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Primary motor cortex changes after amputation correlate with phantom limb pain and the ability to move the phantom limb

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ABSTRACT

A substantial body of evidence documents massive reorganization of primary sensory and motor cortices following hand amputation, the extent of which is correlated with phantom limb pain. Many therapies for phantom limb pain are based upon the idea that plastic changes after amputation are maladaptive and attempt to normalize representations of cortical areas adjacent to the hand area. Recent data suggest, however, that higher levels of phantom pain are associated with stronger local activity and more structural integrity in the missing hand area rather than with reorganization of neighbouring body parts. While these models appear to be mutually exclusive they could co-exist, and one reason for the apparent discrepancy between them might be that no single study has examined the organisation of lip, elbow, and hand movements in the same participants. In this study we thoroughly examined the 3D anatomy of the central sulcus and BOLD responses during movements of the hand, elbow, and lips using MRI techniques in 11 upper-limb amputees and 17 healthy control subjects. We observed different reorganizational patterns for all three body parts as the former hand area showed few signs of reorganization, but the lip and elbow representations reorganized and shifted towards the hand area. We also found that poorer voluntary control and higher levels of pain in the phantom limb were powerful drivers of the lip and elbow topological changes. In addition to providing further support for the maladaptative plasticity model, we demonstrate for the first time that motor capacities of the phantom limb correlate with post-amputation reorganization, and that this reorganization is not limited to the face and hand representations but also includes the proximal upper-limb.

Introduction

After amputation, the human primary sensorimotor cortex (SM1) undergoes massive reorganization involving both structural (Jiang et al., 2015; Preissler et al., 2012; Simoes et al., 2012) and functional (Elbert et al., 1997; Karl et al., 2001; Kew et al., 1994; Knecht et al., 1996; Montoya et al., 1998; Yang et al., 1994) changes in SM1 contralateral to the amputation as input-deprived regions are recruited by body-parts with neighbouring cortical representations. Nearly all studies investigating functional reorganization in hand amputees report an inter-hemispheric asymmetry of the face representation (e.g. Karl et al., 2001; Makin et al., 2015b), and the majority also describes a significant correlation between this asymmetry and the degree of phantom limb pain (Flor et al., 1995; Flor et al., 1998; Karl et al., 2004; fMRI: Lotze et al., 2001; Lotze et al., 1999; MacIver et al., 2008). This correlation supports the *maladaptive plasticity model*, which postulates that representations of body parts adjacent to the missing limb's representation expand and invade the deprived cortex, and that this 'invasion' leads to phantom limb pain. This model is further supported by evidence that interventions that reduce phantom limb pain also reduce the inter-hemispheric asymmetry of the face representation (Birbaumer et al., 1997; Chen et al., 2013; Flor, 2002; Flor et al., 2001; Huse et al., 2001; Lotze et al., 1999; MacIver et al., 2008).

The maladaptive plasticity model ignores the persistence of the missing limb's representation (MacIver et al., 2008; Mercier et al.,

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2006; Raffin et al., 2012a), however, and assumes a “take-over” by other body parts rather than a “cohabitation” (see Reilly and Sirigu, 2007 for a discussion). On the basis of structural and functional MRI data, Makin and colleagues proposed an alternative model: the *persistent representation model*. This model postulates that persistent pain is associated with preserved structure and function in the former hand area rather than reorganization of neighbouring body parts (Makin et al., 2013b). These authors found that individuals with more intense phantom limb pain had well preserved structure in the former hand territory and greater activation intensity during phantom movements, as well as decreased resting state connectivity between the bilateral sensorimotor hand regions. In a more recent paper, the same authors examined lip activations only and while they did observe some lip reorganization, in contrast to previous studies, it was uncorrelated with pain. Instead it was most reliably predicted by tactile acuity and dexterity of the intact hand (Makin et al., 2015b).

While there is empirical evidence in support of both models, neither provides a complete explanation of post-amputation sensorimotor reorganization and its relationship with phantom pain and the structure and function of the former hand territory. Furthermore, both models ignore the complex relationship between phantom mobility and phantom pain (Gagné et al., 2009; Raffin et al., 2012b) and neither attempts to explain why the majority of non-pharmaceutical therapies for phantom limb pain try to strengthen the missing limb's representation by training voluntary or imagined phantom movements (Brunelli et al., 2015; Foell et al., 2014; Giraux and Sirigu, 2003; MacIver et al., 2008; Mercier and Sirigu, 2009; Trojan et al., 2014).

A recent modelling study suggests that these two models could co-exist in the primary somatosensory cortex (Bostrom et al., 2014). Here, we investigated their possible co-existence in the primary motor cortex by examining reorganizational patterns of both amputated body parts (which are informative about representational plasticity) and non-amputated body parts (which are informative about maladaptive plasticity). We performed both structural imaging and functional recordings by measuring BOLD responses associated with three different movements: lips, hands, and elbows. Furthermore, given the clinical importance of the ability to voluntarily move the phantom limb we quantified the individual phantom limb motor performance as well as chronic phantom pain and correlated them with reorganizational changes of each of the three body parts.

Materials and methods

Participants

Eleven traumatic upper-limb amputees participated in the experiment (mean age 42 years [range: 22–67], 4 females and 7 males). On average, the accident occurred 7.5 years [5 months–30 years] before testing. The Edinburgh Handedness Inventory (EHI) revealed that eleven amputees were right hand dominant prior to the amputation, and five of these lost their dominant hand (see Table 1 for patient details). Seventeen healthy volunteers (7 females and 10 males; mean age 32.1 years [21–42], one left-handed person) were recruited from the general population. A detailed medical history together with careful examination of the anatomical scans confirmed that neither amputees nor controls had suffered a brain lesion or had a history of neurological or psychiatric illness. The nature of the experimental procedures was explained to all subjects who gave their written informed consent prior to participating in the experiment. This study was approved by the Local Ethics Committee of Lyon Sud-Est IV (A 09-115), and conformed to the ethical aspects of the Declaration of Helsinki.

Assessment of phantom limb pain and phantom limb motor performance

Clinical data related to the amputation were collected prior to the neuroimaging exam using a structured interview which included an evaluation of phantom sensations and chronic phantom limb pain intensity perceived over the last three months (PLP), and rated on a continuous 10 cm visual-to-analog scale (VAS) (Flor et al., 1995). During this interview we also used a standard technique to perform a quantitative assessment of their ability to make voluntary movements with the phantom limb and of EMG activity associated with these phantom movements (see Gagné et al., 2009 for details). Patients were asked to produce cyclic voluntary movements with their phantom and to verbally report when they had completed five movement cycles. EMG activity in the stump muscles verified that amputees were not performing motor imagery (see Raffin et al., 2011, 2012a) and was used to check the movement times recorded from the verbal start and stop signals. All amputees were able to open and close their phantom hand and to oppose each of the four fingertips to the thumb. Since hand opening and closing was used during the imaging session to assess motor cortex activity we quantified phantom motor performance (MP) as the speed of finger-to-thumb opposition (five divided by the time taken to complete the five cycles), with larger MP values associated with better performance.

Table 1
Clinical and phantom limb motor control characteristics of the amputee group. Patients are presented in order of decreasing phantom motor performance.

Age (years)	Time since amp. (months)	Amp. side/Dom. Side	Amp. level/length of remaining limb (%)	Prosthesis use	Chronic PLP (VAS) (0–10)	Phantom motor perf. (cycles/s)
33	84	R/R	D/80	No use	0	0.34
22	27	L/L	P/25	No use	4	0.25
39	360	L/R	D/43	No use	0	0.24
28	204	R/R	D/48	No use	4	0.22
40	102	R/R	P/24	Myo (constant)	6	0.21
29	24	L/R	P/25	No use	5	0.14
27	12	L/R	P/42	Mechanic (part-time)	3	0.12
67	37	L/R	P/32	Esthetic (rarely)	5	0.11
55	106	L/R	P/15	Esthetic (rarely)	6	0.11
65	5	L/R	P/24	No use	5	0.10
62	24	L/R	P/15	Esthetic (constant)	7	0.09

Amp: amputation/amputated; Dom: Dominant; Myo: Myoelectric; L: Left; R: Right; D: Distal; P: Proximal.

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