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Neural correlates of evoked phantom limb sensations

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ABSTRACT

Previous work showed the existence of changes in the topographic organization within the somatosensory cortex (SI) in amputees with phantom limb pain, however, the link between nonpainful phantom sensations such as cramping or tingling or the percept of the limb and cortical changes is less clear.

We used functional magnetic resonance imaging (fMRI) in a highly selective group of limb amputees who experienced inducible and reproducible nonpainful phantom sensations. A standardized procedure was used to locate body sites eliciting phantom sensations in each amputee. Selected body sites that could systematically evoke phantom sensations were stimulated using electrical pulses in order to induce phasic phantom sensations. Homologous body parts were also stimulated in a group of matched controls.

Activations related to evoked phantom sensations were found bilaterally in SI and the intraparietal sulci (IPS), which significantly correlated with the intensity of evoked phantom sensations. In addition, we found differences in intra- and interhemispheric interaction between amputees and controls during evoked phantom sensations. We assume that phantom sensations might be associated with a functional decoupling between bilateral SI and IPS, possibly resulting from transcallosal reorganization mechanisms following amputation.

1. Introduction

Phantom limb phenomena include the persistent awareness of the amputated limb as well as specific sensory or kinesthetic sensations referred to the missing limb and are perceived by almost all amputees (Sherman, Devor, Casey Jones, Katz, & Marbach, 1996). Phantom sensations can be spontaneous or evoked by sensory inputs from the existing body parts (Hunter, Katz, & Davis, 2005). The sensations reported by the amputees can be diverse and may include feelings of warmth or cold, itching, tingling, electric sensations, and in some cases unpleasant or painful sensations (i.e. "phantom limb pain").

Few studies have investigated neural changes related to non-painful phantom sensations. For example, Björkman et al. (2012) used functional magnetic resonance imaging (fMRI) during tactile stimulation of the residual limb and reported bilateral activation of the primary somatosensory cortex (SI), contralateral parietal and premotor cortices. However, they were not able to dissociate the neural activation induced by the stimulation of the residual limb from the percept of phantom sensations as they might have activated inputs from the residual limb to the brain region that formerly represented the amputated limb and they did not assess ratings of evoked phantom sensations. Similarly, Brugger et al. (2000) reported parietal and ventral premotor activation but not activation of SI related to the phantom percept in a congenital amputee. However, transcranial magnetic stimulation of the sensorimotor cortex evoked phantom sensation. Roux et al. (2003) reported activations in the sensorimotor areas when phantom sensation was present as did Flor et al. (2000) although they did not observe reorganization of the cortical map as suggested by Ramachandran, Rogers-Ramachandran, and Cobb (1995) and Ramachandran, Brang, and McGeoch (2010). The current literature on tactile illusions in non-amputees also suggests the involvement of SI where the percept rather than the actual physical stimulus seems to be represented (Bufalari, Di Russo, & Aglioti, 2014). SI has also been involved in sensory illusions such as the cutaneous rabbit illusion (Blankenburg, Ruff, Deichmann, Rees, & Driver, 2006), the funneling or rubber hand illusion (Chen, Friedman, & Roe, 2003; Schaefer, Konczak, Heinze, & Rotte, 2013), or supernumerary phantom limbs, which are similar to a phantom sensation (Khateb et al., 2009; McGonigle et al., 2002). However, it seems that not only SI but also the inferior frontal cortex (Brodmann area (BA) 44, BA45), premotor and posterior parietal areas (e.g. intraparietal sulcus, IPS) could be involved in the perception of abnormal somatosensory phenomena (Brancucci, Franciotti, D'Anselmo, & Della Penna, 2011; Ehrsson, Spence, & Passingham, 2004; Knapen, Brascamp, Pearson, van Ee, & Blake, 2011 Zaretskaya, Anstis, & Bartels, 2013). For example, illusion experience related to the rubber hand was associated with increased activity in brain areas related to the integration of multisensory representation of body parts, such as

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the intraparietal and ventral premotor cortices (Brozzoli, Gentile, & Ehrsson, 2012). Hari et al. (1998) showed that a supernumerary limb is characterized by suppression of activity in contralateral secondary somatosensory cortex (SII). Similar neural networks might also be underlying evoked phantom sensations in amputees, although these networks might undergo cortical reorganization resulting from limb amputation. A main argument for such reorganization mechanisms is the sensory map of the body, which has been shown to change in amputees, such that touching the face could evoke illusions of tactile sensations on the phantom, in a stable, topographically organized manner (Ramachandran and Hirstein, 1998; Ramachandran et al., 2010). Plastic changes to the body map have also been related to altered interhemispheric interactions from the recruitment of horizontal connections of the intact limb representation to the deafferented cortex (MacIver, Lloyd, Kelly, Roberts, & Nurmikko, 2008). For example, compared with two-handers, amputees have been shown to have a reduced interhemispheric structural (Xie et al., 2013) and functional connectivity in SI (Makin et al., 2013). The neural correlates of nonpainful phantom sensations and the relationship between phantom sensations and interhemispheric reorganization have not yet been investigated.

We aimed to explore the brain representation of evoked non-painful phantom sensations (referred sensations) in limb amputees by using functional magnetic resonance imaging (fMRI) in five chronic limb amputees (selected from 156 patients) where phantom sensation could be reliably turned on and off while electrically stimulating body areas adjacent to or remote from the amputation site (Fig. 1). This permitted a passive activation of phantom sensation without any mental effort or physical induction such as hypnosis-, imagery- or movement-elicited phantoms (Raffin, Mattout, Reilly, & Giraux, 2012; Willoch et al., 2000). In addition, five controls matched for sex, age and stimulated body site (yoked controls) were included.

2. Materials and methods

2.1. Subjects

We selected five unilateral limb amputees out of 156 based on the criterion of showing phasic and reliable referred sensations in the phantom. These amputees were all male and included four upper- and one lower-limb amputee with a mean age of 42 years (range 35–59). Five yoked healthy controls were also tested (all male, right-handed, mean age 44 years, range 33–62). Patients with a history of neurological or mental disorder were excluded from the study. For a detailed description of the sample, see Table 1. Ethical committee approval was received from the Ethical Review Board of the Medical Faculty Mannheim, Heidelberg University, and written informed consent was obtained from all participants.

2.2. Laboratory screening: psychometric assessment of phantom phenomena

The amputees participated in a psychometric evaluation including a structured interview about the amputation and its consequences and included a detailed assessment of painful and non-painful phantom phenomena such as MPI (German version of the Multidimensional Pain Inventory adjusted to separately measure phantom and residual limb pain), (Flor, Rudy, Birbaumer, Streit, & Schugens, 1990; Flor et al., 1995; Winter et al., 2001).

2.3. Laboratory screening: procedure for detecting evoked phantom sensations in the missing limb

Referred sensations were assessed by using consecutive mechanical (cotton swabs, pin pricks) stimulation over 57 standardized sites spread over the entire body using a standardized procedure (Grüsser et al., 2004). Ten sites were located in the face, 23 on the upper body part and the remaining sites covered the lower body. The subjects had to indicate where they felt a sensation and described its quality and rated the intensity. They were naïve to the procedure of testing evoked phantom sensations. The localization of sensations perceived at the site of stimulation as well as on the phantom was marked on the subject's body and drawn on a body template. A total of 25 body sites which were responsive to mechanical stimulation and elicited phantom sensation in the amputee group, with five sites for amputee A1, three sites for A2, ten sites for A3, three sites for A4 and four sites for A5 (Fig. 1). When referred sensations were obtained, electrical stimulation was used to test if this would also elicit the sensation.

We applied monophasic constant current stimuli of 200 ms duration each (DS7A, Digitimer, Hertfordshire, England) using transcutaneous custom-designed foil electrodes. Using the method of limits, the perception threshold was determined as the mean of three series of ascending electrical stimuli, evoking sensations either at the stimulated body site or in the missing limb or both. Electrical stimulation over the selected body sites elicited phantom sensations in 10 body sites, with three sites for A1 and A2, two sites for A3, one site for A4 and for A5. The quality of phantom sensations was different across amputees (see Table 1). In the control group, no sensation was reported outside of the stimulated site.

Sites eliciting robust evoked phantom sensations that could be

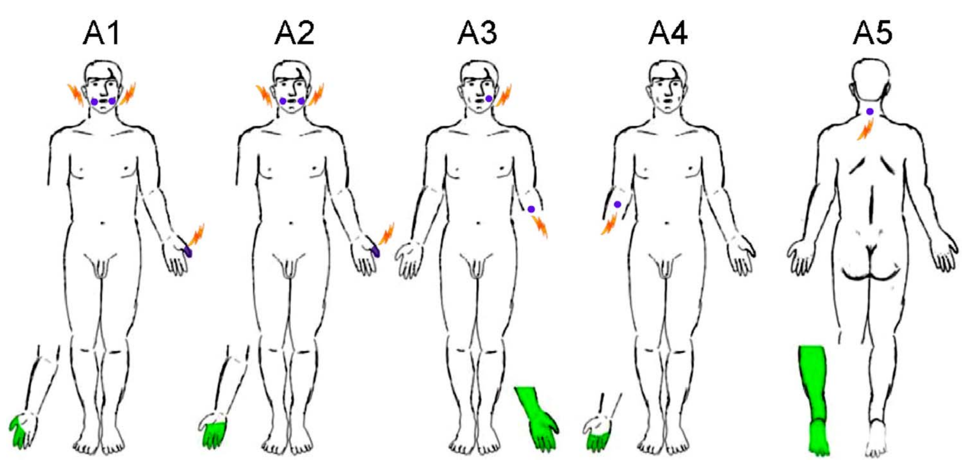

Fig. 1. Body templates of five limb amputees with phasic referred phantom sensations. Purple dots indicate the body sites that were electrically stimulated and green surfaces indicate areas in the missing limb in which amputees perceived phantom sensations. A1–A5: reference of amputee respective to data provided in Table 1. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)