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Cortical Remapping and the Phantom Breast Phenomenon after Radical Mastectomy

Remapeamento Cortical e o Fenómeno da Mama Fantasma após Mastectomia Radical

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Abstract

The occurrence of phantom limbs after amputations has been linked, in the last two decades, to maladaptive brain plasticity and reorganization. Phantom breasts are also frequent after mastectomies, and there is published evidence that the same mechanisms are at play in such cases. However, the notion that after amputations somatotopic representation areas of lost body parts in the somatosensory cortex (SC) often merge with adjacent ones was to some extent challenged, in the case of breast amputations, by lack of knowledge of the precise localization of the ear and nipple representation areas in SC. Here we report cases of SC reorganization after mastectomies. We have studied 25 women, 32 to 78 years old who underwent radical mastectomy. Sixty-four percent presented with phantom breast sensations after the surgery and 12.5% also reported phantom pain. We have examined the results of clinical sensory testing in view of new imaging studies that have shed new light upon the representation of the concerned body parts in the sensory homunculus.

Keywords: mastectomy, phantom breast, brain plasticity, Penfield's homunculus, somatotopy, breast cancer

Resumo

A ocorrência de membros fantasmas após amputações tem sido ligada, nas últimas duas décadas, à plasticidade cerebral aberrante. Mamas fantasmas também são frequentes após mastectomias, e há evidências publicadas de que o mesmo mecanismo pode estar operante nesses casos. Entretanto, a noção de que, após amputações, áreas de representação somatotópica das partes corporais perdidas no córtex sômato-sensorial (CS) frequentemente se mesclam com áreas adjacentes foi de certo modo prejudicada, no caso das mastectomias, pela falta de conhecimento acerca das localizações precisas das representações do mamilo e da orelha no CS. No presente estudo são relatados casos de reorganização do CS após mastectomia. Vinte e cinco mulheres, com idades de 32 a 78 anos, submetidas à mastectomia radical, participaram do estudo. Sessenta e quatro por cento apresentaram mama fantasma, 12,5% com dor fantasma. Os resultados da avaliação clínica da sensibilidade foram examinados à luz dos recentes estudos de neuroimagem que têm esclarecido detalhes da representação somatotópica das partes corporais envolvidas.

Palavras-chave: mastectomia, mama fantasma, plasticidade cerebral, homúnculo de Penfield, somatotopia, cancro de mama

Introduction

The phenomenon of phantom limbs after amputations has been well recognized in the medical literature. Phantom breasts and phantom breast pain have also been reported, as well as phantom genitals, after radical mastectomies and gender-reassignment surgeries (Ramachandran & McGeoch, 2007; Ramachandran & Rogers-Ramachandran, 2000).

Although the phantom limb phenomenon has been explained in the past on the basis of peripheral neural changes related to amputation neuroma formation (Katz, 1992), nowadays it is regarded as a mainly cortical phenomenon related to somatosensory cortex (SC) remapping. It has been demonstrated, for example, that after amputation or deafferentation of a limb the somatotopic cortical representation areas of the lost body part are usually not silent, and tend to merge functionally with nearby cortical areas in Penfield's homunculus (Cohen et al., 1991). This in turn might lead to the spurious continuing perception of a lost limb or body part.

Animal studies have shown this kind of cortical plasticity mainly in the SC (Bruno, Merzenich, & Nudo, 2012; Pons et al., 1991), whereas human studies have concerned mainly the motor cortex (Chen, Corwell, Yaseen, Hallett, & Cohen, 1998) . However, a classical experiment was able to demonstrate acute reorganization of the rat motor cortex following a facial nerve lesion (Sanes, Suner, Lando, & Donoghue, 1988). A similar acute reorganization was also demonstrated in the human motor cortex after forearm anesthesia (Brasil-Neto et al., 1992).

Pons et al. (1991) have shown, in monkeys with a long-standing deafferented arm after dorsal rhyzotomies, that tactile stimulation of the deafferented arm resulted in neuronal activity in the face somatotopic representation area. In humans, cortical remapping of SC representation areas has been elegantly demonstrated (Ramachandran & Rogers-Ramachandran, 2000) by tactile stimuli applied to body parts which have cortical representation areas adjacent to those of the amputated limb; sensations are usually referred to the stimulated area and to the phantom limb (Ramachandran, Blakeslee, & Sacks, 1998; Aglioti, Bonazzi, & Cortese, 1994).

In the motor realm, a classical study (Sanes et al., 1988) demonstrated that, after facial nerve section in the rat, cortical stimulation of the vibrissae somatotopic representation area obviously did not produce movement of the vibrissae, but resulted instead in forepaw movement, an effect not present in the intact animal. Moreover, this remapping of cortical motor areas occurred within minutes of facial nerve section, thus ruling out axonal sprouting and strongly suggesting unmasking of previously existing synaptic connections between forepaw and vibrissa cortical representation areas. Moreover, it was found that, in rats with an intact facial nerve, motor cortex perfusion with bicucculine, a GABA antagonist, produced a similar effect, suggesting that such connections between the vibrissae and forepaw cortical areas are present in the intact animal, but are actively inhibited by GABA.

In humans, motor cortex mapping by transcranial magnetic stimulation has revealed acute reorganization after forearm deafferentation by regional anesthetic blockade (Brasil-Neto et al., 1992). Within minutes of forearm anesthesia there was an increase in excitability of the motor cortical somatotopic representation areas of muscles proximal to the anesthetized forearm. This, again, suggested unmasking of previously existing synaptic connections, rather than axonal sprouting.

If phantom limbs are due to persistent activation of SC topographic representation areas of a missing body part, how can one account for the phenomenon of phantom pain? One explanation, favored by Ramachandran (Ramachandran, Brang, & McGeoch, 2010) is that learning plays a major role: if pain has been present for a long time in a limb before amputation, then learned pain can be transferred to the phantom limb.

However, in spite of this new knowledge regarding phantom limbs, few attempts have been made to explain in detail the pathophysiology of phantom breast, a notable exception being the study by Aglioti, Cortese, and Franchini (1994). These authors found that stimulation of skin areas which are represented in cortical areas which are probably close to the breast representation area in the SC gave rise to simultaneous sensations in the ipsilateral phantom breast. These regions were the pinna, shoulder and dorso-thoracic areas. This finding suggested that neurons originally functionally connected to breast skin areas were responding instead to stimuli emanating from the stimulated skin regions. Moreover, such remapping was already in place as soon as 5 days after mastectomy. However, at the time little was known about the SC representations of the ear and nipple. Penfield's classical depictions of SC somatotopy did not include the ear (Nihashi et al., 2001) or the breast (Di Noto, Newman, Wall, & Einstein, 2013).

We have prospectively followed 25 patients who underwent radical mastectomy for breast cancer and recorded the appearance of the phantom breast phenomenon, as well as clinical evidence for remapping of cortical representation areas, according to the methods proposed by Ramachandran and Aglioti.

Patients and Methods

Twenty-five women, aged 32 to 78 years (mean 52.32) , participated in the study.

All underwent radical mastectomy for breast cancer. All patients were free from neurological signs or symptoms and had normal results in the Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975). The study was approved by the local Ethics Committee.

All patients were evaluated in the hospital prior to and after surgery, and also at home up to 14 days after surgery. A questionnaire was used to evaluate the presence of phantom breast and phantom pain was assessed by means of a Visual Analog Scale (VAS). In those with phantom breast, cortical remapping was clinically assessed by stimulating the skin of both pinnae, face, and contralateral nipple with fingertips and/or cotton swabs. During the procedure, patients kept their eyes closed and told the examiner where they perceived the elicited sensations.

Results

Sixteen women (64%) presented postoperatively with a phantom breast. Thirteen of these (81.25 %) perceived a phantom breast already on the first postoperative day; 11 (68.75 %) of them perceived a complete breast. Two patients (12.50 %) experienced phantom breast pain. Phantom pain intensity was judged by these patients to be equal to 5.0 and 6.5, respectively, in the VAS. The stimulation of other skin areas produced simultaneous sensations in the phantom breast in 5 patients (31.25 %).

Figure 1 shows the percentage of patients who presented with a phantom

Figure 1. Total incidence of phantom breast (PB), phantom pain (PP), local tissue pain and cortical remapping. Percentages are relative to all 25 patients. It can be seen that PB is a frequent occurrence, but PP is relatively rare.

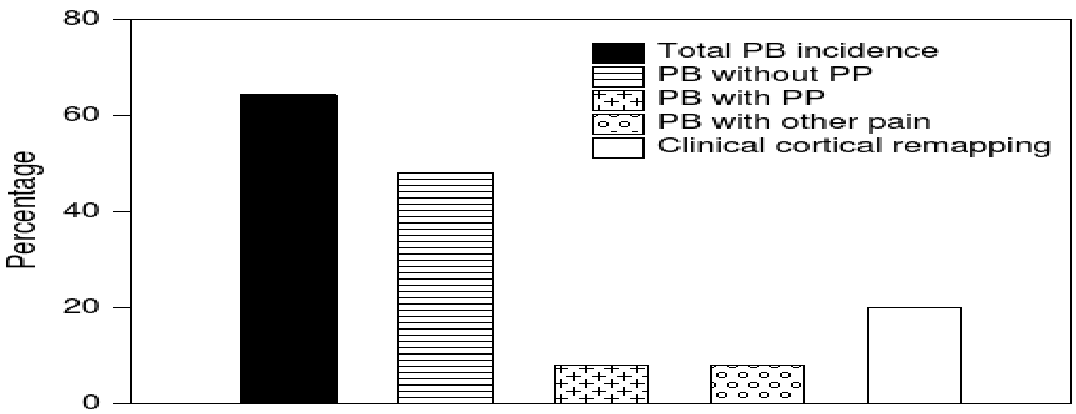

Figure 1. Clinical evidence of cortical remapping was obtained according to the methods proposed by Ramachandran and Aglioti.

breast, comparing the incidence of phantom pain to that of prosthesis and local tissue pain; it also shows the percentage of patients in whom stimulation of other body areas induced sensation referred to the phantom breast, suggesting somatosensory cortical remapping.

Figure 2. Shows the detailed results of stimulation trials performed to disclose cortical remmaping

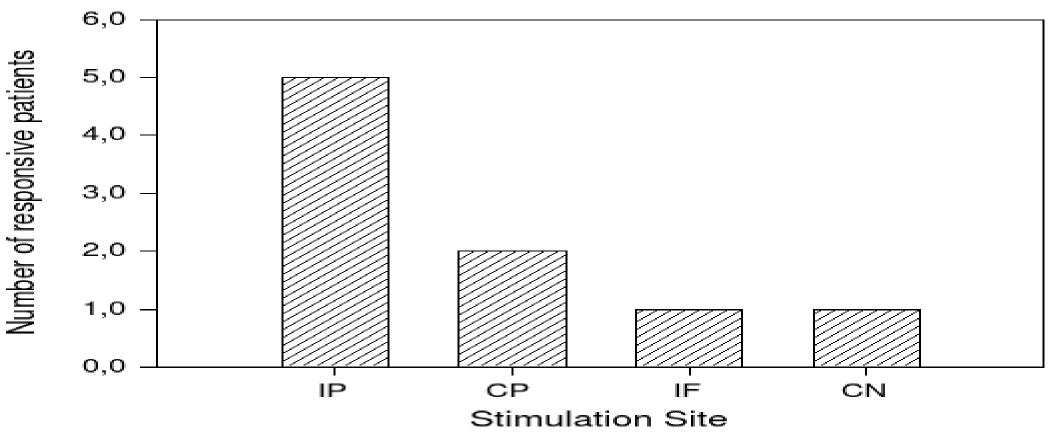

Figure 2. Number of patients in whom phantom breast sensations were evoked by stimulation of: IP=ipsilateral pinna; CP= contralateral pinna; IF=ipsilateral face; CP=contralateral nipple.

Discussion

We have confirmed the findings of Aglioti et al.(Aglioti, Cortese, & Franchini, 1994) of SC remapping, especially involving the ipsilateral pinna, in patients who have undergone radical mastectomy.

Our results are also in keeping with recent studies of the somatotopic representation areas of the ear and the nipple(Nihashi et al., 2001; Komisaruk et al., 2011). Nihashi et al. (2001) localized the ear representation in the SC by means of magnetoencephalography. It was found to be localized in the trunk area, but also overlapped with the face area in a few subjects. Although the nipple area, mapped by one fMRI study, has been described as occupying the same region as the genitals, deep in the medial aspect of the inter-hemispheric fissure (Rothemund, Schaefer, Grüsser, & Flor, 2005), and therefore far from the trunk SC representation area, an additional representation has been found by other authors in the trunk region of the homunculus (Komisaruk et al., 2011). Thus, the representation areas of the breast and pinna may actually be located in neighboring portions of the SC.

Five of our patients (31.25 % of those with PB) reported phantom sensations in response to stimulation of the ipsilateral pinna and one patient was also responsive to ipsilateral face stimulation. The latter is in contrast to Aglioti's series (Aglioti, Cortese, & Franchini, 1994), in which no patient reported PB sensations to face stimulation. However, this patient may well have an overlapping of ear and face representation areas in SC, as described above.

Two patients reported PB sensations to stimulation of the contralateral pinna and one of the contralateral nipple. This is really not surprising, since fMRI studies have shown bilateral cortical activation to unilateral finger and lip stimulation, a phenomenon thought to be mediated by the corpus callosum (Blatow, Nennig, Durst, Sartor, & Stippich, 2007).

Conclusions

This study confirms previously published results (Aglioti, Cortese, & Franchini, 1994), which are now also supported by new findings regarding the somatotopic representation areas of the nipple, ear and breast (Komisaruk et al., 2011). It is noteworthy that, due to poorly understood reasons, the ear and breast were largely absent in classical descriptions of the sensory somatotopic homunculus (Rothemund et al., 2005).

The confirmation that pinna stimulation causes sensations in the phantom nipple could not be reasonably explained were it not for the discovery that the nipple seems to have two cortical somatotopic representation areas, one near the genitals area and another near the trunk area (Komisaruk et al., 2011).

Although very likely, it remains to be demonstrated that genital stimulation in women with phantom breasts would result in sensation referred to the nipple, since neither the previous study (Aglioti, et al., 1994) nor this one have tested such hypothesis.

Finally, our study differed from that of Aglioti et al. (1994) in that one of our patients experienced phantom breast sensation after stimulation of the face, which is in keeping with recent studies showing some degree of overlapping of ear and face areas in normal subjects (Nihashi et al., 2001).

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