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**Plasticity of Body Representations: an empirical and
theoretical contribution to the study of these functions.**

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Summary

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General Introduction

In recent years the study of *Body Representations* has interested experts from various disciplines. This interest, always present in the history of western thought, has lately gained greater importance thanks to both the current close examinations within the epistemological debate on the mind-body relationship and the emphasis put on the acknowledgment of corporeality by contemporary culture. Moreover, conception and development of the body representations constitute a research field of great interest to science because of their several theoretical, practical and clinical implications. With particular reference to the neurological area, well known are cases of patients with brain lesions who show a series of peculiar phenomena: the denial of body parts (somatoparaphrenia), the inability to distinguish right from left (right-left disorientation) and the unawareness of paralysis occurred to arms (emisomatoagnosia). In the psychiatric area we find situations in which patients are unable to have a correct perception of their body shape and weight or parts of it (anorexia nervosa, dysmorphophobia). Despite the lack of a comprehensive theoretical construct, over the years these disorders have been interpreted and treated by means of the most diverse approaches (pharmacological, psychodynamic, neurorehabilitative) depending on the reference

discipline. As a matter of fact, the expression “body representation” has embraced different meanings over time to such an extent that nowadays it can hardly be explained by one single definition. Depending on the theoretical frame it’s inscribed in and the discipline it refers to, different phrasings have been used to describe it, such as “body scheme” and “body image” (Head and Holmes, 1911).

The psychiatric point of view about the body scheme precedes the neurological one, but later it gets a development parallel to it and sometimes it intersects with it. These studies have largely focused on the bodily experience of neurotic patients or, in case of a more severe disease, schizophrenic patients. Schilder (1950) distinguishes four different groups of symptoms. One group includes the alteration of feeling oneself of the opposite sex or with parts of the opposite sex, for example half man and half woman. A second group of alterations refers to feelings of deterioration and disintegration of the body, such as destroyed internal body parts and parts of the body that are being destroyed by the attack of some external influence. In a third group there are patients who complain about their estrangement from their body, as if it belonged to another person. There is then a final category in which the patient has a feeling that things happening elsewhere actually happen to him, and he is not able to clearly delimit his body from that of

others. As inferred from these indications, it's about alterations of their bodily experience which often fall within a wide range of different symptoms. But the importance attributed to the body scheme from a psychiatric point of view is indicated by the attention with which psychiatrists observe this bodily experience in the patient. Schilder (1923) conceives the concept of body scheme as consciousness, knowledge, experience of our body, even considering it as the result of the synthesis of different sensory impressions, admitting the existence of a cortical device whose lesion causes its perturbations. Schilder (1935) believes that the body scheme is the result not only of the sensations (kinesthetic, tactile, etc..), but above all of the integration of these sensations with the existential and emotional experiences of the individual. In his view, the psychological and neurological sides are closely related. The theories on the body scheme elaborated by Schilder are generally still recognized as offering an interdisciplinary approach, which overcomes the Cartesian dichotomy between *res extensa* and *res cogitans* or soma-psyche dualism. Assisted by modern techniques of investigation, the important steps forward taken, aimed at the understanding of a mental faculty necessary to the performance of routine activities as well as implicated in the most complex neurological and psychiatric disorders, have allowed to better understand the

mechanisms at the base of the brain's ability to represent the body. Several studies (Serino and Haggard, 2009; de Vignemont, 2005) have highlighted how the representations of the body, play a functional role in the perception and/or action and start working through the sensory information coming from the whole body. They are basically proprioceptive and kinesthetic inputs, but also tactile, visual and auditory information. The final processing of these impulses is a unitary representation of ourselves, as an entity that has clear boundaries from the outside world and that we call body. In order to guarantee a higher terminological clarity, here by this expression I intend to indicate different abilities of our brain to represent the body in processing levels of increasing complexity. In fact, even without expressing either a specific cognitive function nor a precise anatomical substrate, the expression "body representation" is often used to indicate a large number of perceptual and motor functions which are interconnected and essential to the performance of diverse functions, that we can summarize as follows: a) perception and localization of somatic stimuli; b) actions programming; c) body awareness. In a recent review of the literature concerning this subject, Longo et al. (2010) have emphasized the polymorphic nature of the body representations thanks to a careful meta-analysis that gathers studies conducted with the assistance of the sense of

touch. The choice of using the sense of touch as preferential access channel to study such representations has different reasons. The main one, in my opinion, is that the skin, which is the organ covering the entire body surface, is provided with different types of receptors able to turn any external object into a nerve impulse. Therefore, more than any other channel, the skin is that wrapping which delimits, protects and provides the basis for the construction of the body representations. Contextually the touch, playing a key role in the development of beliefs about both the external world and the reality of our body, represents the sensory channel more faithful to study this function. What is touched holds the true character of reality, which diverts from hallucinations and deceptions of vision. In fact, the sense of touch gives information about the object that gets in contact with the skin through the information about the body itself. There are, indeed, studies showing that tactile afferents and the body representation affect each other (see Longo et al. 2010 for a review). In particular, Serino and Haggard (2009) in an interesting review present a model that explains:

1) how the contributions of the primary somatosensory areas combine to the definition of the body representation, 2) how the body representation itself influences the processing of tactile stimuli in the somatosensory

cortex through feedback mechanisms 3) how the body representations mediate the tactile perception of the objects (see Figure 1).

Figure 1.

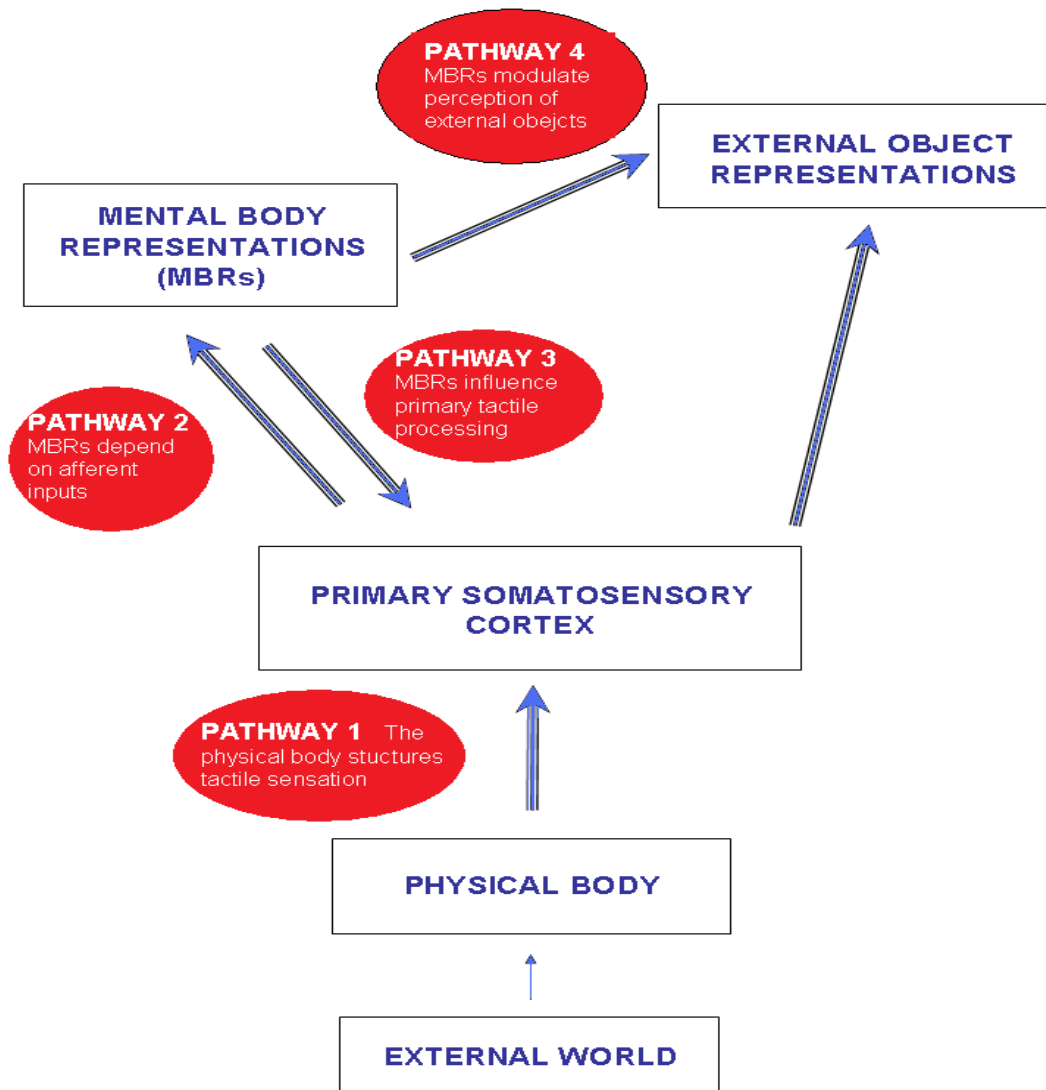


Figure 1. A model of mental body representations processing (from Serino & Haggard, 2009).

These studies show that both primary somatosensory processes and higher order cognitive processes contribute to the definition of our experience of the body and of the external world. In such a context Longo et al. (2010) identify and classify three levels of processing which are closely interdependent but separable from each other. The first level corresponds to elementary mechanisms of somatosensation mainly determined by the peripheral receptors and anatomically represented by primary somatosensory areas (S-I) and secondary somatosensory areas (S-II). Unfortunately, these sole areas are not enough to a consistent and realistic phenomenological definition, since they are affected by distortions already observed by Weber in 1877. In the matter in question, the phenomenon known as "illusion of Weber" refers to the different perception of the intensity of a tactile stimulus depending on the skin's density of innervation. This physiological misrepresentation is corrected by a superior level of processing called somatoperception, that is a reference scheme which allows the scaling of the tactile input according to the physical characteristics of our body. By this word (somatoperception), the authors refer to processes that let us detect size and posture of the body in real time and perceive characteristics of external objects (shape, size, localization, etc.) passed unnoticed to the first level of processing. The third level consists in the

somatorepresentation, a mental representation delegated to the general encyclopedic knowledge and our body awareness, to the knowledge of the body structural configuration and the workings of its parts (see Table 1).

Table 1.

	Functions	Neural bases
Somatosensation	Primary sensory processing of somatic stimuli	Primary somatosensory cortices (Kaas, 1983; Mountcastle, 2005)
Somatoperception		
Superficial schema	Localisation of somatic stimuli on the body surface	Parietal lobes (Denny-Brown et al., 1952), esp. anterior parietal/TPJ (Porro et al., 2007; Van Boven et al., 2005)
Postural schema	Perceiving the current posture of the body	Superior parietal (Pellijeff et al., 2006; Wolpert et al., 1998), and lateral intraparietal (LIP; Fasold et al., 2008; Snyder et al., 1998), esp. in right hemisphere (Sterzi et al., 1993)
Model of body size and shape	Perceiving metric properties of tactile stimuli	Unknown, presumably parietal lobes
Conscious body image	Construction and maintenance of sense of self, self-recognition	PPC (Bisiach et al., 1986; Salanova et al., 1995), esp. in right hemisphere (Critchley, 1953)
Emotion-in-body	Affective processing of and responses to somatic stimuli	Anterior insula (Olausson et al., 2002; Schreckenberger et al., 2005)
Somatorepresentation		
General/encyclopaedic knowledge about bodies	General semantic knowledge	Unknown, likely diffuse
Lexical-semantic knowledge about bodies	Naming and communication	Left hemisphere, esp. inferior parietal (Kemmerer & Tranel, 2008; Laiacona et al., 2006; Suzuki et al., 1997), anterior temporal (Dennis, 1976), and inferior frontal (Kemmerer & Tranel, 2008) cortices
Structural/topological knowledge of one's own body	Semantic knowledge about arrangement of body parts	Left hemisphere, esp. superior parietal cortex (Felician et al., 2004), intraparietal sulcus (Corradi-Dell'Acqua et al., 2008), left temporal lobe (Schwoebel & Coslett, 2005)
Emotion-about-body	Formation of attitudes towards the body	Right hemisphere (Loetscher et al., 2006), esp. parietal and frontal lobes (Blanke et al., in press; Critchley, 1953)

Table 1. Major components of somatoperception and somatorepresentation, describing their basic functions and neural bases (from Longo et al. 2010).

As a result of what said until now, it will be clear that, in order to follow the body's physiological evolution (growth) and pathological evolution (amputations, transplants), the body representations must necessarily be constantly changing, self-building and self-destroying through continuous differentiations and integrations, in order to ensure a realistic

representation of the body. In fact these representations are not static, but can be modified using mechanisms of neuroplasticity. *Neuroplasticity* is the ability of the central nervous system to adjust to structural and functional changes in response to physiological events, environmental stimuli (learning, for instance), and pathological events (phenomena of neuroplasticity are one of the mechanisms at the base of the spontaneous recovery for patients with lesions of the CNS). Of great interest and charm are the laboratory researches performed to prove the existence of reorganization and reworking processes in the central nervous system. The first works, dating back to early 80s, were about studies on animals and they mostly used the method of sensory deprivation (Merzenich et al., 1983a, 1983b, 1984) . Only later researchers have undertaken the study of such phenomena in humans, by means of two opposite methods: the increase of information given to certain nerve centers, for example during the acquisition of specific skills, and, as in animals, the reduction of inputs caused by sensory deprivation. Such studies are nowadays facilitated by the introduction of functional neuroanatomy techniques (such as positron emission tomography –PET–, functional magnetic resonance imaging –fMRI– and magnetoencephalography –MEG–), that let us observe the changes of cortical representations.

Studies on Plasticity

In support of this treatise, I will highlight studies on plasticity conducted after traumatic events and natural events with particular reference to the rearrangements occurring in the somatosensory areas (for a detailed discussion on this matter, see Recanzone et al., 1992; Jenkis et al., 1990; Elbert et al. , 1995).

Figure 2.

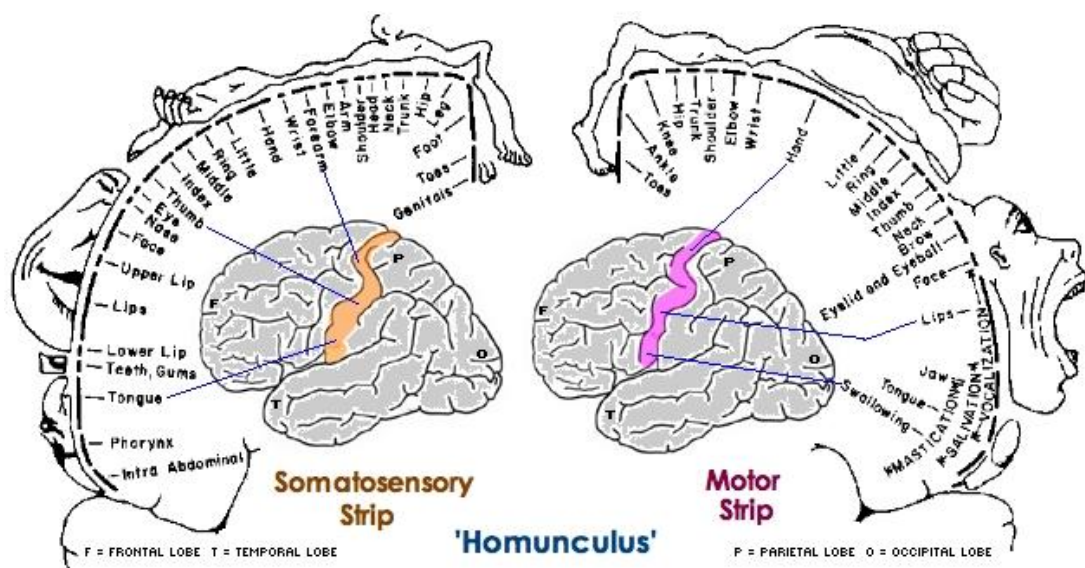


Figure 2. Schematic representation of homunculus.

The reason of this choice is that, since Wilder Penfield drew the boundaries of the cortical areas corresponding to the sensory territories

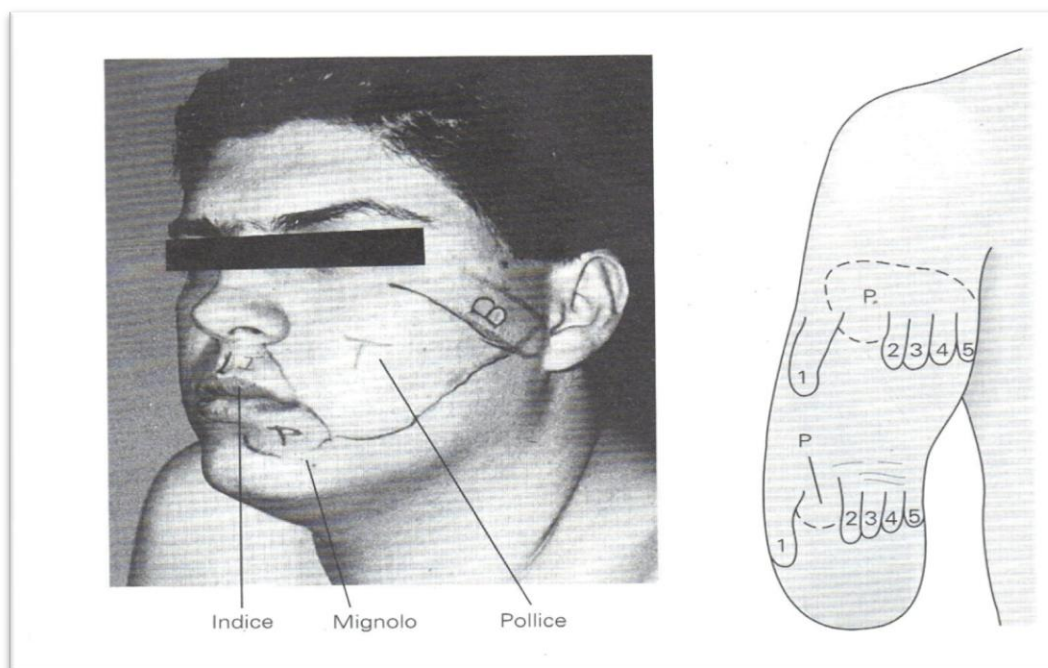
(sensory homunculus) and motor territories (motor homunculus) of the whole body by stimulating with electrodes the cerebral cortex of awake patients without skull vault (Flor, 2008), researchers have questioned the possibility of adapting such topography to normal and pathological changes occurring in the life of an individual (see Figure 2).

An exciting research, which shows how the representation of the different parts of the body depends on their use and experience of the individual, is that conducted by Thomas Elbert and colleagues (1995). These researchers examined a group of violinists and players of stringed instruments, on the assumption that playing these instruments the two hands are differently used and could, therefore, give differentiated inputs to the central nervous system. The fingers of the left hand, with the exception of the thumb, are indeed continuously involved in the control of individual strings, a task that requires considerable manual skill and that causes an important sensory stimulation. The thumb of the same hand is instead leant on the back of the instrument and slides along the handle, undergoing various degrees of pressure. Finally, the right hand holding the bow performs a task which is not different for each single finger, but overall, with variations of lower tactile and pressure stimulations. All this should cause a different cortical representation of these body parts. So, the researchers went to stimulate the first and fifth

finger of both hands of nine musicians and other subjects, non-musicians, which served as control group, recording the areas of cortical representation. As expected, the response on the fifth finger of the left hand of the musicians was significantly wider and more intense than that of the first finger and much higher than the projection areas of the right hand. Conversely, no significant difference emerged between the right hand of the group of musicians and that of the control group. Another interesting result is the correlation that the authors found between the age of onset of musical practice with the instrument and the extent of the areas of representation in the cortex, indicating that the more early the subjects had started to play, the more evident was this phenomenon. Other studies on musicians have shown that the modifications of the neuronal responses don't pertain only to the somatosensory cortex, but also to the auditory one (Pantev et al., 2001). Many of the contributions to the understanding of the mechanisms involved in neuroplasticity come from studies on patients with amputated limbs. These people keep on having intense perceptions of the missing limb; a phenomenon that has been called *phantom limb syndrome*. They feel the presence of the absent body part, they feel it moving and even have excruciating pain. Experiments about the display of the somatosensory cortex, led by Vilayanur Ramachandran (1992) on patients who had been amputated an

hand, suggest that these feelings are due to a reorganization of cortical circuits. The afferent passages, adjacent to the area which is usually occupied by afferents from the hand, expand into the area of this latter one. What we see is that the cortical area, that before the amputation was occupied by the representation of the hand, instead receives inputs from at least another cutaneous region. has called this phenomenon *remapping of referred sensations*.

Figure 3. From Ramachandran, 1992.



These referred sensations are not distributed randomly on the body. Some patients have two centers of sensations referred to the amputated hand, one on the face and the other one in the upper limb. This condition occurs because the afferents from the face and the upper limb, which are normally located next to those coming from the hand, end up occupying the cortical territory previously occupied by these latter ones. Normally, the phantom limb sensation is most felt after amputations of the arm or leg, but there are cases describing the same effect about other body areas (Scholtz, 1993; Aglioti et al., 1994, Hoffman, 1955; Sacks, 1992). Experiments carried out on animals have enabled a closer investigation about these events and have shed light on the neural mechanisms of plasticity. For a long time Merzenich et al. (1984), have studied the effects of amputation on the topographic representations of the areas 1 and 3b in monkeys (corresponding to S-I in humans). Two months after the amputation of the finger, most of the cortical area, previously mapping the amputated part, responds to inputs from adjacent body parts and not from topographically distant parts. The last decade has witnessed an increase of medical knowledge in the surgical field, which have enabled the development of techniques that make possible the transplant of missing body parts. Recently, the executive field has been expanded to the hand transplant, obviously from corpses, which has met

very skilled surgeons in our country too. It is undoubtedly a practice of extraordinary technical ability considering the many and delicate connections to be restored, especially among muscles and (above all) nerves, in order to give back to the transplanted hand acceptable functionality. These surgical techniques are based on the principle of regeneration property of the peripheral nerves. Fundamental have been the pioneering studies of Head and River (1908), who monitored the recovery of sensitivity after nerve transection and reunification on the same arm of Head. These authors have described two distinct phases of return to sensitivity: in the first phase the sensations are confused without clear tactile discrimination and localization skills; while in the second phase of the regeneration process there is a return to the characteristics of normal skin sensation. The progressive nerve regeneration is directly proportional to the recovery of tactile sensitivity, even though it does not return to the status previous to the surgery. This basic mechanism works in cases of transplantation too. An extraordinary demonstration is given by the case of the patient CD, who was subjected to bilateral transplantation of the hands (Giroux et al., 2001). The patient was tested in tactile discrimination tasks on the hands 5 and 11 months after surgery. Initially C.D. was able to perceive tactile stimuli on his hands, but the stimulation of the limb was vain if at the same time the

ipsilateral cheek was stimulated too. This is due to the attempt of the afferent inputs from the hands to get again possession of the areas that originally mapped these latter ones at the expense of the face's areas, which have expanded to the cortical territories of the hands after the amputation. This competition between the representation areas of the hands and those of the face has completely disappeared 11 months after the graft. This suggests that the inputs coming from the transplanted hands have guided the reorganization of the somatosensory cortical representations. In support of this exposition, it seems appropriate, if not due, to refer to the mechanisms of brain plasticity produced by the limb lengthening surgery. A recent surgical technique, called *Ilizarov method*, allows to progressively increase the limbs length of achondroplasia patients in few months (for a detailed description, see experiment 1), enabling so the possibility to observe the resulting cortical changes. In a recent study, Di Russo et al. (2006) have examined the cortical and perceptual reorganization as a result of the lower limbs lengthening in two patients. Three sessions of tests have been run: before surgery, after surgery and a follow-up 6 months after the surgery. By means of fMRI scans and the use of somatosensory evoked potentials (SEP) during the tactile stimulation of knee and foot, changes on the cortex in S-I have been detected. In this case, the cortical representation

of the foot is extended and moved medially, so allowing the lengthened leg to be adequately represented (see Figure 4). This process shows how even the areas adjacent to the lengthened limb mobilize after the new somatotopic organization of this latter one.

Figure 4.

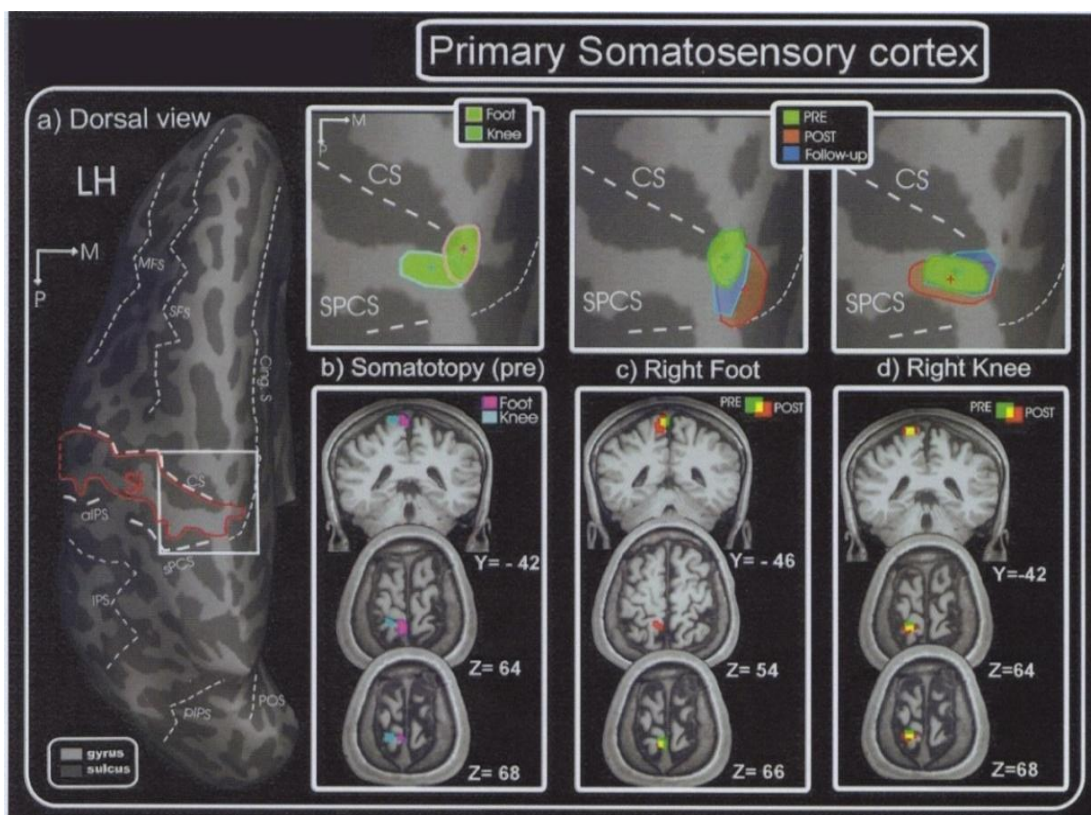


Figure 4. fMRI data of primary somatosensory cortex in the pre-surgery, post-surgery and follow-up sessions (from Di Russo et al., 2006).

The same study provides evidence of the fact that the change of information about the body, such as the change of the afferent tactile

inputs, provokes a change in the body representation. In this case, through the test of the body schema (Daurat-Hmljeak, 1978), they noticed that during the plastic reorganization in S-I the patients' performance worsened after the surgery and the 6 months follow-up. It indicates that the changes in the primary sensory areas affect the plasticity of the body representations through projections to the parietal lobe (involved in various processing of information about the body).

Anatomical basis of the Body Representations

As previously stated, the expression *body representations* does not refer to a single anatomical structure assigned to the fulfillment of this function. On the contrary, depending on the kind of body-related information to be processed, different cortical networks seem to be implicated. In recent years, driven by the need to better understand the cerebral organization of the body representations, scientists from different disciplines have contributed to an improved knowledge of the neural basis involved in this function. Far from offering an exhaustive understanding, the results have anyway contributed to the creation of

cognitive models of operation necessary for diagnosis and treatment of the numerous disorders involving the body representations. Below I'll report researches conducted on human beings that have identified the cortical areas underlying the various forms of body representations, but I will mention first studies conducted on animals. Thanks to these studies, and to the analogy between the human brain and that of monkeys, it's been possible to understand mechanisms that can hardly be put in evidence without the use of invasive methods of research. Functions similar to the body representations in humans have been identified in cortical structures (premotor and parietal areas) and subcortical structures (putamen) of the macaque's brain. The macaque's putamen contains neurons which respond to somatosensory stimuli, such as light touch, joint movement, or deep muscle pressure. The receptive fields of this area are arranged to form a map of the body. Some neurons in this area are bimodal and respond to both visual and somatosensory stimuli. These bimodal properties provide a map of the visual space immediately surrounding the monkey. The map is organized somatotopically, rather than retinotopically as happens in most of the visual areas. The cortical areas 6 (ventral premotor area, PMv), 7b and ventral intraparietal (VIP) contain multimodal cells with properties very similar to those of the putamen and respond to tactile, visual and auditory stimuli (Graziano et.

al, 1997, 1999). In particular, the PMv contains a somatotopic representation of arm, head, face and mouth (Gentilucci et al., 1988), while the VIP area responds to tactile stimulations on the face and nearby or to visual stimuli only at a few centimeters distance from the tactile receptive fields (Colby et al., 1993). These different properties of the neurons work together so that space and movements close to the body are correctly processed and their discharge increases in the proximity of stimuli closest to the body. Several experiments conducted on monkeys show that the information coded from these areas are related to body parts such as arm, head, etc., and this suggests that the bimodal cells in area 6, 7b, VIP, and putamen are part of an interconnected system that represents the extrapersonal space in a somatotopic way (Fogassi et al., 1996). A basic function of the motor system of all animals is to protect the body from attacks or collisions (King et al., 1992; Yeomans et al., 2002). Experiments show that the electrical stimulation of two closely interconnected cortical areas, VIP and the polysensory zone (PZ) located in the precentral gyrus, evokes a specific set of movements. These movements correspond to those typically used to defend the body from objects that are close to or touch the skin (Cooke et al., 2003; Dearworth and Gamlin 2002; Graziano et al. 2002; Thier and Andersen, 1998). Studies conducted on humans are as well

fascinating, though they use less invasive techniques of investigation. Below I will report an overview of the main contributions had in recent years. As regards somatoperception the computation of the localization of tactile stimuli on the body and their form is processed by distinct networks, as shown by the fMRI study by Van Boven et al. (2005). fMRI data, concerning the tactile perception of the shape (measured through the "Gratings Orientation Task"), show an activation lateralized to the left intraparietal sulcus in the somatosensory system. Regarding the localization, (measured through the "Gratings Location Task), the authors report instead different observations in relation to the egocentric or allocentric space. In the allocentric space the localization of objects requires a bilateral processing by the parietal and dorsal areas. The position of objects that instead get in contact with skin (egocentric space) concerns right dominant regions on the level of the temporal-parietal junction. In the same way, a recent fMRI study (Spitoni et al., 2010) shows two different types of activation in response to the same tactile stimulation in two different tasks, a task of tactile distances judgment and a task of intensity judgment. Using the same set of stimuli, consisting of pairs of nylon filaments of variable distance, the authors invited the participants to report which was the greater distance produced by two pairs of stimuli or asked them to make judgments about the

intensity of the same stimulation. fMRI data show that both tasks activate bilaterally the parietal and frontal areas. Instead, they show a selective activation of the angular gyrus and of the right temporo-parieto-occipital junction in response to the sole task of distance judgments. The reason for this additional activation is due to the fact that, in order to discriminate tactile distances, it's necessary to refer to a metric model of our own body according to which we compute the actual dimensions of the objects it comes into contact with. Collectively, these studies reinforce the hypothesis according to which, depending on the type of body-related information to be processed in the somatoperceptive level, distinct areas are involved (see table 1). It's well known in literature that there are cortical regions of the human brain which respond in a selective way to the visual appearance of various objects, such as tools, homes, places, animals, faces and so on. Similarly, recent researches have identified the neural basis of the identification of the body or parts of it. In an fMRI study, Downing et al. (2001) have found that the lateral occipito-temporal region of the right side gives a significantly stronger response when the subjects imagine human bodies and/or body parts than when they see inanimate objects or faces or parts of the face. These authors have named this area *Extrastriate Body Area* (EBA), which in subsequent experiments has confirmed its activation

selectivity for the body parts, except the faces. The evidence of a specialization of the EBA in the identification of the body or parts of it are strongly supported by studies in which the functional interference with the neural activity in EBA, through rTMS, hinders the visual processing of images of the human body but not of images not related to the body (Ugesi et al., 2004). Similarly, studies on patients with cortical lesions have let detect that the whole semantic-lexical knowledge about the body, belonging to the domain of the somatrepresentation, is delegated to distinct brain areas. A study by Kemmerer et al. (2008) has examined 104 patients with brain injuries by means of a set of 12 tests able to analyze lexical and semantic aspects. The neuropsychological data of this study highlight that, out of a total of 104 patients with left or right focal lesion, 10 patients showed an impairment of the ability to name (naming) relative only to body parts. In particular, 9 of these patients had a damage on the left hemisphere and 8 of these ones showed a condition of overlap between the lesion of the frontal opercular cortex and that of the frontal/inferior parietal opercular cortex. The remaining patient (of the above 10) showed, instead, an occipital lesion that concerned the EBA. Besides, 4 out of 9 patients with the left hemisphere damaged had a worse performance in the task of naming body parts than in the task of naming other categories of concrete entities like objects.

Anyway, the more surprising and worthy of note observation is probably referable to the fact that no patient with body parts anomia revealed any difficulty in understanding the meaning of words and terms related to the same body parts (for which they presented anomia). The insula also seems to be closely involved in neurological disorders such as anosognosia for hemiplegia, the sense of body ownership and the out-of-body experience (OBE). The anosognosia for hemiplegia (Spinnazzola et al., 2008), is characterized by the patients' unawareness of the paralysis of one side of their body. The right posterior insula is often damaged in hemiplegic patients with left anosognosia for hemiplegia, but it is generally spared in similar patients without anosognosia. There are cases in which this neurological condition is worsened by a complete sense of no ownership of the paralyzed half of the body (Aglioti et al., 1997), or by a constant belief that these body parts belong to other people (Vallar and Ronchi, 2009). In order to identify the neural bases involved in these disorders, Baier and Karnath (2008) have compared, by means of MRI, the lesions of anosognosic patients for hemiplegia with and without bodily disownership. The results show an involvement of the posterior insula of the right side which was damaged only in those patients with sense of no ownership of the paralyzed half of the body. Neuropsychological studies indicate that lesions of the left parietal lobe

are implicated in the autotopagnosia, a typical alteration of body awareness because of which patients are not able to verbally indicate their body parts while being able to successfully give verbal commands about everything unrelated to the body. It frequently happens that these patients have difficulty in describing the spatial relationships between body parts (e.g. reporting that the mouth is located between eyes and nose). The lesions associated with the autotopagnosia typically involve the posterior parietal lobe of the left side, and fMRI studies on normal subjects indicate the angular gyrus and the intraparietal sulcus as critical areas for the processing of information about body parts and their interconnections (Corradi-Dell'Acqua et al., 2008).

Transcranial Electrical Stimulation (tDCS)

In addition to imaging techniques, in recent years the study of brain function has been facilitated by the wide dissemination of transcranial electrical stimulation techniques (tDCS, TACS) or magnetic (TMS, rTMS), with which we can interact with the cortical functions. In particular, the direct current transcranial stimulation (tDCS) is a non-

invasive technique that enables the polarization of the cerebral cortex by stimulation with direct current (see Figure 5). Studies conducted on animals (Bindman et al., 1964; Purpura e McMurtry, 1965; Artola et al., 1990) and humans (Nitsche e Paulus, 2000) have showed that the positive polarization (anodic stimulation) increases the excitability of the cerebral cortex, increasing the frequency of spontaneous neuronal discharge and the amplitude of evoked potentials, while the negative polarization (cathodic stimulation) reduces its excitability.

Figure 5.



Figure 5. tDCS set up.

The tDCS doesn't seem to directly induce a substantial neuronal depolarization, but rather modulate the activation of the channels of voltage-gated sodium and calcium and NMDA receptors. Several studies (Brown et al., 1989; Lynch et al., 1984) show a clear involvement of NMDA receptors in the long-term potentiation through the use of medications (AP5) able to block the activity of these receptors. The long-term potentiation (LTP) and long-term depression (LTD) of the synaptic activity have therefore been proposed to explain the effects of tDCS (Hattori et al., 1990; Moriwaki, 1991; Islam et al., 1995; Malenka and Nicoll, 1999). The possibility to cause temporary effects on brain functions through the induction of neuroplasticity phenomena has led to the birth of studies on humans that have considered the possibility of inducing cognitive changes by tDCS. These studies have mainly made use of the stimulation of the visual cortex (Antal et al., 2003, 2004), parietal cortex (Matsunaga et al., 2004; Schweid et al., 2008; Sparing et al., 2009, Stone et al. 2009) and prefrontal cortex (Kincses et al., 2004, Dockery et al., 2009; Merzagora et al., 2009; Fertonani et al., 2009). Nitsche and colleagues (2003) have also highlighted a facilitation of the implicit motor learning after stimulation of M1. Similarly to what happened in recent years about the repetitive magnetic stimulation, tDCS is also subject of numerous studies aimed at evaluating its therapeutic

potential in neurological and psychiatric pathologies (Fregni and Pascual-Leone, 2007). Although to this day a smaller number of clinical studies has been carried out on tDCS compared to that on rTMS, a point in favor of tDCS is represented by its lower cost and greater ease of administration. Combined with the traditional neurorehabilitation techniques, the tDCS seems to have enormous potential in the recovery from disability consequent to the damage of the central nervous system. Finally, in neuroscience area the use of this technique offers the possibility to investigate the cognitive functions and the involved respective cortical networks in complete safety and with absolutely unimportant side effects.

Introduction to the studies

In this work I'll report two studies from our laboratory, united by the idea that it is possible to investigate cortical plasticity through the study of a cognitive function which is plastic by definition. In fact, in order to adapt to physical changes of the body, so as to guarantee a constant integrity of our Self, the body representations integrate information coming from different sensory sources, including touch, in a constant way. In other studies the sense of touch has proved to be a faithful indicator of the mechanisms of reorganization of the body representations, and therefore it's been used in the first experiment as indicator of such changes. In particular, we've used a tactile discrimination task of distances, which has enabled to measure the metric representation of body parts both in a patient with achondroplasia (Experiment 1). Specifically, in the first study we treat by the methods of psychophysics the reorganization of the somatosensory system resulting from a surgical lengthening of the limbs. This surgical technique allows to observe in a relatively short time the consequences that a limb lengthening has on the ability to discriminate tactile stimuli. At the same time, the need to provide a methodological contribution to the use of an equipment with such an amazing potential has prompted us

to carry out an investigation on the effects of the direct current flow (Experiment 2). Specifically, we've investigated the modulation of the alpha rhythm in normal subjects by EEG recordings in rest state. The recordings have been made after anodic and cathodic stimulation on the right parietal area in order to highlight effects, diffusion and duration of the stimulation according to certain parameters of stimulation.

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EXPERIMENTAL PROJECT

Experiment 1: Plasticity of body representations after surgical arm elongation in an achondroplastic patient.

Abstract

Purpose: A realistic body representation needs to be constantly updated. In case of physiological modifications, body representations integrate information coming from different sensory sources, including the sense of touch. Previous studies described transient modifications of these representations following illusory distortions. In this single case study, we documented the changes occurred in lower-level, primary somatosensory, and higher-level representations, in a case of upper arms elongation.

Method: We explored effects of arm lengthening on primary tactile perception (sensitivity and acuity), an implicit perceptual measure of body size (tactile distance judgement), body image (Daurat-Hmelijak test), and peri-personal space representation (audio-tactile interaction task).

Results: We show that patient's arm representation was changed after surgery. Specifically, we observed significant changes on tactile distance judgments, body image test and audio-tactile interaction task; also even though no changes were found on primary tactile perception a significant modification emerged in tactile acuity.

Conclusions: These findings are in line with evidence of cortical reorganization after arm elongation. They also support the view that the body representation of achondroplasics are modified after body-size reconstruction, and became similar to that of healthy controls.

1. Introduction

Several lines of research with healthy volunteers and neuropsychological patients suggest that the brain maintains a range of representations of the body. While several different models and classifications have been proposed (Schwoebel and Coslett, 2005), all agree on a broadly hierarchical arrangement. Lower-level representations are concerned essentially with the location of somatic stimuli (e.g., touch) on the body, while higher-level representations are concerned with the more global configuration of the body as a physical object, spatial relations between body parts, and identity and naming of body parts. Identifying these different body representations in experiments with healthy volunteers is difficult, since any specific body-related stimulus used in testing will be processed by many or all of these representations. In contrast, neuropsychological studies of lesion patients have made important contributions to fractionating these different representations. For example, individual patients may show isolated deficits in peripersonal space representation (Làdavas and Serino, 2008), spatial configuration of body parts (Gerstmann, 1940, 1957), or in semantics of body parts (Semenza, 1988; Sirigu et al., 1991). However, inferences from patients are subject to both general and specific difficulties. First, there is a

general difficulty in inferring normal brain organisation from cases of brain damage, because of non-focal damage, and possible compensatory adjustments (Basso et al., 1989; Levine and Mohr, 1979). Second, many lesions of parietal areas thought to house higher-order body representations also affect the postcentral areas that house low-level somatosensory function. Therefore, damage to high-level functions with intact low-level body representation is rare. Nevertheless, the causal nature of inference in lesion cases means that neuropsychological studies of body representation have had enduring influence. On the other hand, studies on healthy subjects have demonstrated that cortical body representations are not fixed entities, but are dynamic and continuously modified by experience. Most of these studies used tactile stimulation to measure body representations, and multisensory stimulation to illusorily manipulate them. For instance, in the so-called Pinocchio illusion (Lackner, 1988), a tendon vibration in the arm produces proprioceptive misinformation about its position and subsequent perceptual distortions regarding the size of the nose. Distorting the visual experience of one's own arm alters the perception of tactile distances on the arm (Taylor-Clarke et al., 2004); similarly, tactile distance perception on the finger is modified by vibration of the biceps and triceps, which induces an illusion of lengthening or shortening the index finger (de Vignemont et

al., 2005). These findings suggest that the brain computes several sources of information (i.e. tactile, visual, proprioceptive) to scale information about skin contact in relationship to the perceived size of the body part tactilely stimulated. However, most previous experimental studies of body representation have been based on very brief illusory distortions in healthy volunteers, often lasting for a few minutes or less (de Vignemont et al., 2005).

1.1. The case of physical body elongation

In the present study, we aimed at overcoming the limitations of neuropsychological studies on brain damaged patients and of psychophysical studies on healthy volunteers by studying a new model of plasticity in an achondroplastic patient, MM, who underwent to a gradual, long lasting modification of her body, i.e. surgery with the Ilizarov technique (Ilizarov and Deviatov, 1971; Cattaneo et al., 1988) to increase the length of her upper limbs (see Figure 1).

FIGURE 1

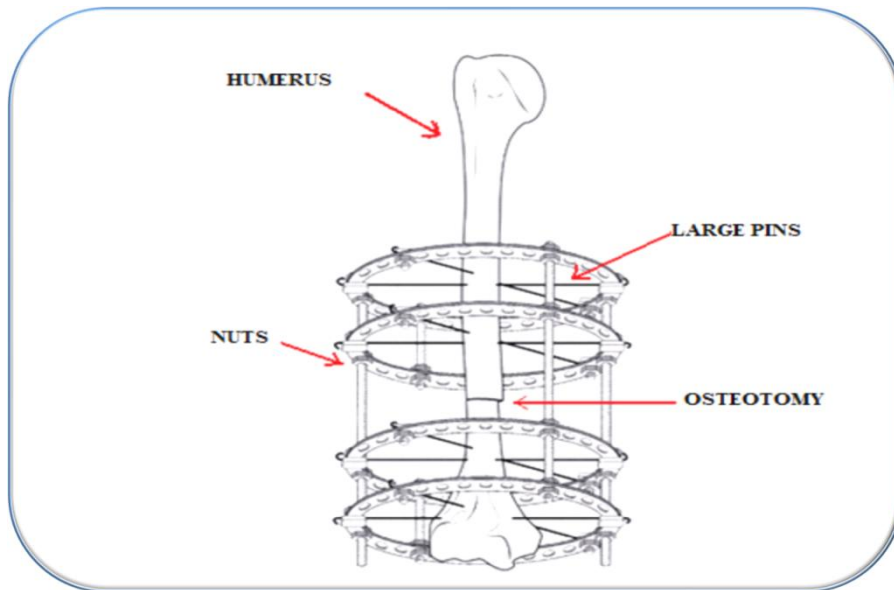


Figure 1. Schematic representation of the Ilizarov bone-lengthening device. The cortex of the bone is partially cut, leaving the medulla intact; an external steel cage, fixed on the bones (fixation), progressively separates the two bone segments by about 1 mm a day. This progressive elongation prevents the formation of a callus and the physiological reconnection of the two parts of the bone. When the desired length is reached, the callus is allowed to solidify; the steel cage is removed only when the cortical structure of the two parts of the bone is consolidated.

This procedure induces surgical lengthening of the arm, but leaves the afferent and efferent connections between the arm and the somatosensory cortices intact and the patients had no brain lesions. The technique also provides an ideal model for studying brain plasticity following a real, not illusory manipulation of the physical body structure. We investigated how surgery affected the representation of the elongated body part at several levels of tactile stimulus processing, that is, from

primary somatosensation to higher levels of body representation. Based on previous findings (Di Russo et al., 2006), we subjected MM to a battery of somatosensory and body representation tests immediately before the surgical elongation procedure (pre), at the end of the procedure (post, i.e. five months after the first evaluation, following removal of the elongation cage), and in a follow-up session performed six months later (follow-up). Low-level tactile perception was investigated using classical tests of detection and acuity (Von Frey's test and the two point discrimination task (2PDT)). Then to investigate how the brain computes intrinsic object properties from preliminary contact information, we used a distance discrimination task (DDt) for pairs of stimuli administered on the arm and on the neck as a reference site. This provided information about the metric representation of body parts. A pressure discrimination task (PDt) was used as a non-spatial control task. Besides processing sensory input from skin stimulation, the DDt also involves spatial computation of the position of incident points on the skin surface and the absolute length of the stimulated body part. We also investigated whether surgical elongation also affected the perceived configuration of the body as assessed by a more explicit visual task, specifically, the Daurat-Hmeljiak task (DH) (Daurat-Hmeljiak et al., 1978). During the DH task, the patient was presented with individual

tiles, each depicting a single body part (nine tiles: right/left leg–arm–hand–hemithorax and the neck), and was asked to put each tile in the appropriate position on an empty board on which only the contour of a face was drawn to reproduce the shape of a standard body. The rationale of the task is that subjects refer to their own body representation to reproduce the shape of a human-like body.

1.2. Changes in the peripersonal space

Finally, we tested whether changes in the representation of the body also influence the representation of peripersonal space (PPS). PPS is the limited portion of space where we can physically interact with external objects, reachable by our upper limb. In order to represent PPS, our brain integrates information related to the position and size of the different body parts with information related to the location, size and movement of objects in space. Proprioceptive and tactile information related to the body are integrated with visual or acoustic information of the external objects present within the boundaries of peripersonal space (Rizzolatti et al., 1997, Graziano and Cooke, 2006, Làdavas and Serino, 2008). As these boundaries are usually defined by the physical dimensions of the

body (Longo and Lourenco, 2007), PPS representation is likely affected by a change in the size of the physical body, and provides a valuable, implicit, and action-oriented test of body representation. We therefore investigated whether surgery for upper limb elongation affects the boundaries of PPS. For this purpose, before and after surgery MM performed an audio-tactile interaction task that probed the extent of PPS around the upper limb.

1.3. The timing of perceptual changes after surgery

Overall, her performance on the sets of experiments showed that soon after surgery MM's arm perception was impaired with respect to that of age-matched healthy controls. Nevertheless, her performance significantly improved six months after the operation, approaching that of controls. This evidence supports the findings of a previous study on cortical reorganization after arm elongation (Di Russo et al., 2006); it also supports the view that achondroplastics' pre-existing body representation can be modified and become similar to that of healthy controls after modification of body size.

2. Materials and Method

We studied how progressive limb elongation affects tactile perception, body and PPS representation in an achondroplastic woman who underwent surgical arm lengthening. At the time of the surgery, patient MM was 29 years old and her arm length was about 10 cm. At the age of 18, thus 11 years before the present testing, she underwent surgical leg elongation (13 cm) and reached a height of 150 cm. In the present study, MM was tested three times: before surgery (pre test), soon after the cages were removed (post test) and about one year after the surgery (follow-up). The control group included 26 age-matched participants (mean age 28, SD ± 1.15 ; 15 female), all of them received tactile acuity assessment and DDt. Among them 20 subjects (mean age 29, SD ± 1.08) also received PDt task and DH. Due to technical problems four DH protocols were excluded from the analysis. Finally the control group for the PPS task consisted in seven participants (mean age 28, DS ± 1.83 , 5 female). None of the participants had neurological or psychiatric diseases. The control group was tested twice, with a five-month interval between the first and the second evaluation. MM and healthy controls resulted strongly right-handed as measured by Edinburgh handedness inventory (EHI) (Oldfield, 1971). Each participant underwent five

experimental assessments. In line with the ethical standards laid down in the 1964 Declaration of Helsinki, this study was approved the ethical committee of the IRCCS Fondazione Santa Lucia of Rome. All participants provided written informed consent prior to their inclusion in the study. Patient MM was recruited from the Manzoni Hospital in Lecco (Italy).

2.1. Primary tactile tasks

Tactile acuity was measured using Von Frey's test and the two point discrimination task (2PD). Von Frey's test is a classic measure of sensitivity to tactile pressure used for diagnosis or research (North Coast Medical, Inc., Morgan Hill, CA, USA). In this test, the tip of a fibre of a given weight (from 0.008 to 300 grams) is pressed against the skin at right angles. The force of application increases as long as the researcher continues to advance the probe, until the fibre bends. In this study, the procedure was repeated using different-weight fibres in both an ascending and a descending staircase. At each level of the staircase, 10 actual stimulation and 5 catch trials (a total of 15 stimulation) were presented. In each trial, the experimenter asked the participants whether

they felt the stimulus, and they had to respond verbally. The threshold was established at the staircase level when the subjects reported 6 out of 10 stimuli correctly. Two-point discrimination thresholds were estimated by using an adjustable aesthesiometer (Med Core, St. Louis, MO, USA) with two spatially separated tips. Stimuli were manually delivered to the ventral skin of the arm just above the elbow, with the two stimuli points oriented vertically. Participants were blindfolded and were requested to discriminate between single and double taps and to respond verbally. In this procedure, double or single taps were given randomly. Only double taps were used to calculate the threshold. The separation between the two starting points were 1 and 5 cm in the ascending and descending mode, respectively. The separation was then reduced progressively by 1 cm after each correct response. When an error was made, the separation was subsequently increased by 1 cm. The participants' threshold was derived from the minimum distance perceived between the two points five times consecutively.

2.2. Distance discrimination task

Stimuli consisted of two simultaneous contacts from a line of four miniature solenoids connected to a device (MSTC3-M&E Solve, UK).

The stimuli were fixed with malleable material and placed on the right humerus and neck. Stimuli administration was controlled by an electronic interface (NI-DAQ, 6800) connected to the computer and driven by a custom-made code written in Lab-View (7.0). Two blocks of 108 trials were administered; in half of the trials, tactile distances were the same on the arm and the neck; in the other half, stimuli were more widely delivered on either the arm or the neck, with equal probability. To make the distance perceivable, we set the stimulators so that adjacent solenoids were separated 5 mm more than the subjective 2PD threshold; the same distance was used to place the solenoid on the neck (see Figure 2). With this arrangement, three different distances could be compared between the stimulated body parts. Stimuli were always delivered first on the right arm and then (after 250msec) on the neck. Subjects were then asked to verbally judge which of the two tactile distances they perceived as greater. The experimenter manually entered the response in the computer. Subjects received no feedback during the task.

FIGURE 2



Figure 2. Solenoid displacement. Subjects judged whether the distance between the active solenoids felt bigger or more intense.

2.3. Pressure discrimination task

The stimuli and protocol were the same as in the DDt, but here we focused on the pressure of each stimulation. Subjects perceived stimulations of different or equal intensity on the arm and on the neck and they had to say which stimulation was more intense. In each trial, stimuli intensity was set using the same software-hardware device as in the DDt. Two blocks of 108 trials were administered, so that 3 different levels of intensity of the stimuli on the arm and the neck. Also in this case, in half of the trials stimuli intensity was the same for the two body

parts, and in the other half stimuli were more intense on the arm or the neck, with equal probability.

2.4. Body image test

Subjects were asked to put one tile depicting a body part in the appropriate position on an empty board, where the contour of the model's face was drawn, in order to ideally reconstruct the model's entire body. As the tiles were all rectangular, there was nothing to suggest their correct location. After each trial, the previously placed tile was removed. Thus, to perform the task the participants had to refer to an internal representation of a human body image that depend on the representation of their own physical body. They performed the task seated at a desk in front of the examiner; they were asked to place the pieces one by one to reconstruct the mannequin frontally. No time limit was given. Performance was recorded by a fixed photo camera positioned perpendicular to the test tablet. The camera was controlled by custom made software that captured the images and saved them in a JPEG format (600 x 800 pixel) for further off-line coding. The x-y pixel coordinates of different critical landmarks (right shoulder, right index

finger, right hip and right big toe), which corresponded to the judged locations, were computed using Microsoft Paint 5.1. The coordinates were used to determine the distance between the landmarks. The distance between the shoulder and index finger and between the right hip and the big toe were then converted into centimetres.

2.5. Peripersonal Space task

In each trial, participants received either a weak (target) or a strong (non-target) electrical stimulus on their right index finger and were instructed to respond vocally (saying “tah”), as quickly as possible, only to the tactile target. Concurrently, a task-irrelevant sound was generated from a loudspeaker nearby (i.e. 5 cm from the hand, thus within the boundaries of peripersonal space) or a distant loudspeaker. The position of the distant loudspeaker was varied in the two block conditions: in the control condition (far-100), the distant loudspeaker was placed 100 cm away from the near one, that is, in extrapersonal space; in the critical experimental condition (far-25), the far loudspeaker was placed 25 cm from the near loudspeaker, that is, just within the putative boundary of the PPS representation (Longo and Lourenco, 2007; Làdavas and Serino,

2008). Although participants were explicitly instructed to ignore the auditory stimulation in this task, we found that nearby sounds, that is, occurring within the PPS, more effectively interacted with tactile stimuli on the hand, fastening tactile reaction time, with respect to distant sounds (Serino et al., 2007, 2011; Bassolino et al., 2010). Thus, we compared the different effects induced by near and far sounds in MM and controls when the far sounds were presented either at 100 cm (i.e., within extrapersonal space) or at 25 cm (i.e. at the PPS boundary). We predicted that in healthy controls, a difference in RTs to near and far sounds would be present only when far sounds were placed at 100 cm (i.e. well outside PPS) and not at 25 cm (i.e. within PPS); by contrast, before surgery a near-far difference was evident in MM in both conditions, because sounds presented at 25cm fell outside her PPS boundaries. But, considering that the surgical procedure elongated MM's upper limbs by 10 cm, after surgery sounds presented at the same point in space should have been processed as falling within the PPS boundaries if MM had incorporated the elongation of her physical body into her mental body representation. If this were the case, no near-far difference would have been found in MM after surgery for sounds presented at 25 cm, as in controls. Tactile stimuli were delivered by two constant-current electrical stimulators (DS7A, Digitimer, Hertfordshire, United Kingdom), via two

pairs of neurological electrodes (Neuroline, Ambu, Ballerup, Denmark) placed on the upper side of the index finger. One pair of electrodes delivered the weak stimulus and the other delivered the strong stimulus. Stimuli intensity was titrated for each subject in a pre-test session so that the weak (target) stimulus could be perceived approximately 90% of the time and the strong (non-target) stimulus could be perceived 100% of the time. Auditory stimuli were 150-msec bursts of white noise; the intensity of the near and far sounds was set to be equal (70 dB) as measured by a sound meter at the subjects' ear. The sounds came from two identical loudspeakers: one was located near and one far from the stimulated hand. Inspection of the phono-spectral waves (recorded by a computer) from the two loudspeakers ensured that the sounds were equal at their origin. The tactile and near acoustic stimuli were delivered simultaneously. The far sound had an onset 5 msec before onset of the tactile stimuli to compensate for the delayed arrival of the far sound relative to the near sound, because of its greater distance. RT was measured by means of a voice-activated relay. A computer running XGen (Rorden, n.d.) software was used to control stimulus presentation and record responses. The task was performed in two conditions: far-100 and far-25. In each condition, a total of 240 trials, divided into two blocks lasting approximately 6 minutes each, were administered: 60

target trials with the near sound, 60 target trials with the far sound, 40 non-target trials with the near sound, 40 non-target trials with the far sound, and 40 catch trials (i.e. trials in which only a sound, 20 near and 20 far, was presented). To counterbalance the order of condition administration, MM performed the experiment in the following block order: far-100; far-25; far-25; far-100. A group of six age-matched healthy controls (all females, mean age 25 years) performed the same experiment; half performed the task in the same block order as MM, and the other half in the reverse order, far-25; far-100; far-100; far-25.

3. Results

3.1. Primary tactile tasks

There was no change in the control group's performance on either tactile sensitivity test in the two evaluations (Von Frey, first session=2.77, s.e.m.=.05; second session=2.75, s.e.m.=.05; $p=.48$; 2DPT, first session=3.54, s.e.m.=.22; second session=3.46, s.e.m.=.20 ; $p=.38$). On Von Frey's test, MM's performance showed a slight change between

prior to surgery (mean diameter 2.44), after surgery (2.36) and at the follow-up (3.61). Nevertheless, the patient's performance was different from that of controls at all three evaluations (all $p < .001$; see Table 1). MM's 2PD threshold showed a major change across the three testing sessions: before surgery (2.50 cm), after surgery (5.50 cm) and at the follow-up (4.50 cm). In the pretest, MM performed better on the 2PDT when compared with the control group ($t(25)=4.87$ $p < .001$). At the post-test and the follow-up sessions, she performed significantly worse than controls [$t(25)=-10.4$ $p < .001$; $t(25)=-5.29$ $p < .001$ respectively]. In summary, we observed dramatic loss of tactile acuity after surgery.

Table 1. Performance on two point discrimination task (2pdt) and the Von Frey test: for both measures smaller value better performances.

	Patient M.M.	Control group (n 26)	Patient M.M.	Control group (n 26)
Evaluation	2pdt	2pdt Mean (SD)	Von Frey	Von Frey Mean (SD)
PRE	2.5**	3.54 (1.09)	2.44**	2.77 (0.27)
POST	5.5**	3.46 (1)	2.36**	2.75 (0.23)
FOLLOW-UP	4.5**		3.61**	

Note: patient vs. age-matched controls * $< .01$; ** $< .001$. Control group were tested only twice.

3.2. Pressure and Distance tasks

Data were analyzed using point of subjective equality (PSE) and just noticeable difference (JND) for both tasks and compared with one sample t-test and paired samples t-test using SPSS software analysis (version 16) . Data were fitted to a sigmoidal function described by the following equation:

$$y = \frac{100}{1 + e^{-\frac{x - x_c}{b}}}$$

where x represents the independent variable (i.e., the separation difference between the two points administered on the arm and on the neck) and y the dependent variable (i.e., probability of reporting the distance on the neck as longer). Upper and lower saturation values are fixated at 100 and 0 respectively. X_c is the value of the abscissa at the central point of the sigmoid (i.e., the value of x at which $y = 50$) and b establishes the slope of the sigmoid at the central point. Point of subjective equality (PSE) scores correspond to the x_c and represent the difference between the two points distance on the arm and the neck yielding to equal probability of perceiving the stimuli separation as longer on the arm or on the neck. Just notable difference (JND) scores are calculated as the difference between X_{75} and X_{25} , that is between the

difference between two points on the arm and the neck yielding to a probability of 75% and 25%, respectively, of perceiving the two points on the neck as longer. No significant difference was found in the PSE (distance task $p=.18$, intensity task $p=.85$) and the JND (distance task $p=.10$, intensity task $p=.66$) in the control group in the two assessments for either the Distance discrimination or the Pressure discrimination task. In the PDt, MM's performance was always significantly different from that of controls at the three different assessments (see Table 2). On the DDt, at the pre-test assessment MM's PSE did not differ from that of the control group [$t(25)=1.15$, $p=.26$], whereas her JND was significantly worse [$t(25)=3.47$, $p<.001$]. In the post-test, MM's PSE and JND were significantly different from controls' [$t(25)=17.3$, $p<.001$; $t(25)=6.07$, $p<.001$ respectively]; this seems to indicate a change in her tactile perception after surgery. At the follow-up assessment, MM continued to show significant differences in PSE but not JND [$t(25)=10.6$, $p<.001$; $t(25)=0.59$, $p=.56$]. When compared with her post-test values, however, her performance tended to be more similar to that of the control group (see Table 3). To summarize, the present results show that after surgery, MM performed steadily on the intensity task but not on the distance task. Specifically, MM perceived the distances on the arm as shorter as

they actual were. The peripheral distortion is progressively restored in order to provide a more realistic perception of the size of the stimuli.

Table 2. Participants' performance on the Pressure Discrimination task

	Patient M.M.	Control groups (n 20)	Patient M.M.	Control groups (n 20)
Evaluation	PSE	PSE Mean (SD)	JND	JND Mean (SD)
PRE	1,54**	0.10 (0.34)	-3.70**	-1.81 (0.67)
POST	1.21**	0.09 (0.33)	-0.57**	-1.79 (0.66)
FOLLOW-UP	0.66**		-1.55	

Note: patient vs. age-matched controls * < .01; **< .001. Control group were tested only twice.

Table 3. Performance on the Distance Discrimination task

	Patient M.M.	Control groups (n 26)	Patient M.M.	Control groups (n 26)
Evaluation	PSE	PSE Mean (SD)	JND	JND Mean (SD)
PRE	0.20	0.14 (0.26)	-1.97*	-1.53 (0.47)
POST	1.12**	0.07 (0.31)	-2.16**	-1.38 (0.64)
FOLLOW-UP	0.71**		-1.50	

Note: patient vs. age-matched controls * < .01; **< .001. Control group were tested only twice.

3.3. Body image test

As shown clearly in Figure 3, before surgery the patient's reconstruction of the body 2D mannequin was different from controls (see also Table 4).

FIGURE 3

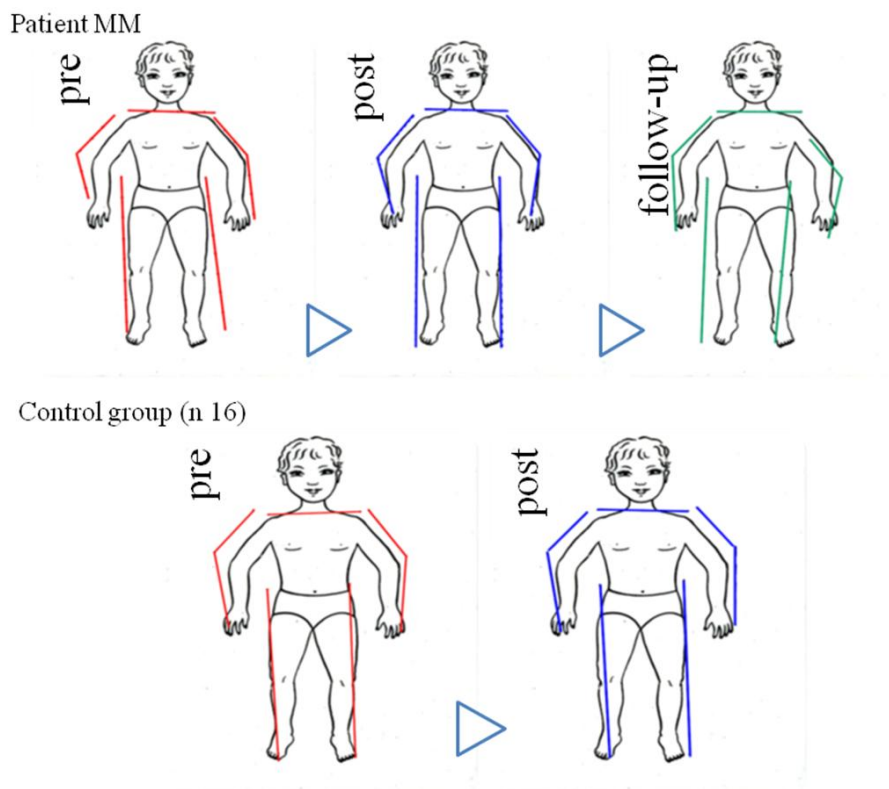


Figure 3. MM's performance on the DH test. The position of the arms and legs of the mannequin is represented graphically by the lines. After surgery (post/follow-up), MM positioning her arms similarly to controls. No difference was found in the positioning of the legs between the three assessments. Control group were tested only twice.

However, after surgery and at the follow-up, the shape of the reconstructed 2D mannequin reproduced by the patient was more elongated and similar to that reproduced by the controls. This suggests that the patient perceived the shape of her whole body as elongated after surgical lengthening of the upper limbs alone. To quantify this effect and study it in relationship to the different body parts submitted to surgery, we measured the perceived length of the upper and lower limbs. For this purpose, we calculated the distance between the right shoulder and the right index finger and between the right hip and the right big toe from the figures reconstructed by the patient and the controls.

Table 4. Performance on the Body Image test

	Patient M.M.	Control groups (n 16)	Patient M.M.	Control groups (n 16)
Evaluation	Right lower limb (cm)	Right lower limb (cm). Mean (SD)	Right upper limb (cm)	Right upper limb (cm). Mean (SD)
PRE	13.99	14.41 (1.29)	7.43**	9.85 (1)
POST	15.36	15.15 (0.72)	8.73*	9.77 (1.12)
FOLLOW-UP	15.53		10.3	

Note: patient vs. age-matched controls * < .01; **< .001. Control group were tested only twice.

As can be seen in Table 4, before surgery MM perceived her upper limbs as shorter (7.43 cm) compared with her aged-matched controls (9.85 cm)

[$t(15)=9.59$, $p<.001$]; even after surgery the performance of MM remained significantly different from those of controls [8.73 cm patient; 9.77 cm control group; $t(15)=3.67$, $p=.002$] and it was no more significant at the follow-up [10.3 cm; $t(15)=-1.88$, $p=.79$]. By contrast, no significant change was found in the three assessments for perceived length of the lower limb, which was consistently different from that of controls [MM pre 13.99 cm, control group 14.41 cm, $t(15)=1.33$, $p=.20$; MM post 15.36 cm, control group 15,15, $t(15)=-1.17$, $p=.26$; MM follow-up 15.53 cm, $t(15)=-2.1$, $p=.053$]. No change in the perceived dimensions of the upper and lower limbs was found in the healthy controls at the two assessments (upper limbs $p=.82$; lower limbs $p=.06$). Thus, results from the DH task suggest that physical elongation of the upper limbs was incorporated into the mental body representation, so that it selectively shaped the perceived length of the upper limb.

3.4. PPS task

MM's accuracy was extremely high. Omissions and false alarms were very low (on average 1.62 and .87 per block, respectively), and thus

were not analyzed. Mean RTs to tactile stimuli were computed and compared for the different experimental conditions (see Table 5).

Table 5. Performance on the Peripersonal space test. Mean RTs (in msec; with s.e.m.) to tactile targets when sounds were presented in near and far space, and the difference between these, in the two experimental conditions.

	Patient MM						Control group (n 7)					
	Near 100	Far 100	Near- Far	Near 25	Far 25	Near- Far	Near 100	Far 100	Near- Far	Near 25	Far 25	Near- Far
PRE	551	579	-28	547	563	-16	584	606	-22	618	612	6
POST	436	452	-16	440	433	7	(38)	(40)		(35)	(35)	

RTs above two standard deviations from the mean were trimmed from the analysis (.75 trials per block, on average). Before surgery, MM responded faster to a tactile stimulus on the hand when a sound was presented near rather than far from the hand, both when the far sound was presented at 100 cm (far-100 condition: near=551; far=579) and at 25cm (far-25 condition: RTs associated with near sounds=547 ms; RTs associated with far sounds=563 ms), with a near-far RT difference of -28 and -16 msec, respectively. In healthy controls, faster RTs associated with near sounds compared with far sounds were evident only in the far-

100 condition, with a near-far difference of -22, and not in the Far-25 condition, with a near-far difference of 7 msec. A 2x2 ANOVA with the factors sound position (near and far) and condition (far-100; far-25) revealed a significant two-way interaction sound position X condition [$F(1,6)=20.45$; $p<.01$], confirming that the speeding effect due to near sounds was present in the Far-100 condition (near=584 \pm 38; far=606 \pm 40; $p<.01$) but not in the far-25 condition (near=618 \pm 35; far=612 \pm 35; $p=.33$). Thus, in the far-100 condition a similar space-dependent modulation of RTs was present in MM before surgery and in controls (MM=-28; controls=-22; one sample t-test on near-far RT difference: $t(6)=1.90$; $p=.10$). Instead, in the far-25 condition, a near-far RT difference was evident in MM but not in controls (MM=-16; controls=6; one sample t-test on near-far RT difference: $t(6)=3.95$; $p<.01$). After surgery, MM still showed faster RTs to tactile stimuli paired with near sounds (436) compared with those paired with far sounds (452) in the far-100 condition, with a near-far RT difference (-16msec) comparable to that found in healthy controls [$t(7)=1.79$, $p=.12$]. However, differently from before surgery, in the far-25 condition, RTs associated with near sounds (440) were no faster than those paired with far sounds (433), with a near-far difference of 7.5 msec, which was not different from that of healthy controls [$t(7)=-29$, $p=.78$]. To sum up, both in MM (before and

after surgery) and in controls, a sound presented 5 cm away from the hand had a stronger effect on the processing of a tactile stimulus on the hand than a sound presented at 100 cm away, suggesting a stronger multisensory interaction effect when both the tactile and auditory stimulus occurred within PPS. No near-far difference was present in healthy controls when far sounds were administered 25 cm from the near stimulus, that is, when both sounds were presented within the putative PPS boundary. This was not true for MM before surgery, when a sound near her hand fastened tactile RTs compared with a sound presented 25 cm away, suggesting that a sound at that distance did not interact with tactile processing of the hand. However, after the surgical procedure had lengthened MM's arm by 10 cm, the difference between the effect due to near and far sounds vanished when the far sound was presented 25 cm away and, analogously to controls, was still present when the far sound was presented 100 cm away. This finding suggests that after surgery the same spatial position was processed as closer to the hand than before surgery, as if the space where the touch on the hand and the sound interacted was extended after the arm was physically lengthened.

4. Discussion

Surgical extension of the upper limbs of an achondroplastic young woman resulted in changes in several levels of body representation. This finding supports the view that body representations are dynamic constructs remodelled by experience throughout life. In particular, the brain's maps of the body surface, and more cognitive representations of body form must both adapt to normal changes in the physical body throughout the lifespan, notably in childhood growth and in ageing. However, these processes have proved difficult to investigate experimentally. Changes in the physical body are normally so small or so slow that the effects are difficult to quantify. Perhaps as a result, the scientific literature on neural representation of the body has relied on transient illusory effects, particularly experimentally-induced changes in the perceived size of body parts (see e.g. Longo et al., 2010 for a review). Such illusions are valuable in showing what sources of information contribute to the representation of the body, but cannot reveal how gradual changes in body configuration lead to changes in body representation. Here, for the first time, we investigated plasticity in body representations after an actual and permanent change in the structure of the physical body and in the absence of any disconnections

between the periphery and the cortex. Overall, the results indicate that the primary level of somatosensory processing are less affected by elongation surgery than higher levels of body representations, which underwent selective alterations soon after the elongation, and progressively re-adapted at 11 months post surgery.

4.1. Primary Tactile Tasks

In the first series of experiments, we investigated whether body part elongation leads to modifications at different levels of stimulus processing, that is, from primary somatosensation to higher levels of body representation. In this hierarchical view, we found that arm elongation did not affect the most primary sensory process of detecting tactile stimulation, since it left unaltered the patient's ability to detect the presence of a tactile stimulus on the arm, as measured by the Von Frey test. However, tactile spatial acuity (as assessed by the 2PDt) decreased after elongation and became worse than that of healthy controls. This finding could simply reflect peripheral effect of stretching the skin. Since tactile acuity strongly follows the density of skin innervations by mechanoreceptive afferents, decrease in tactile innervations density

caused by skin stretch should produce a decrease in tactile acuity. However it is impossible to determine from our data, whether stretching the skin requires some additional central adaptation of somatosensory processing. It is important to highlight that previous research documented that after Ilizarov surgery a partial denervation in the motor distribution of the deep nerves can occur and that this consequence does not affect sensory conduction (Galardi et al. 1990). Moreover patient MM didn't suffer from any kind of denervation so we can strongly support the issue regarding the integrity of the basic afferent pathways. Direct assessment of skin innervation before and after surgery by skin biopsies would be required to distinguish central from peripheral explanations, but this was not ethically appropriate in this case.

4.1. Distance and Pressure Discrimination Tasks

At a subsequent step of processing, we observed that the elongation surgery affected the patient's ability to process two contacts on the surface of the arm when she had to focus on the metric properties of the stimuli on the skin, but left unaffected her ability to judge the pressure intensity of the same contacts on the same body location. One year post-

surgery, her sensitivity to pressure remains stable, whereas her metric perceptual functions have improved toward her pre-surgery evaluations. The dissociation between these two forms of touch perception was investigated in a previous fMRI study (Spitoni et al. 2010), where it was found that the same tactile stimuli requiring either spatial distance judgement or contact pressure judgement bilaterally activated parietal and frontal areas. However, spatial distance evaluation on the body surface also selectively activated the angular gyrus and the temporo-parieto-occipital junction in the right hemisphere. They interpreted these results as the need to refer tactile stimulations to a metric body representation in the tactile distance judgement task, whereas judging contact pressure can be performed without this representation. In the case of MM, it seems that surgical modification of the arms selectively altered tactile judgements only when these required mediation by body representation. Compared to control group, she perceives, after stretching, tactile stimuli on the arm as closer, while in the follow-up she tends to return towards the pre surgery discrimination. This result can be related to Weber's studies (1996) on tactile illusions. The author found that the perception of tactile distances were related to tactile sensitivity and that the size distortion derives from density of the mechanoreceptors on the skin. We can speculate that the sudden elongation of MM's arms

led to a kind of diffusion of the mechanoreceptors toward the entire area of the stretched skin; in other words the same amount of receptors that the system used before the elongation, were now utilized to cover a larger area. This effect could partially account for why MM perceived stimuli as closer. Conversely, at follow-up evaluation we observed that the distance judgments were more veridical than post surgery. This suggests that additional process of tactile size constancy are required to correct the distortions inherent in primary representations. The need for such additional processes has been also suggested by Longo et al. (2010), who describe two classes of higher-order processing beyond the preliminary somatosensation: somatoperception and somatoprepresentation. Obviously in this case we refer to the former which deals to the process of perceiving the body and ensuring the constancy of somatic percept. Summarizing, after intervention, we observe that the perception of distance between two points decreases, but subsequently the metric properties of the stimuli are scaled by somatoperception which correcting such a distortions.

4.2. Body Image Test

On the other hand, we can also describe MM's performance on the DH Body Image Test as an adjustment of somatopresentation. Before the elongation, MM's body representation (as measured by the DH test) was consistent with the shape of her own body at the time. Specifically, MM exhibited a selective bias in reconstructing the shapes and dimensions of the upper, whereas the lower limbs were within the normal range. After surgery, her performance improved, and at the follow-up her reproduction of the shape of the body was similar to that of the healthy controls. This normalization effect could be seen in MM's placement of the tiles reproducing the upper limbs as if they were longer. No such change occurred in her placement of the lower limb tiles. The patient had previously undergone elongation surgery for her lower limbs, and this may be the reason why her placement of the leg tiles was similar to that of the controls. This pattern of results suggests that the elongation of the arms was specifically incorporated in an updated representation of the body, without changes in representations of the rest of the body. This evidence supports the finding of a previous study (Di Russo et al., 2006) in which we observed that the body representation of achondroplasics was partially restored after elongation. Given this evidence, we can

speculate that achondroplasics' pre-existing body representation can be modified towards a body template more similar to that of healthy controls when surgical reconstruction is used to change limb size.

4.3. Peripersonal Task

Finally, elongation surgery also affected the patient's PPS representation. We used the differential effect of near and far auditory stimuli on tactile processing (Serino et al., 2007; Bassolino et al., 2010) as a probe of the extension of PPS around the arm. For MM before surgery and for healthy controls, a sound administered close to the hand resulted in faster tactile RT compared to a sound presented 100 cm away, in extrapersonal space. This near-far difference was taken as evidence of stronger audio-tactile interaction for stimuli falling within PPS. In keeping with this, in healthy controls a far sound presented just inside the PPS boundary (i.e. at a distance of about 25 cm) affects tactile RT similarly to a near sound. This was not the case when MM was tested before surgery: then near sounds induced faster RTs than far sounds administered at 25cm, suggesting that stimuli presented at 25 cm fell outside her PPS boundary. Importantly, after MM's arm was lengthened

by about 10 cm, the near-far difference was abolished for sounds presented at 25 cm but not for sounds presented at 100cm, so that MM's behaviour was analogous to that of healthy controls. This finding suggests that once MM's arm was elongated, the PPS boundary shifted to include a portion of space that is part of the PPS of healthy individuals. Longo and Lourenco (2007) used a line bisection task, in which lines were presented at different distances from the subject, to measure the extension of PPS in healthy adults. They found a correlation between the physical length of the arm and the extension of PPS as measured by the line bisection task, suggesting that arm length constitutes a metric for representing the space around the body. Our results confirm this finding and also show that the relationship between body part dimensions and PPS representation is dynamic and updates to changes in the physical body. This mechanism might be particularly relevant during development, when the brain needs to keep track of the continuous changes in body dimensions due to growth and also to plan and correctly execute actions toward objects placed at different distances from the body.

5. Conclusions

Some final considerations are needed to qualify the plasticity of somatoperception and somatrepresentation. The forms of plasticity demonstrated in the present study are selective in several ways. First plasticity is selective for specific perceptual processing: pressure evaluation on the skin is not affected by surgical elongation, but distance perception is significantly modified. Second, plasticity is confined to the modified body segment. This part-specificity rules out accounts based on general factors such as perceptual learning, or non-specific effects of surgery. Although this observation would be trivial in the case of the illusory elongation produced by tendon vibration (de Vignemont, 2005), it is not so in our case. A 10 cm increase in the length of the arms produces considerable improvement in the ability to explore external space (i.e. grasping, throwing, pointing etc.). The changes were also space-specific: the effect of the audio-tactile interaction indicates a change in peripersonal but not extrapersonal space. Similarly, the capacity to represent different body segments to form a complete body image (DH test) showed significantly improvement regarding representation of the relationship between the arms and the body, but left unchanged the relationship between the leg and the body. These plastic

effects involving high-order body representations require time, and some plasticity phenomena occurred months after the elongation procedure ended.

To summarise, we have documented changes in several levels of bodily awareness as a result of a surgical elongation procedure in a single case.

We found improvements in measures of primary tactile sensation (detection, intensity coding), which were not necessarily sustained at follow-up. Changes in tactile spatial acuity were consistent with a plastic change in receptive fields. Immediately after surgery, tactile acuity was decreased, presumably reflecting a decrease in mechanoreceptor density due to the extended skin area. This was reversed at follow up, presumably reflecting a reorganisation of receptive field territories. Finally, we found major changes at the levels of somatoperception and somatrepresentation. An explicit body image task showed rapid and sustained adjustment to the elongation. We also found an immediate expansion of the zone of peripersonal space, as measured by multisensory interactions.

Overall, our results suggest that most aspects of somatosensory awareness show considerable plasticity when the body itself changes. Such plasticity is generally assumed in development. MM's performance suggests that the same plasticity persists in adulthood. In

this sense, this case offers a unique window into how the brain tracks the state of the body, and adjusts perceptual mechanisms accordingly.

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Experiment 2: Modulation of Spontaneous Alpha Brain Rhythms by Low Intensity Transcranial Direct Current Stimulation

Abstract

When using transcranial direct-current stimulation (tDCS) for clinical rehabilitation, it is crucial to position the stimulating electrodes on the head so as to produce an electric field in the target area and avoid current diffusion to other cerebral areas. The overall aim of this study was to explore the main features of the current flow routes in the cortex when tDCS set up is used to rehabilitate cognitive functions. For this purpose, we used modulation of the spontaneous electroencephalogram (EEG) as a marker to directly describe the perturbation induced by direct current (DC). We used a DC of 1.5 mA for 15 min. In all conditions (anodal, cathodal and sham), an active electrode was placed over the right posterior parietal cortex and a reference electrode over the ipsilateral deltoid muscle. The EEG was recorded using a 64-channel system. Results showed that 1) the largest effect of DC was on alpha rhythm; 2) anodal tDCS significantly affected alpha rhythm, but cathodal tDCS produced no modifications; 3) a modulation of alpha activity was observed not only in areas directly stimulated by DC but also in non-contiguous areas; 4) the anodal effect was maximum at the beginning of the stimulation (7.5 min after DC stimulation) and decreased over time. The present study confirms that tDCS can alter spontaneous EEG by modulating underlying activity.

1. Introduction

Transcranial direct-current stimulation (tDCS) is a non-invasive technique that modulates the neuronal excitability of targeted cerebral areas by sending constant low direct-current (DC) from the scalp through a pair of electrodes. The alteration of cellular excitability modulates several brain functions including motor, sensory, and high-level cognitive functions (Nitsche et al., 2005; Calvo-Merino et al., 2004). Concerning the latter, it has been shown that modulating behaviour through non-invasive brain stimulation with an increment or a decrement of the levels of the performance represents a useful tool for research and rehabilitation. Since the seminal studies in motor tasks (Rosenkranz, Nitsche, Tergau, Paulus . 2000; Lang, Nitsche, Paulus, Rothwell, Lemon. 2004), research has increasingly focused on the effect of tDCS on cognitive domains such as language (Floel, Rosser, Michka, Knecht, & Breitenstein, 2008; Fiori et al., 2011; Fertonani, Rosini, Cotelli, Rossini, & Miniussi, 2010), spatial attention (Bolognini, Olgiati, Rossetti, & Maravita, 2010), executive functions (Dockery, Hueckel-Weng, Birbaumer, & Plewnia, 2009), Hecht, Walsh, & Lavidor, 2010), visual processing (Antal & Paulus, 2008,a), emotions (Boggio, Rocha, da Silva,

& Fregni, 2008), and implications for neuropsychological rehabilitation (Vallar and Bolognini, 2011).

Physiological studies have shown that DC electricity goes through the skull and outer layers of the cortex, modifies neuronal cross-membrane resting potentials, influences the level of neuronal excitability, and modulates firing rates (Nitsche et al., 2003). Depending on the orientation of the cells with respect to the current, the membrane potentials may be hyperpolarized (anodal stimulation) or depolarized (cathodal stimulation) by a few mV (Paulus, 2004). This change in neuronal excitability can trigger several alterations in brain function (Nitsche et al., 2008).

The DC flows following routes that are influenced by the impedance of the tissue crossed by the current. This means that tissue impedance and cell orientation can strongly affect the flow of the current, resulting in different polarization patterns. Many studies in the literature assume that the maximum effect of tDCS occurs in areas perpendicular to the stimulating electrode and that cell polarization-depolarization is predominantly localized in these underlying brain structures (Datta et al., 2010; Niche and Paulus, 2011).

It has also been observed that a variable amount of current can also spread to contiguous areas (Datta et al., 2010; 2009; Sadleir et al., 2010).

The overall aim of this study was to explore the main features of current flow routes in the cortex following tDCS. This issue is particularly important because tDCS is a promising tool in cognitive rehabilitation (Vallar and Bolognini, 2011). To pursue this goal, we measured the modulation of the spontaneous electroencephalogram (EEG) as a practical marker to directly describe the perturbation induced by DC.

Previous works have investigated EEG oscillations following DC stimulation. For example, Keeser et al. (2011) found that 20 min of anodal DC (2 mA) over the left dorsolateral prefrontal cortex (DLPFC) produced a significant reduction of left frontal delta activity. In a study on motor imagery, Matsumoto et al. (2010) showed that Mu event-related desynchronization significantly increased after anodal stimulation of the primary motor cortex (M1) and significantly decreased after cathodal stimulation. In a recent work by Polanà et al. (2011), anodal tDCS over M1 produced an increment of EEG functional connectivity in the premotor, motor, and sensorimotor areas of the stimulated hemisphere during motor activity in the 60–90 Hz frequency range and intra-hemispheric and inter-hemispheric connectivity changes in all frequency bands observed.

As far as we know, no EEG studies have explicitly investigated the effects of tDCS on the posterior parietal lobe, which is very important in

many cognitive domains such as visuo-spatial attention. Despite the seeming lack of interest in the effectiveness of tDCS over the parietal areas, many studies have investigated the use of tDCS to rehabilitate visuo-spatial deficits (for a recent review see Hesse, Sparing, Fink, 2011).

Furthermore, few studies have tried to predict the exact current flow during tDCS and most of them used realistic human head models to calculate field distributions in the different brain structures (Miranda et al 2006; Datta, 2010; Parazzini et al., 2012; Neuling et al. (2012). These modeling studies show that the position and the size of the electrodes greatly affect the specificity and direction of the current flow. For the reasons described above, we decided to focus on the modulation of spontaneous EEG activity after anodal and cathodal stimulation of the right posterior parietal areas in an ecological setting.

A second aim of our work was to study the duration of the tDCS effect. Antal and coauthors (2008b) found that DC stimulation had a significant effect in a time window of 5-10 min after anodal stimulation around motion visual area V5 and in a time window of 10-15 min after anodal and cathodal tDCS over the primary motor area. These effects remained stable for about 25 min and faded away after some hours. Furthermore, Keeser et al (2011) found that the effect of tDCS was stronger in the first

5 min of stimulation. According to our knowledge no systematic studies have focused on the duration of the tDCS effect over time in the posterior parietal areas and, indeed, this could be very important for those who use tDCS to rehabilitate neuropsychological patients.

In the literature, two different montages have been used (i.e. bicephalic and monocephalic) to determine the optimal electrode position for targeting a certain area. As suggested by Nitsche et al. (2003), the monocephalic one has the benefit of preventing the confounding effect caused by the reference electrode. Therefore, we decided to use a monocephalic montage with one electrode placed over the posterior parietal areas and the other on the right shoulder (DaSilva et al., 2011). Although this electrodes displacement might modulate brainstem neuronal excitability, we hypothesized that the electrical effect of DC would primarily affect the cortex under and around the active electrode and would decrease at a distance from it (Miranda et al., 2006; Wagner et al., 2007).

2. Methods

2.1. Participants

A total of 19 subjects participated in the study. Four were excluded because a considerable amount of muscular artifacts on the EEG. The remaining 15 participants (8 female) were all right-handed, as assessed by a modified version of the Edinburgh Inventory (mean handedness 95 ± 12) (Salmaso and Longoni, 1985). Participants' ages ranged from 21 to 34 years (mean age 23.3; SD = 3.4).

Inclusion criteria included the following: (1) no history of neurological or psychiatric disorders; (2) no history of substance abuse or dependence; (3) no use of medication affecting the central nervous system.

All participants provided written informed consent in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

The study was approved by the Ethics Committee of the IRCCS Santa Lucia Foundation of Rome.

2.2. DC stimulation

We used the safety protocol suggested by Brunoni et al (2012): a direct current of 1.5 mA (impedance limit 50 kOhm) induced by two saline-soaked surface sponge electrodes (7x4.5 cm) and delivered by a battery-driven, constant-current DC stimulator (neuroConn GmbH, Ehrenbergstr, Ilmenau, Germany).

In both anodal and cathodal conditions, the active electrode was placed over the posterior parietal cortex around the right angular gyrus and a reference electrode was placed over the ipsilateral deltoid muscle). Localization was established according to the 10-10 EEG standard montage by placing the active electrode over P2, P4 and P6 (Okamoto et al. 2004 Fuggetta et al., 2006).

In the stimulation sessions, the current increased in ramp-like fashion from 0 to 1.5 mA in 60 sec. Stimulation onset elicited a transient tingling sensation on the scalp (Hummel et al., 2005). Fifteen minutes after stimulation onset the current was slowly turned off over 60 sec. In the sham condition, the electrodes were placed in the same positions as the anodal/cathodal conditions, but the device was slowly decreased after 60 sec. (30 sec ramp-up and 30 sec ramp-down). This procedure guaranteed

that the participants would experience the typical tingling sensation at the beginning of the stimulation (Gandiga et al., 2006).

Participants were seated in a quiet room and asked to either open or close their eyes; this instruction was given vocally by the experimenter every 30 sec. Table 1 shows the stimulation and recording protocol.

Table 1.

	Spontaneous EEG	tDCS	Spontaneous EEG	tDCS	Spontaneous EEG
1 session	15 minutes	10 minute sham	10 minutes	15 minute anodal	15 minutes
2 session	15 minutes	10 minute sham	10 minutes	15 minute cathodal	15 minutes

Sequence of stimulation/recording. During spontaneous EEG recording, eyes were alternatively open or closed every 30 sec.

2.3. EEG recording and analysis

The EEG was recorded using a BrainVision system from 64 electrodes placed according to the 10-10 system montage (see Di Russo et al., 2002). All channels were initially referenced to the left mastoid (M1), and the ground electrode was located to the CPz. Horizontal eye movements were monitored with bipolar recording from electrodes at the right corner of the eyelid. Blinks and vertical eye movements were recorded with an electrode below the left eye, which was referenced to

Fp1. The electrode impedance was kept below 10 KOhm throughout the experiment and was periodically checked. The EEG from each electrode site was digitized at 250 Hz with an amplifier bandpass of 0.01 to 80 Hz, including a 50 Hz notch filter, and was stored for off-line averaging. In both open and closed eyes conditions EEG data were segmented into single epochs of 30s and corrected by ocular correction and filtered (2-30 Hz). Computerized artifact rejection was performed to discard segments in which deviations in eye movements, blinking and physical artifacts occurred (difference criterion 100 μ V). Therefore, only the EEG segments free from artifacts were accepted for Fast Fourier Transformation (FFT) with a resolution of 0.5 Hz and a Hanning window at 10% of length. Results are presented in the form of power values (μ V²).

The entire EEG spectrum was analyzed and divided into the four main frequency bands: 2-4 Hz (delta), 4-8 Hz (theta), 8-12 Hz (alpha) and 13-30 Hz (beta). A preliminary running t-test between pre- and post-stimulation activity in the four studied EEG bands did not find significant effects within the delta, theta and beta bands, while consistent effect were found in the alpha band, which was studied in detail.

Averaged power of the alpha frequency band was calculated for each participant and used for statistical analysis in the three following areas of

interest. According to the 10-10 system. A right parietal region was defined by P2, P4 and P6 electrodes placed within the stimulating electrode. A medial parieto-occipital region, where alpha is usually maximum, was defined by Pz, POz and Oz. As a significant modulation of stimulation was observed in the anterior regions, we also studied a medial anterior region defined by AFz, Fz and FCz. To accurately analyze the effect of stimulation, the post-test period was divided into two parts: post-test1, which referred to the first 7.5 min, and post-test2, which indicated the successive 7.5 min.

Alpha power scores were entered in a 4x2 within-subjects repeated measures ANOVA with test (pre-test, sham, post-test1, post-test2) and eyes (open, closed) as factors. Analyses were conducted separately for each area of interest in the parietal, occipital and frontal regions. LSD post-hoc tests corrected for multiple comparisons ($p < .05$) were also conducted. Anodal and cathodal tDCS were analyzed separately.

To study the effect of DC over time, a 9x2 within-subjects repeated-measures ANOVA, with Time (9 levels) and eyes (open, closed) as factors was run. The 9 levels of the Time factor were the Pre-test and 8 epochs of about two min (110 sec) each in the post-test. Also here, the anodal and the cathodal effect were calculated separately. As in the previous analysis, LSD post-hoc tests corrected for multiple comparisons

($p < .05$) were conducted. Moreover, to better study the scalp distribution of the stimulation effect on the alpha rhythm, post-test1 minus sham difference waves were obtained .

3. Results

3.1. EEG rhythm and topography

Group-averaged power spectra of the EEG during anodal and cathodal stimulation sessions for open- and closed-eyes conditions are reported in Figures 1 and 2, respectively. Alpha power was enhanced after anodal tDCS but remains stable after cathodal stimulation. ANOVA showed a main effect of anodal stimulation in the right posterior parietal areas ($F_{(3,42)}=3.56$, $p<.02$) and a significant effect of eyes ($F_{(1,14)}=10.7$, $p<.001$) but no significant interaction ($F_{(3,42)}=2.11$, $p=n.s$) was found. The latter seems to suggest that anodal stimulation is effective both when alpha activity is strong and when it is weak, , e.g., when the eyes are open. Post-hoc tests revealed a significant difference between pre-test and post-test1 conditions ($p<.01$) but no significant difference between pre-test and the other two conditions, sham and post-test2 ($p=.98$, $p=.93$ respectively). The remaining post-hoc comparisons showed a significant difference between sham and post-test1 ($p<.001$) and between post-test1 and post-test2 ($p<.01$). No difference was found between sham and post-test2 ($p=.92$).

Figure 1.

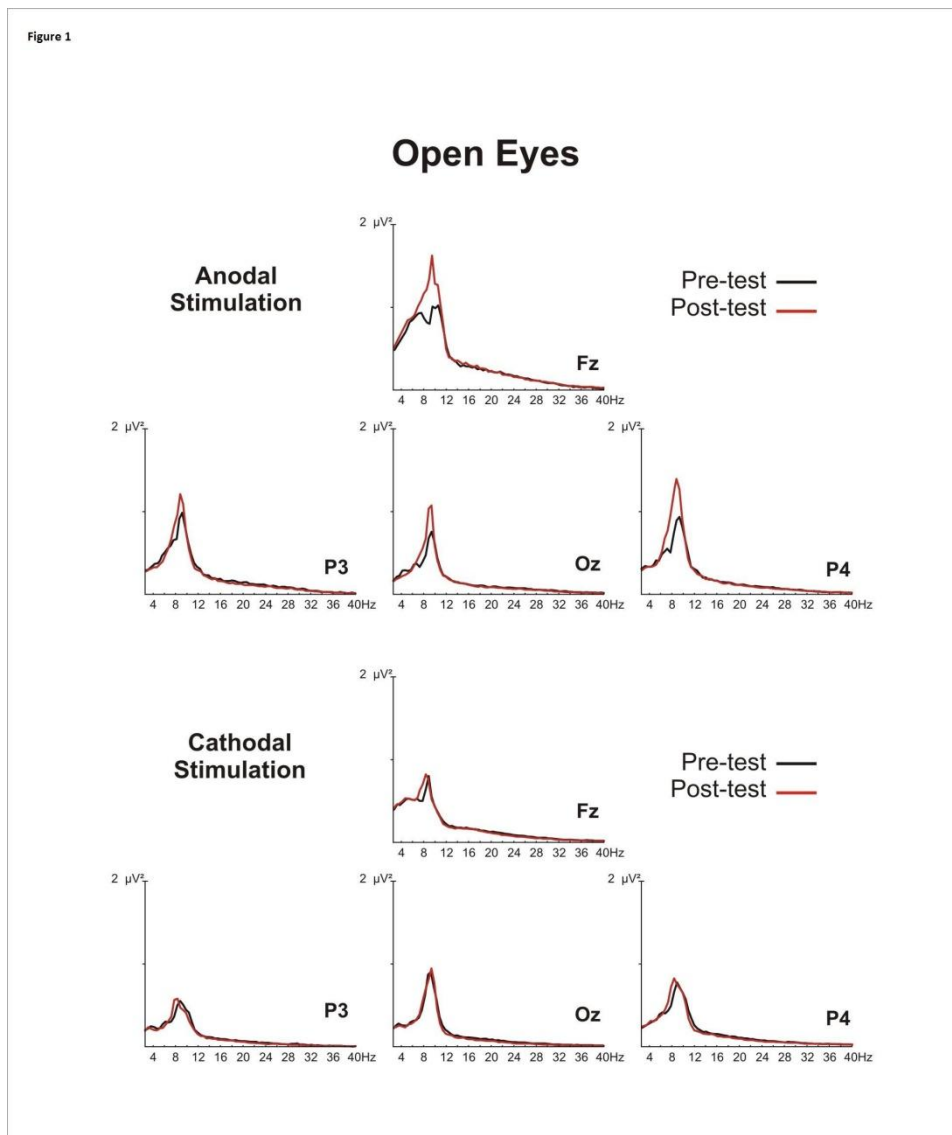


Figure 1. Group grand averaged EEG spectra of anodal and cathodal stimulation when eyes were open. Black line shows activity before tDCS (pre-test) and red line shows activity after tDCS (post-test).

Figure 2.

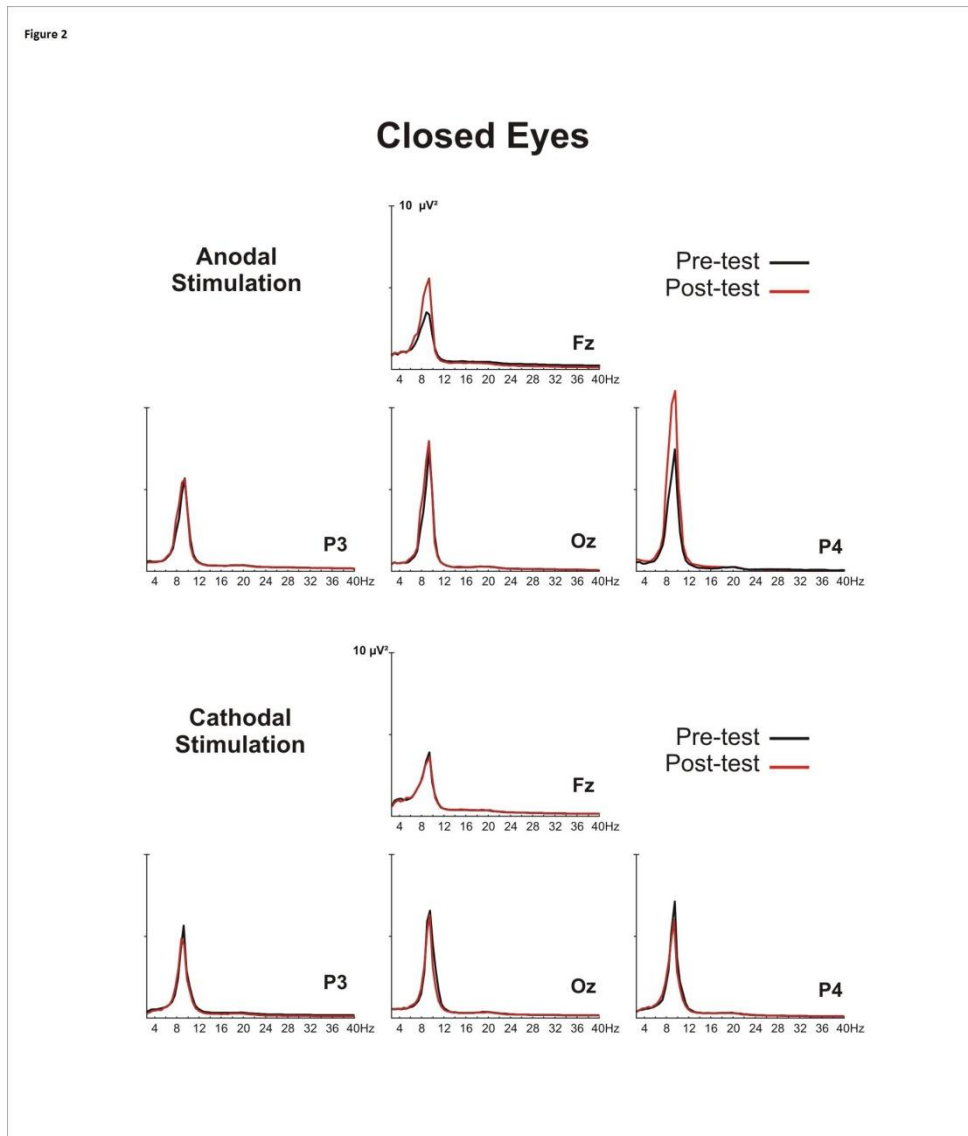


Figure 2. Group grand averaged EEG spectra of anodal and cathodal stimulation when eyes were closed. Black line shows activity before tDCS (pre-test) and red line shows activity after tDCS (post-test).

ANOVA comparing alpha activity on frontal regions revealed a main effect of stimulation ($F_{(3,42)}=2.82$, $p<.05$) and a significant effect of eyes ($F_{(1,14)}=7.36$, $p<.01$) but no significant interaction ($F_{(3, 42)}=1.00$, $p=n.s$). Post-hoc tests revealed a significant difference between pre-test and post-test1 ($p<.01$) but not between the pre-test and sham or post-test2 ($p=.85$, $p=.51$ respectively). Other post-hoc comparisons showed significant difference between sham and post-test1 ($p<.01$) and between post1 and post-test2 ($p<.05$) but no significance between sham and post-test2 ($p=.64$).

In the occipital region, ANOVA showed a significant effect of eyes ($F_{(1,14)}=28.3$, $p<.001$). No other significant effects were found (stimulation: $F_{(3,42)}=.99$, $p=n.s$; interaction: $F_{(3,42)}=.52$, $p=.66$). Statistical analysis of cathodal stimulation confirm the absence of significant main effect of stimulation in the right posterior parietal areas ($F=1.02_{(3, 39)}$, $p=.86$) and the presence of a significant effect of eyes ($F_{(1,13)}=10.03$, $p<.001$), no significant interaction was found ($F_{(3,39)}=2.32$, $p=.08$). Figure 3 shows a summary of the main findings of the post-hoc comparisons. The effect of stimulation was also absent in the occipital and frontal areas of interest. Statistical comparison are also showed in Figure 3.

Figure 3.

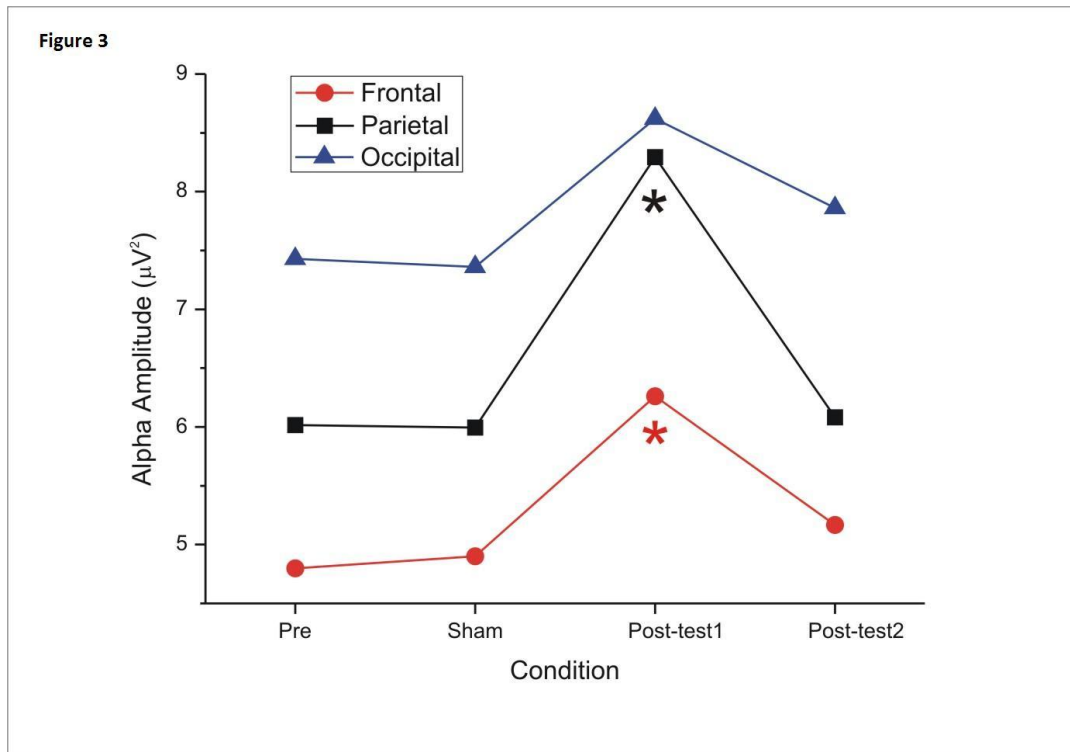


Figure 3. Effect of anodal tDCS on alpha amplitude recorded on frontal, parietal and occipital electrodes.

Topographical maps of the alpha rhythm peak (10.5Hz) are shown in Figures 4 and 5 for open and closed eye condition, respectively. With both open and closed eyes the alpha power in pre-test and in sham conditions was quite similar and most prominent in medial bilateral posterior parieto-occipital electrodes, interestingly a smaller but consistent activity was also present in medial frontal electrodes.

Figure 4.

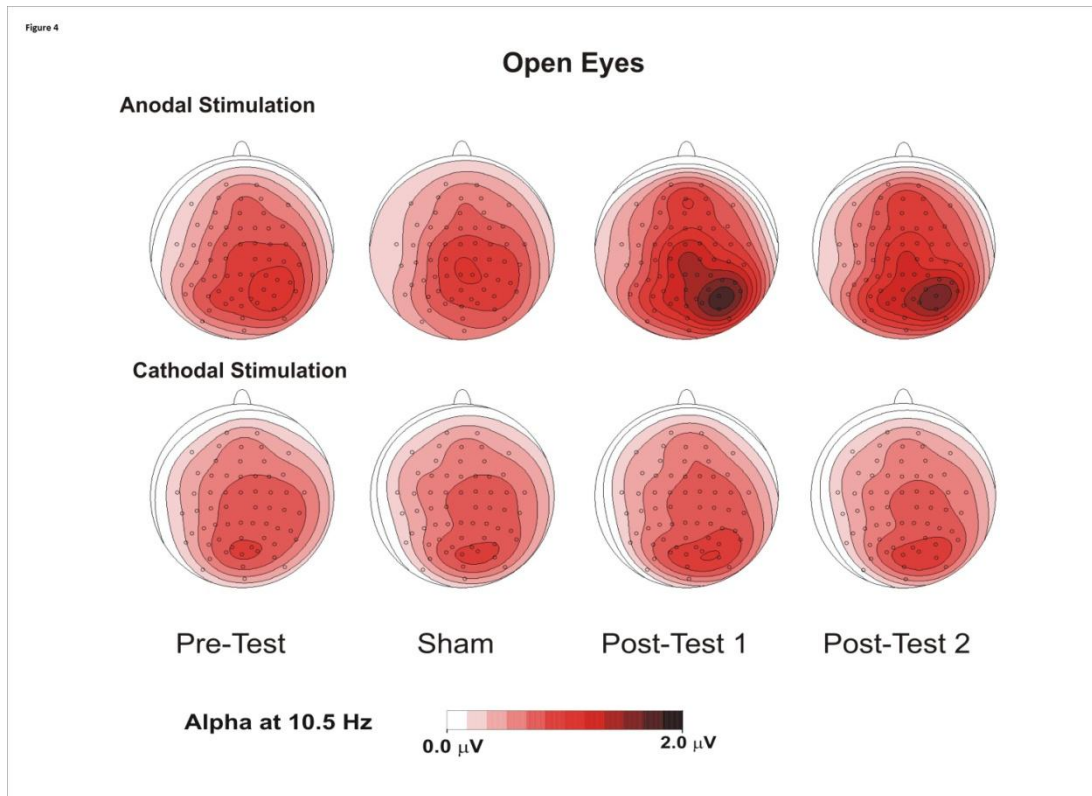


Figure 4. Topographical maps (top flat view) of the alpha rhythm at 10.5 Hz in the four conditions (pre-test, sham, post-test1, post-test2) when eyes were open.

Furthermore, in both eye conditions, the spontaneous alpha activity was larger in the post-test1 and decreased in the post-test2 for anodal stimulation. With open eyes the topography in the post-tests was less medial and prominent on right parietal areas. This effect was also present the closed eyes but less pronounced.

Figure 5.

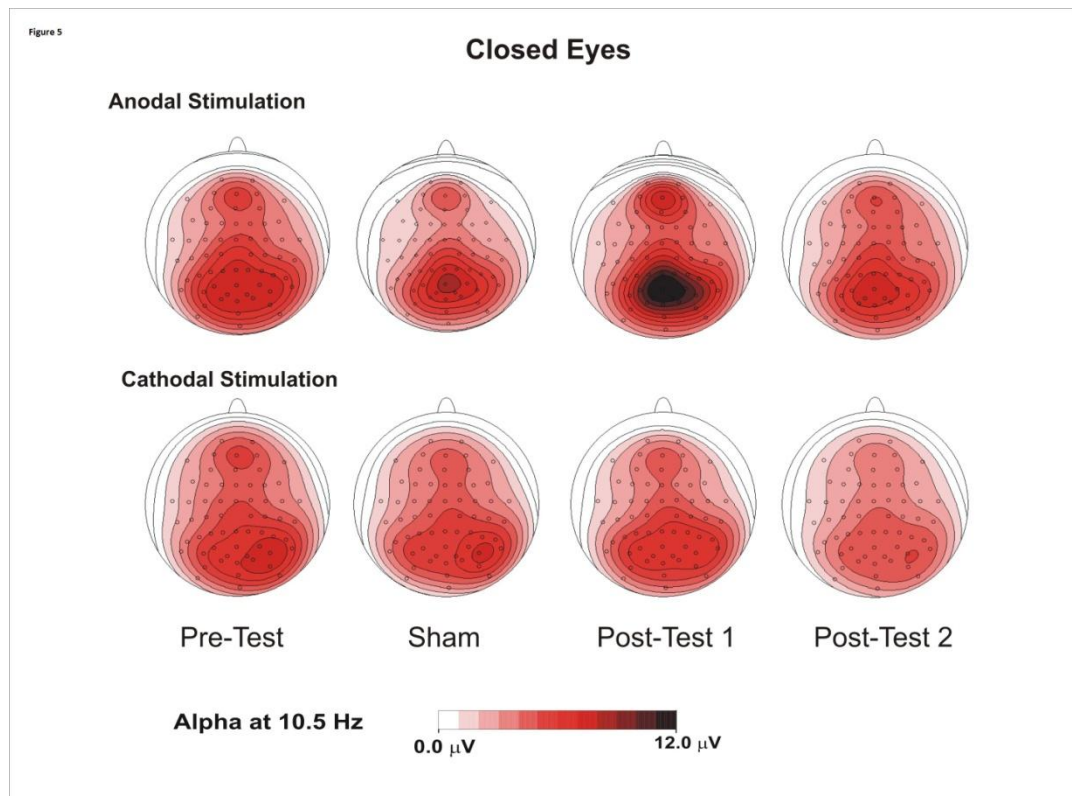


Figure 5. Topographical maps (top flat view) of alpha rhythm in the four conditions (pre-test, sham, post-test1, post-test2) when eyes were closed.

Figure 6 displays the topography of the post-test1 minus sham activity showing the presence of a fronto-parietal alpha band modulation following anodal but not cathodal DC.

Figure 6.

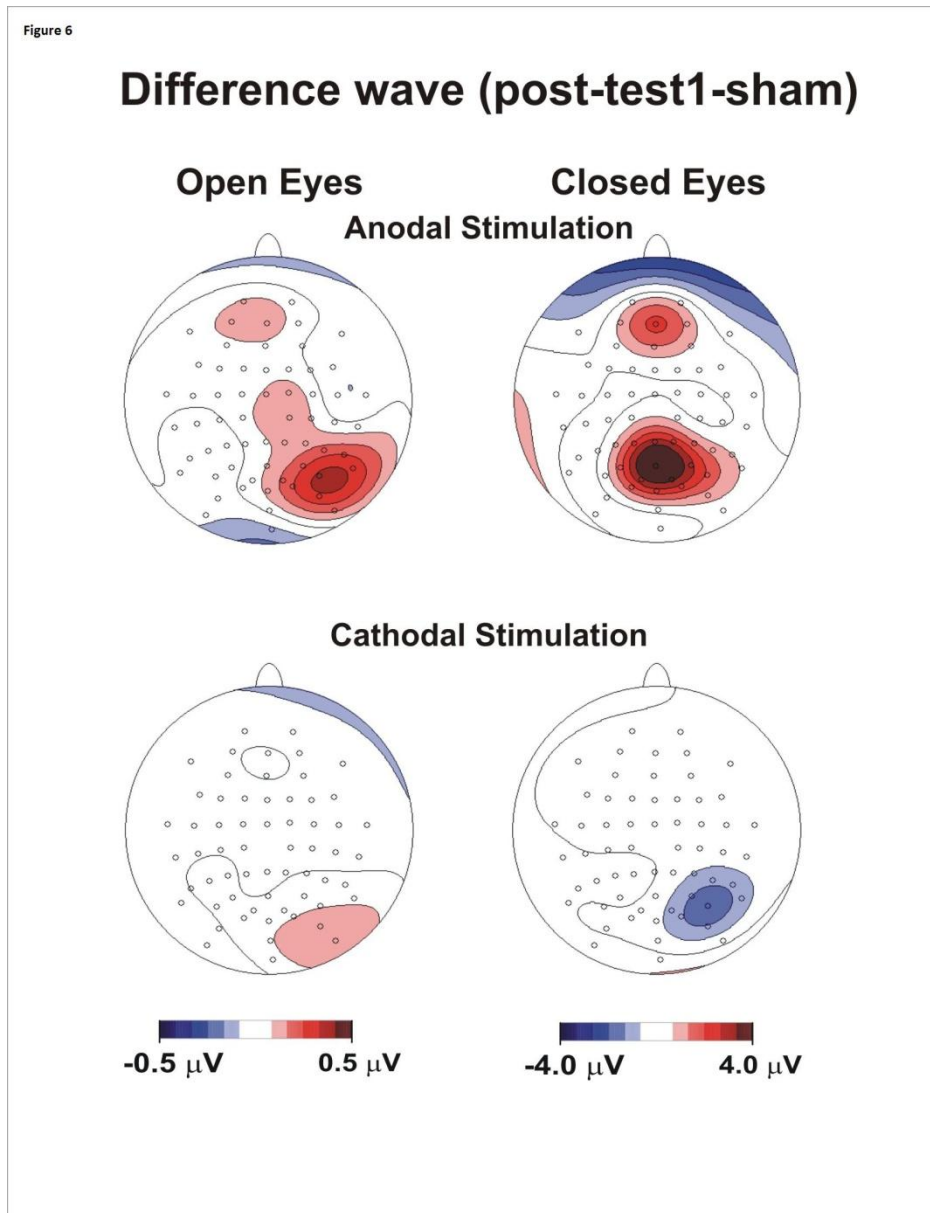


Figure 6. Topography of the tDCS effect for open and closed eyes and for anodal and cathodal stimulation. Maps were obtained by subtracting the sham condition from post-test1.

As one would expect, the difference was stronger in the closed eyes condition. Also, in this latter, we also observed a drift towards more

medial distribution. This occurrence maybe due to the prominent posterior alpha rhythm that is known to reflect the idling status of the brain in which the participants of this study were requested.

3.2. tDCS effect over time

As previously described, we studied the effect of anodal tDCS over a time period of 15 min. To better detail the time course of the stimulation effect, the post stimulation recording was divided in 8 epochs of about 2 min. each and the alpha amplitudes of the pre-test were compared with those of the 8 epochs (Figure 7). Repeated-measures ANOVA showed a significant main effect of anodal stimulation ($F_{(8,112)}=2.92$, $p<.05$) and a significant stimulation per eyes condition interaction ($F_{(8,112)}=2.27$, $p<.02$). This data showed that when eyes were closed DC was significantly effective for about 8 min;, but no significant difference was found when eyes were open. Specifically, a post-hoc test revealed that the difference between the pre-test and the stimulation epochs was maintained over the first 4 epochs (t_1 $p<.02$; t_2 $p<.04$; t_3 $p<.01$; t_4 $p<.01$), but after these phases the effect was no longer significant.

Figure 7.

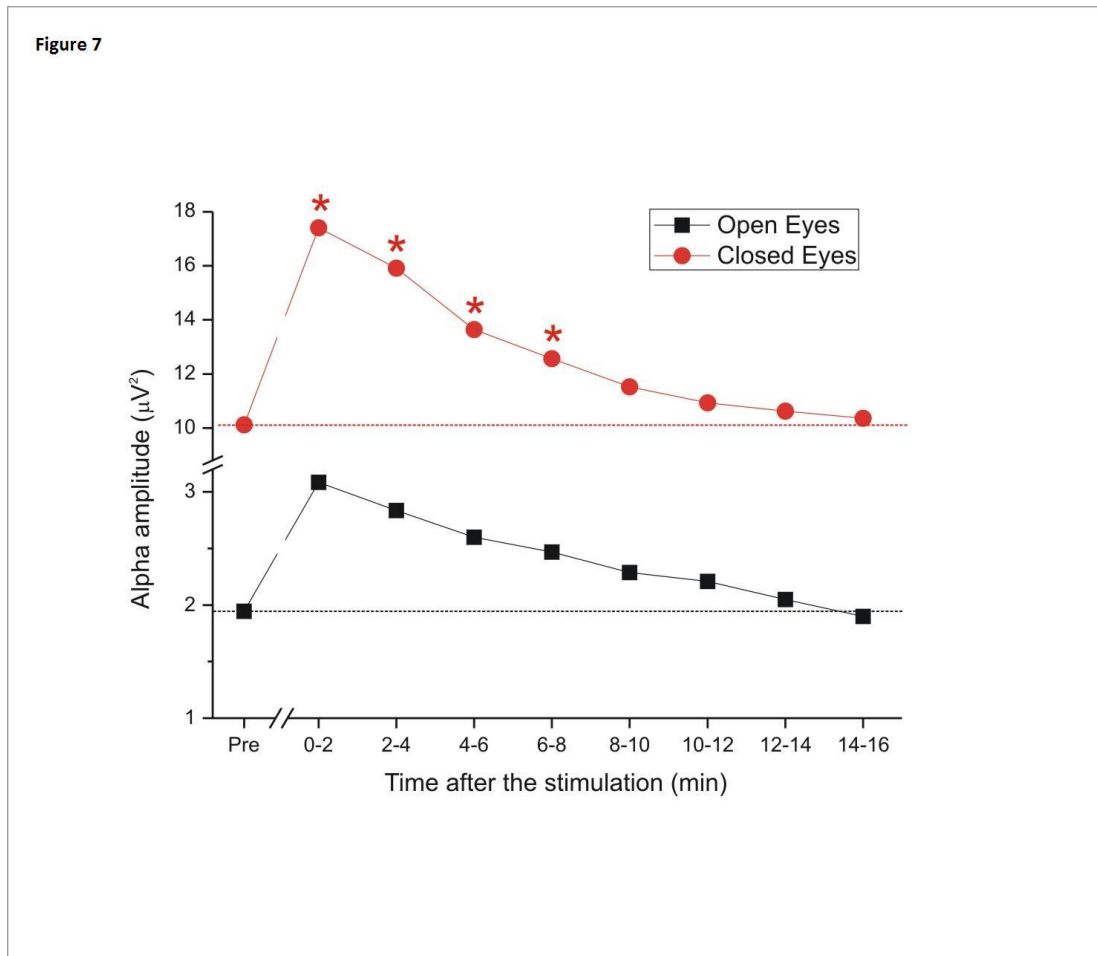


Figure 7. Time-course of alpha activity during the pre-test and after the end of anodal tDCS in eight epochs of two minutes each.

4. Discussion

When tDCS is used clinically, it is essential to know whether the position of the stimulating electrodes on the head will produce an electric field in the target area or whether the current will diffuse to other cerebral areas. In fact, direct observation of the current flow in ecological settings, such as those used in tDCS rehabilitative protocols, is lacking. To simulate a resting state, we studied the effect of tDCS stimulation over the spontaneous EEG rhythm. In particular, we stimulated the scalp over the right angular gyrus with electrodes that were the same size as those typically used for rehabilitation.

Five main findings emerged from the present study. First, The only effect of DC was on alpha rhythm band. Second, anodal tDCS significantly affected alpha rhythm, but cathodal tDCS did not. Third, alpha activity was modulated in non-contiguous areas as well as areas underlying the active stimulating electrode. Fourth, anodal DC led to significant changes in alpha peaks both when eyes were open and closed (but no statistical interaction was observed between these two factors). These changes were particularly strong in parietal areas. Milder but significant changes were also observed in more anterior regions. Fifth, the anodal effect was greatest at the beginning of the period following

the stimulation (i.e. 7.5 min after tDCS ended) and it decreased with time. It is not surprising that the stimulation effect was present only in alpha rhythms, because it is the dominant rhythm during the relaxed awake state. The lacking cathodal tDCS effect might be due to the fact that depolarization of the cell during cathodal stimulation leads to suppression of ongoing cognitive activity, which in our case was absent. This evidence partially supports the idea of Kanai et al. (2008) that current alternating stimulation (tACS) interacts with the ongoing oscillatory activities measured by EEG.

Alpha activities emerge preferentially with the closing of the eyes and relaxation and attenuate with eye opening or mental exertion (Gevins et al., 1980). In our study, we showed that the DC effect was significant for anodal DC stimulation both when the eyes were closed and open. However when the dependent variable was divided in 8 epochs, the DC effect was significant only for eye closed: this result is probably due to a decreased statistical power and to decrease of signal to noise ratio.

An interesting and unexpected finding was the presence of a significant alpha modulation in the anterior frontal brain regions. We know from the literature that DC flow can spread into cerebral areas that are near or contiguous with those stimulated (i.e. Datta et al, 2010). Here, we found an effect of anodal DC in cerebral regions located quite far from the

stimulated ones. In particular, we recorded alpha modulation in correspondence with electrode sites AFz, FCz and Fz when we stimulated over P2, P4 and P6. This evidence seems particularly important for those who use tDCS as a rehabilitative tool. As stated above, if tDCS is used in rehabilitation many factors have to be considered such as electrode montage and size of the electrodes and the route of the current under the skin. Each of these factors can be crucial for the accurate outcome of the rehabilitative protocol. In this study, we focused on the parietal areas because they are the ones most stimulated during neuropsychological rehabilitation. The finding of an effect also over the anterior regions can be explained by the diffusion of the anodic DC along the parieto-frontal connections. A recent study (Thiebaut de Schotten et al., 2012) based on advanced tractography described three branches of the superior longitudinal fasciculus: the second branch of this long-range association pathway “originates in the anterior intraparietal sulcus and the angular gyrus and terminates in the posterior region of the superior and middle frontal gyrus (BA. 6, 8, 9)”. Indeed, this association pathway might explain the present findings. We would like to stress that the frontal effect was observed in almost all examined subjects in a resting state with eyes closed (13 subjects) and eyes open (11 subjects).

The effect of tDCS over time is a critical issue because the duration of the after effect of the stimulation might last from minutes to hours depending on the intensity and exposure time of the stimulation. As suggested by Nitsche & Paulus, (2000), to obtain after-effects at least three minutes of exposure at an intensity of at least 0.6 mA are required. Also, the direction of the electrode polarization is crucial in the direction of the after-effects. According to recent literature, many factors can influence the interval of the tDCS effect. For example, Antal et al (2010) found that when tDCS intensity and duration were the same, the effect of stimulation lasted more on motor areas than posterior regions. It is also known that the effect of DC depends greatly on the subsequent observed behavior. The authors found that when subjects were given the same DC stimulation over the same cerebral areas, the effect lasted longer on general memory tasks than working memory. Recently, Paulus (2011) reviewed the literature on the technical features of tDCS and tACS and found that even when DC was first used it seemed that the longer the stimulation lasted the longer the after-effects would last. Most recent data have shown that there is an upper limit for sustaining the excitatory after-effects from anodal tDCS. Monte-Silva et al.(2011) found that after continuous stimulation with anodal tDCS for 26 min, cellular excitation switched to inhibition.

In this study, we explored the effects of DC on a pure variable, that is, spontaneous EEG. We found that the strongest change occurred in the first two minutes after stimulation ended. The effect systematically decreased every two minutes and was effective in a time window of about 6-8 min after the stimulation. Although this evidence comes from a specific condition, several statements can be made. First, it seems that tDCS is most effective immediately after the stimulation. This evidence contrasts with the previous belief that DC has a summative power over time and strongly supports the findings of Monte-Silva et al. (2011). In other words, a short stimulation of about 10 min could have the same effect as a longer exposure to DC. The findings of our study suggest that the preferential window for a rehabilitative intervention is at the very beginning of stimulation.

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Conclusions

The results described in this experimental work have allowed to clarify two points:

- 1) The consequences on the somatosensory system in response to a real increase of body dimensions.
- 3) The potential of tDCS in the modulation of the brain electrical activity, with particular attention to the spread of the current flow and the duration of the post-stimulation.

In the first experiment the upper limbs lengthening surgery has enabled to investigate, in a relatively short time, how the body representation adapts to the new physical condition. Thanks to the use of tests (2PDT, Von Fray, pressure task) dedicated to the investigation of elementary processes of tactile discrimination (somatosensation), as well as of test (Distance task, Daurat-Hmkljack test, peripersonal task) able to measure higher-order cognitive processes (somatoperception, somatopercception, somatopercception, peripersonal space), it's been possible to observe the changes in the various types of body representation. These changes do not stop at the end of lengthening, but they go on for several months, revealing plastic mechanisms of reorganization of the new body dimension still in progress. Particularly interesting, in my opinion, are

the differences in the adaptation of the different levels of processing during the after surgery period. In first instance, the primary sensory processes go through an immediate distortion due to the important peripheral modifications, such as the density reduction of the mechanoreceptors. This change is evident in the performance of the patient at the 2pdt, who needs a greater distance between the two points to perceive them as separated. In order to correct this physiological distortion of the perception, the brain reorganizes itself to adjust to the metric characteristics of the lengthened body part (as shown in distance task). This upgrade does not take place immediately, but it is evident only after several months (follow-up) and allows the patient to judge the stimuli that come into contact with her body in a more truthful way. This phenomenon partly contrasts with the results of other studies which highlight a rapid update of the brain's ability to estimate the metric properties of the body after experimental manipulations of the physical body (Taylor-Clarke et al., 2004; de Vignemont et al., 2005). The main difference between these studies and the present research, in my opinion, is due to the fact that they have mainly used illusions to observe these phenomena, while here for the first time we've used a realistic model of body growth. This real growth of the physical body necessarily entails the integration of a greater amount of new parameters from different

channels (mechanoreceptors, proprioceptors, etc.), which will have to be included in the previous model of the body's metric properties. The duration of this progressive change is consistent with the time required by the cortical maps of SI to expand in favor of the "new" body part, as previously reported by other authors (Di Russo et al., 2006). Similarly, the update of the structural knowledge about the location of the body parts, defined by someone "Body Structural Description" (Baxbaum and Coslett, 2001), is visible only in the last analysis (follow-up). The interesting thing is that the changes in the performance (measured by the Daurat-Hmlejack test) are exclusively related to the lengthened limbs. The topography of the effect would seem to suggest that also this level of processing could be influenced by visual maps. The most convincing evidences in favor of visual maps of the body come from the patients with autotopoagnosia (Corradi-Dell'Acqua and Rumiati, 2007). These patients generally fail a task (very similar to the Daurat-Hameljak test) according to which they have to build a whole body using pieces depicting body parts, while they are skilled in a similar task using body parts of animals. Furthermore, the same body parts that they are not able to place are called correctly. This dissociation indicates that it's not about a generalized deficit of spatial skills nor about a deficit of semantic-lexical knowledge of the body (Corradi-Dell'Acqua et al.,

2008). In the present study the observation that only the pieces depicting the lengthened body parts are positioned differently after surgery contrasts with some previous studies. In this case, some authors (Kinsbourne, 1995; Kinsbourne and Warrington, 1962) argue that the topological knowledge about the body appear to be approximately homogeneous and are included in a holistic representation of the entire body rather than in a map of it. According to what just said, we can deduce that the performance of our patient with achondroplasia results as particularly unusual. Even knowing the results' limits to be generated, implicit in the studies "single case", I believe that this point deserves to be further investigated in the future in order to examine more accurately the characteristics of this body representation.

Finally, in the experiment 2 we've faced methodological issues concerning the use of the tDCS in a more strictly ecological setting. Specifically, we've observed that the spread, the duration and the effect of the stimulation follow precise rules that should necessarily be taken into consideration for the purpose of an effective use of the same stimulation.

In my opinion, we should pay particular attention to some aspects listed below.

The first is about the transient effect of the stimulation, which in our case has lasted a few minutes. Currently, in the rehabilitative field the tDCS is used preliminarily to the motor and/or cognitive treatment. Therefore, in order to exalt the advantages that the tDCS offers, it would be appropriate to consider a redefinition of the times of administration of the technique. In fact, sessions of stimulation with tDCS concurrent to the respective phases of rehabilitation protocols would provide better outcomes. The use of tDCS in the rehabilitation field should therefore take place, where possible, in conjunction with the rehabilitation protocols (both motor and cognitive rehabilitation).

A further aspect to consider is the stimulation area from which peculiar effects follow also occurring in areas far from those directly affected by the same stimulation. For example, in this experiment it appears that the anodic stimulation of the parietal lobe influence anterior structures. Therefore, it would be appropriate to carefully consider this effect in the experimental protocols in order to safeguard validity and reliability of the studies that make use of such method. On the contrary, instead, the peculiar dissemination of the current flow could assure best results in certain rehabilitation protocols that need to stimulate more areas simultaneously. A case exemplifying what just stated is the rehabilitation of patients with neglect, who often suffer at the same time from parietal

and frontal lesions which well lend to benefit from the overexposed peculiar diffusion pattern.

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