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Sensory-motor integration in focal dystonia

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Abbreviations:

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

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

Abstract

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

1. Introduction

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

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

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

2. Sensory-motor integration: neurophysiological and neuroanatomical aspects

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

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

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

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

3.1. Sensory processing

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

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

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

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

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

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

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

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

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

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

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

3.2. Cognitive representation of movement

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

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

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

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

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

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

3.3. Sensory-motor integration in focal dystonia

Behavioral tasks that require the integration of sensory information in order to plan and execute 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 collegues (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

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

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

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

4.1 Cerebral cortex

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

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

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

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

showed significantly less rCBF in the contralateral vs. ipsilateral primary sensorimotor cortex during sustained flexion or extension of the wrist. Furthermore, there was a significant decrease of rCBF in the left premotor cortex with writing, but there were no differences during tapping. Lerner et al. (2004) found a significant rCBF increase in the primary sensory cortex and in the right cerebellum and rCBF decrease in the supplementary motor area (SMA) in patients with writer's cramp during writing and tapping compared to controls. Increased blood flow of the primary sensory cortex might reflect more intense processing of the sensory information or possibly expanded cortical representation of the hand area. With regards to sensory tricks, in a seminal paper by Naumann and coworkers (Naumann, Magyar-Lehmann, Reiners, Erbguth, & Leenders, 2000) the effect of a sensory trick on cortical activation patterns in patients with cervical dystonia has been assessed by using H2(15)O PET. The application of the sensory trick stimulus, resulting in a near-neutral head position, led to an increased activation mainly of the superior and inferior parietal lobule (ipsilateral to the original head turn) and to a decreased activity of SMA and the primary sensorimotor cortex (contralateral to the head turn). The authors proposed that a perceptual disbalance induced by a sensory trick maneuver leads to a relative displacement of the egocentric midvertical reference to the opposite side and a decrease in motor cortex activity (Naumann, et al., 2000).

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

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

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

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

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

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

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

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

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

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

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

Focal dystonia is a good candidate for the therapeutic use of neuromodulation with the aim of restoring the abnormal activity in the sensory-motor network. As already summarized in section 4.1 of the present review, a single session of neuromodulation by using rTMS on the premotor cortex resulted in clinical improvements (Murase, et al., 2005). These promising results have led to a subsequent multiple-session study in focal hand dystonia. Twelve patients underwent five daily-sessions of 1 Hz rTMS to contralateral PMd (Kimberley, Borich, Arora, & Siebner, 2013). Patients 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**

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

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