex. The cerebellar cortex was excited or inhibited by means of rTMS before artificial sensory-  
542 motor plasticity was induced in M1 by paired associative stimulation. In healthy subjects, cerebellar  
543 cortex excitation prevented the paired associative stimulation to induce sensory-motor plasticity in  
544 M1, whereas cerebellar inhibition led the paired associative stimulation to be more efficient in  
545 inducing the plasticity. In patients with writer's cramp, cerebellar excitation and inhibition were  
546 both ineffective in modulating sensory-motor plasticity. It was postulated that the loss of cerebellar  
547 control over sensorimotor plasticity might lead to build up an incorrect motor program to specific  
548 adaptation tasks, such as writing.

549

#### 550 **5. Sensory-motor integration in dystonia: a clue for therapeutic approaches?**

551 As evidenced so far, a number of studies have suggested that some forms of focal dystonia  
552 may, at least partially, result from disturbances in sensory function and problems with sensory-  
553 motor integration. The therapeutic implications of these findings are significant in that they suggest  
554 why therapies promoting the reorganization of sensory-motor regions can sometimes be effective in  
555 treating dystonic symptoms. These approaches modulate sensory-motor processing by means of  
556 neuromodulation of areas involved in this process, that is sensory retraining and learning-based  
557 sensorimotor re-education.

558 Focal dystonia is a good candidate for the therapeutic use of neuromodulation with the aim of  
559 restoring the abnormal activity in the sensory-motor network. As already summarized in section 4.1  
560 of the present review, a single session of neuromodulation by using rTMS on the premotor cortex  
561 resulted in clinical improvements (Murase, et al., 2005). These promising results have led to a  
562 subsequent multiple-session study in focal hand dystonia. Twelve patients underwent five daily-  
563 sessions of 1 Hz rTMS to contralateral PMd (Kimberley, Borich, Arora, & Siebner, 2013). Patients  
564 held a pencil and made movements that did not elicit dystonic symptoms during rTMS, according to



565 the hypothesis that an active but non-dystonic motor state would increase the beneficial effects of  
566 rTMS. The data were compared to those of five additional patients who received sham-rTMS  
567 protocol. Behavioral measures included pen force and velocity during handwriting and subjective  
568 report. Results showed that pen force was reduced at day 1 and 5 and 68% of patients self-reported  
569 as ‘responders’ at day 5, and 58% self-reported as ‘responders’ at follow-up (Kimberley, et al.,  
570 2013). These findings, yet not supporting a strong therapeutic potential of this rTMS paradigm in  
571 focal hand dystonia, nevertheless encourage further investigation.

572 A recent neuromodulation study targeted the abnormal cerebellar function in focal dystonia  
573 (Koch, et al., 2014). In a sham-controlled trial, the effect of two-weeks of cerebellar continuous  
574 theta burst stimulation was tested in a sample of cervical dystonia patients. The results showed a  
575 small but significant clinical improvement and a modification of the connectivity between the  
576 cerebellum and M1. These data provide novel evidence that the cerebello-thalamo-cortical circuit  
577 could be a potential target to partially reduce some dystonic symptoms and deserves further in-  
578 depth studies.

579 With regards to the possibility to re-train the sensory systems in order to improve the motor  
580 outcome, different approaches have been applied so far in dystonia. One type of interventions  
581 consisted in potentiating the proprioceptive input by means of muscle vibration (Rosenkranz, et al.,  
582 2008). This procedure not only induced sensorimotor organization of the hand area, but also helped  
583 to improve the hand motor functions of patients with musician’s dystonia (Rosenkranz, Butler,  
584 Williamon, & Rothwell, 2009). Vibration of the neck muscle was applied in a single case of  
585 cervical dystonia and again resulted in beneficial effects with regards to the head and trunk position  
586 (Karnath, et al., 2000). These findings suggest that the sensory-motor connection in focal dystonia  
587 can re-adapt following a proprioceptive intervention. Moreover, proprioceptive stimulation has a  
588 beneficial influence also on the plasticity of the motor cortex (Avanzino, et al., 2013), further  
589 hinting at a link between this kind of stimulation and motor functions. Another way of targeting the  
590 sensory systems in focal dystonia is by means of transcutaneous electrical nerve stimulation. The

591 rationale is to re-establish a balanced activation between agonist and antagonist muscles (Tinazzi, et  
592 al., 2005). Namely, in patients with focal hand dystonia two weeks of transcutaneous electrical  
593 nerve stimulation of the forearm flexor muscle improved dystonic symptoms and these effects  
594 lasted for 3 weeks after treatment (Tinazzi, et al., 2005; Tinazzi, Zarattini, et al., 2006). Finally  
595 another promising approach to induce muscle-stretching and promote a better sensory processing in  
596 patients with focal hand and cervical dystonia is through kinesio-taping (Pelosin, et al., 2013).

597 The opposite approach to the abovementioned augmented feedback techniques is sensory  
598 deprivation. One way to reduce sensory feedback is by means of limb immobilization. In this  
599 regard, immobilization of the upper limb in patients with focal hand dystonia resulted in changes of  
600 the cortical map toward a more normal topography (Lissek, et al., 2009; Roll, et al., 2012).  
601 Immobilization of specific body parts was also applied together with motor training (Candia,  
602 Rosset-Llobet, Elbert, & Pascual-Leone, 2005; Zeuner, et al., 2005). For instance in a study by  
603 Zeuner and colleagues (2005) motor exercises of one finger were performed for a period of 4 to 12  
604 weeks while the other four fingers were immobilized. This procedure resulted in subjective  
605 improvement, assessed by a self-rating scale, in 6 out of 10 patients with focal hand dystonia.

606 Sensory-motor re-education can be induced even with visual or auditory electromyographic  
607 biofeedback techniques, that may be effective in cervical dystonia (Cleeland, 1973; Korein, et al.,  
608 1976; Leplow, 1990). The inspiring principle here is to increase the patients' volitional control over  
609 the abnormally active muscles.

610 Unfortunately, so far most of the studies in novel rehabilitative therapeutic approaches in  
611 dystonia lacked of a controlled sham condition or involved a small number of patients. Future  
612 research efforts should better address this topic in order to delineate the best approach for  
613 alternative therapeutic options in focal dystonia.

614

615 **6. Conclusions and future venues of research**

616 In this review we summarized a large amount of behavioral, neurophysiological, and  
617 neuroimaging data demonstrating sensory and sensory-motor dysfunctions in patients with focal  
618 dystonia. Available evidence supports the hypothesis that abnormalities in dystonia extend beyond  
619 the sole motor control, and involve also processing of sensory inputs and cognitive representation of  
620 movement. Instead of being conclusive, however, the presented studies leave open some questions  
621 that could direct future research efforts on sensory integration processes in dystonia. For example, it  
622 is still unclear which level of the sensory-motor loop plays a predominant role in the sensory-motor  
623 deficits in dystonia. In other words, the question is still open on whether these deficits are more  
624 related to sensory abnormalities, to an impaired motor planning at the cognitive level or to the  
625 process of integrating these two aspects. The attempt to propose a model of sensory-motor  
626 integration (Perruchoud, et al., 2014) represents an important step toward a better understanding of  
627 the sensory-motor integration deficits in focal dystonia, but more experimental evidence is needed  
628 to uncover the crucial level of dysfunction.

629 Moreover, future lines of research should better tackle the interplay between different sensory  
630 modalities and the motor systems. Namely, movement execution can be modulated by extrinsic  
631 inputs (such as visual and acoustic) and by intrinsic inputs (such as proprioceptive and tactile).  
632 Interestingly, looking at data on sensory and sensory-motor processing in dystonia, available  
633 evidence suggests that changes in the external world are processed normally in patients with focal  
634 dystonia, except when they are used for movement planning or execution. In other words, when  
635 visual or acoustic information is processed “per se”, and not for planning or executing volitional  
636 movements, patients with dystonia do not show particular deficits. As an example, temporal  
637 discrimination of visual stimuli is preserved both in cervical and in focal hand dystonia (Fiorio, et  
638 al., 2003; Tinazzi, et al., 2004), whereas it is impaired in generalized forms of dystonia (Aglioti,  
639 Fiorio, Forster, & Tinazzi, 2003). This suggests that, specifically for the focal types of dystonia, the  
640 visual system works properly. Furthermore, visual processing is preserved even in the case of action  
641 observation. In this regard, two studies demonstrated that during passive observation of movements,

642 patients with focal hand dystonia present with adequate recruitment of cerebral areas (Castrop,  
643 Dresel, Hennenlotter, Zimmer, & Haslinger, 2012) and corticospinal excitability (Fiorio, et al.,  
644 2010). All these studies did not require movement planning or execution, but only processing of  
645 visual information. The situation completely changes when visual information is encoded in order  
646 to create a motor plan or to execute volitional movements, i.e., when it is used for sensory-motor  
647 integration. In this case, indeed, patients with focal dystonia present with deficits compared to  
648 healthy control subjects (Avanzino, et al., 2013).

649       Regarding sensory signals originating from the body, i.e. internal sources of information  
650 (proprioceptive and tactile inputs), patients with focal dystonia misprocess this information even  
651 before it is used for sensory-motor integration process, hinting at a dysfunction addressing the pure  
652 sensory level. Further, these abnormalities are not specific for a single type of dystonia and/or for  
653 the affected segment in focal dystonia, thus suggesting that, with regards to the somatosensory  
654 system, dystonia is characterized by a widespread impairment of sensory and sensory-motor  
655 control. These sensory abnormalities may impair the process of sensory-motor integration, by  
656 interacting with other dysfunctional mechanisms in dystonia, i.e., loss of inhibition and abnormal  
657 plasticity (Quartarone & Hallett, 2013). In this regard, it was suggested that “*misprocessing of*  
658 *sensory feedback coupled with an abnormal excitability within inhibitory motor circuits at different*  
659 *level (spinal cord, brainstem, cerebellum, basal ganglia, and cortex) may result in a progressive*  
660 *abnormal plasticity in local and distant nodes, culminating in an overt dystonia*” (Quartarone &  
661 Hallett, 2013).

662       All this evidence well fits with the hypothesis that primary dystonia may be a network disorder,  
663 in which the crucial nodes in the cerebral cortex are located in S1 and in those associative sensory  
664 and motor areas that play a role in integrating different sensory modalities coming from the  
665 “external” world and “internal” body in order to create a cognitive representation of movement for  
666 motor planning and understanding. To these aims, the supposed network includes also subcortical  
667 structures, like the basal ganglia and the cerebellum, that act in concert with the cerebral cortex.

668 Some issues need to be further elucidated. First, it is not known whether all these abnormalities play  
669 a causative role or are the results of compensatory mechanisms of the central nervous system in  
670 response to the dystonic motor symptoms. Data from non-manifesting *DYT1* and *DYT6* mutations  
671 carriers and from relatives of patients with adult-onset focal dystonia, as well as the observation that  
672 all these deficits address not-affected body segments, hint at a causal link rather than at  
673 compensation.

674 Second, even in the scenario of a causal role, it is yet to elucidate if there is a “leading”  
675 structure whose dysfunction provokes a cascade of events that at the end will turn in the  
676 malfunctioning of a number of cortical and subcortical areas. If this is the case, it is of primary  
677 importance to identify the possible leading structure, in order to plan the most suitable therapeutic  
678 approach to selectively target the dysfunctional brain region.

679

680 **Figure Legends**

681 **Figure 1.** Schematic representation of the complex brain network involved in sensory-motor  
682 integration. Sensory input (red) is elaborated by subcortical (firstly Thal, Cer and then BG) and  
683 cortical (SI) regions and integrated with the motor plan (green) through associative areas (PPC and  
684 PM). Deficits of sensory-motor integration in dystonia could arise from dysfunctions at different  
685 levels of this network. BG = basal ganglia; Thal = thalamus; Cer = cerebellum; SI = primary  
686 somatosensory cortex; PM = premotor cortex; PPC = posterior parietal cortex; M1 = primary motor  
687 cortex.

688

689 **Figure 2.** Simplified model of the interaction between sensory information (red) and motor  
690 elaboration (green). The tasks in which dysfunctions have been found in dystonic patients are  
691 indicated in *Italics*.

692

693 **Figure 3.** Schematic representation of the connections between some multisensory areas and the  
694 primary motor cortex (M1). A) The connections toward M1 deriving from the premotor cortex  
695 (PM), the posterior parietal cortex (PPC) and the cerebellum (Cer) are of fundamental importance  
696 for sensory-motor integration and, consequently, for optimal movement planning and execution. B)  
697 Neurophysiological and neuroimaging studies revealed impaired connections between multisensory  
698 areas and M1 in the dystonic brain (represented by striped arrows). The lack of efficient  
699 connections results in a disorganized motor output from M1.

700

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