

Magnetoencephalographic investigations of cortical reorganization in humans

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Functional cortical organization can be determined by means of magnetic source imaging

The central representation of sensory perception relates in an orderly way to the spatial arrangement of receptors in the periphery. The cortical maps of visual space (retinotopy), the body surface (somatotopy), or tone frequency (cochlear place; tontotopy) can be individually determined by means of magnetic source imaging. In a similar manner, it is possible to map motor organization along the central sulcus.

Usually, a first major peak of the magnetic field evoked by a sensory stimulus is determined and a single equivalent moving dipole is fitted to the field measured from sensors over the respective primary cortical area. Tactile evoked fields, for instance, show a first major peak around 30–70 ms after stimulus onset. The field pattern of short-latency somatosensory components is fairly dipolar and a single moving dipole is an adequate model to localize the generator of this SEF component in most cases. This generator is located in area 3b contralateral to the stimulated site [1–5].

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In a similar fashion, magnetic source imaging detects the tonotopic organization in auditory cortex [6–11]. The N100m (M100) sources of the auditory evoked magnetic fields have been localized in the vicinity of the primary auditory cortex (primary association areas) bilaterally on the superior temporal surfaces. These sources of the N100m wave exhibit higher frequencies at progressively deeper locations.

Cortical reorganization as a consequence of deprived afferent input

Behaviourally relevant alterations in afferent input lead to functional cortical modifications, i.e. to cortical reorganization of sensory maps, resulting in alterations in the cortical responses to stimuli. Animal studies by Merzenich and colleagues [12–16] demonstrated as early as 1984 that the loss of afferent input, e.g. by the amputation of digits, results in an altered representation of the hand in area 3b. Today such plastic changes can also be observed in humans by means of non-invasive neuroimaging. In humans, cortical reorganization has primarily been demonstrated for the somatosensory cortex. Amputation of an upper extremity results in alterations of the homuncular organization. MEG-based source imaging has revealed that

the focus of cortical activation elicited by facial stimulation was shifted up to several centimetres toward the representational zone which would normally receive input from the now amputated hand and fingers [1,17,18] (Fig. 1). A similar tendency was observed for the representation of the upper arm (stump) [1,19]. Additional responsiveness of these reorganized cortical areas was evidenced by an enhanced evoked potential and magnetic field, compared to stimulation on the intact side. Observed alterations provide evidence for extensive plastic reorganization in the adult sensory cortex of humans following nervous system injury [20]. Together with Knecht and coworkers [21–23], we investigated perceptual thresholds in patients with amputation of the arm. The sensory discrimination thresholds in the face were lower on the side of the amputation, compared to the intact side. Recently, we found a positive correlation between tactile acuity (two-point discrimination in

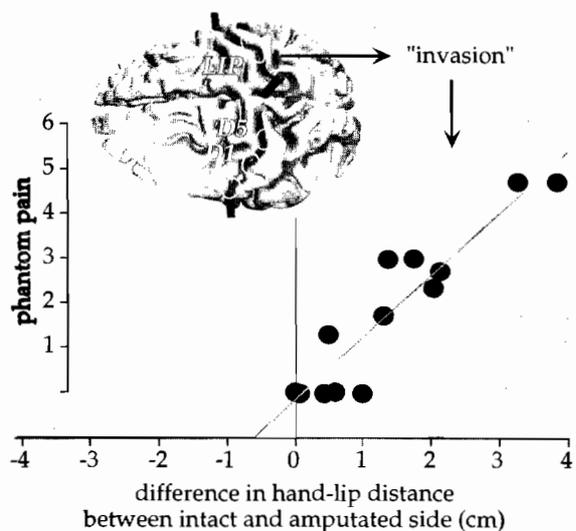


Fig. 1. The amount of reorganization in the primary somatosensory cortex in 13 upper extremity amputees with varying degrees of phantom limb pain was determined non-invasively by the use of neuromagnetic recording techniques. The insert on the upper left illustrates data from a representative subject with intense phantom limb pain. The area of the lip contralateral to the amputated hand (right hemisphere) has shifted from its original position towards the former cortical hand region. The scatterplot depicts the degree of phantom limb pain experienced by the amputees as a function of the magnitude of cortical reorganization. (Data from Flor et al. [18].)

the face of the amputation side) and cortical reorganization [20], suggesting that the alteration of cortical representation may have perceptual consequences. In Ref. [18], we determined the extent of cortical reorganization in the primary somatosensory cortex in upper extremity amputees with varying degrees of phantom limb pain. The magnitude of cortical reorganization showed a highly significant positive association with the amount of phantom limb pain experienced by the amputees (Fig. 1). These data indicate that phantom limb pain may be a consequence of plastic changes in the primary somatosensory cortex.

Circumscribed loss of afferent input may also occur in the auditory system. Tinnitus (a subjective ringing in the ear that may also take the form of a buzzing or roaring noise) has been discussed as a phenomenon akin to phantom perceptions [24]. The question is whether tinnitus is thus also related to altered cortical reorganization. Studies from our laboratories indicate that certain features of cortical reorganization (such as the organization of the tonotopic map and parameters of asymmetry) may be related to the experience of subjective tinnitus [24–25].

Other types of auditory reorganization caused by loss of afferent input, have been observed as well. Mäkelä and coworkers [26–27] presented auditory stimuli to the healthy ear of patients who were deaf in one ear, for example, after an acoustic neuroma operation. Surprisingly, the amplitude of the responses was initially dampened in both hemispheres and then recovered towards normal values in both hemispheres during the year after the operation, even exceeding the pre-injury values in some cases [27]. The activation of both auditory cortices appeared to become more brisk and concise during the recovery. This is one of several observations that suggest that hemispheric interactions may have their own rules, distinctly different from those that underlie cortical reorganization in just one hemisphere. In Ref. [28], we observed an invasion of the digit representation by the cortical face area in one hemisphere of amputees while an expansion of the representation of the digits could be observed in the other. It is thus likely that the processes taking place in the two hemispheres can

be separate from one another. Transfer of either of these effects across the corpus callosum [29] should have resulted in an interference of the process taking place in the other hemisphere. This was not the case.

The growth or the sprouting of axons has been considered to be one basic mechanism underlying plastic cortical alterations [30–31]. In extreme cases, however, expansions spanning an area of several millimetres have been observed in the relatively small brains of monkeys [32], and MSI has revealed corresponding alterations that are in the range of centimeters in humans. It would be difficult to explain those massive changes by sprouting. Therefore, unmasking of normally silent connections (e.g. [32]) and/or changes in synaptic efficacy that follow Hebb's rule [33–35] have been discussed as mechanisms of cortical plasticity. Consequently, peripheral lesions can demonstrate hidden pathways, which would normally not be sufficiently activated to result in a firing of the post-synaptic neuron [13,36]. Even simple behavioural training may result in similar phenomena and produce an enlargement of the cortical area that is activated by a particular task [37]. The thalamus and the brain stem have been discussed as alternative loci of reorganization under the assumption that these reorganizational changes are then reflected in the cortex (e.g., [32,38]).

Cortical reorganization as a consequence of increased afferent input

Not only deafferentation, but also a prolonged increase, for instance in tactile stimulation to the distal pad of one or two phalanges, has been reported to result in a greatly increased cortical representation specific to that circumscribed portion of the hand [12]. Suggestive evidence has also been reported that there is an increased cortical representation of the reading index finger in blind Braille readers [39–40]. Violinists and other string players provide a good model for the study of the effects of differential afferent input to the two sides of the brain in humans. During practice or performance, the second to the fifth digits (D2–D5) of the left hand are continuously engaged in fingering the

strings, a task involving a great deal of manual dexterity and enhanced sensory stimulation, while the thumb grasps the neck of the instrument and remains relatively stationary. The right hand, in manipulating the bow, engages in a task involving much less individual finger movement and fluctuation in tactile and pressure input than D2–D5 of the left hand. By using MEG-based source imaging, we have demonstrated that the representation of the digits of the left hand of string players was substantially expanded compared to the digits of the left hand in normal control subjects [41]. For the thumb, which has the less active task of holding the neck of the instrument, the expansion was not as great as for the digits involved in the fingering. The effect was greatest in musicians who started playing the instrument early in life but was still substantial in those who began practising in adulthood (Fig. 2).

Furthermore, it has been assumed that chronic stimulation leads to changes in the cortical representation of pain, e.g., an increased cortical representation for the painful area. Consequently, stimulation of the affected body part should lead to increased cortical evoked magnetic fields as a result of enlarged cell assemblies representing the

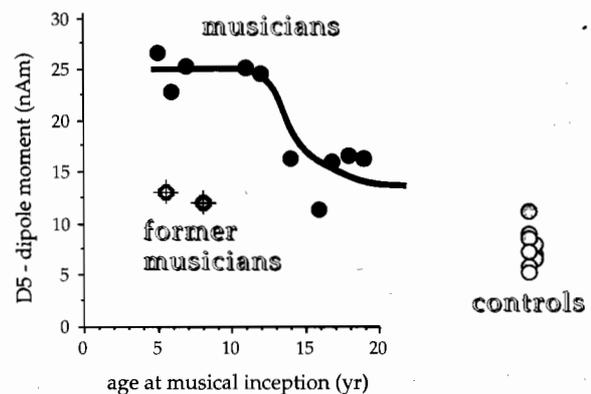


Fig. 2. Neuronal activation resulting from tactile stimulation of the fifth digit of the left hand as expressed by the dipole moment is plotted against the age at which subjects began musical practice. Compared to the healthy controls, musicians with early onset of training show the greatest amount of activation but even those who began playing the instrument later in life produced significantly larger activations than the non-musician controls. Musicians who ceased to play the instrument (former musicians) show considerably lower activation. Data from Elbert et al. [41].

painful body area. In another experimental series [23,42,43], we investigated patients who suffered from continuous chronic lower back pain of either muscular or degenerative origin, and matched controls. Sub-threshold, supra-threshold, and standard stimuli were applied to the site of most intense pain and to a control site. The magnitude of the earlier part of the evoked fields (70–75 ms) was significantly correlated with the chronicity for both the sub- and supra-threshold stimulation, only when the stimuli were applied to the back. This result suggests that patients who experience chronic noxious stimulation over extended periods of time produce more extensive activation of neural assemblies when phasic somatosensory stimuli are applied to the location of their pain. Caution is necessary, however, as our attempts to identify similar relationships based on high-resolution EEG have not yet been successful [43]. The quality of stimulation that is part of the chronic back pain syndrome differs with respect to spatial extension and time course from other forms of massive stimulation that have been shown to produce changes in the cortical representation of stimulated body parts in S-I. Thus, the current database is not sufficiently large to allow definitive conclusions about the nature of plastic alterations in chronic pain patients.

Map distortions caused by chronic synchronous and behaviourally relevant stimulation

Another MEG study [44] demonstrated reorganization of the somatosensory cortex after surgical separation of webbed fingers (treatment of syndactyly). After surgical intervention, the fingers received differential input and the representational zones of the digits became segregated. Using MSI we could investigate [40] the opposite effect: repetitive chronic synchronous and behaviourally relevant stimulation to several digits resulted in a fusion and in a disordered arrangement of digit representation. At the same time subjects consistently mislocalized light pressure stimuli applied to the fingertips. Consistent with earlier work in animals, e.g. [45–46], we conclude that synchronous stimulation creates a fusion of cortical representational zones while asynchronous stimulation leads to separation.

These processes may underlie certain mysterious illnesses such as the focal dystonia of the hand in musicians [20,47–48]. This work has indicated that digital motor incoordination resulting from digital overuse can be associated with an induced disorder in the cortical representation of the digits. We observed overlap or smearing of the homuncular organization of the digits in musicians with focal hand dystonia (Fig. 3) [20]. This observation does not imply causal primacy of the central mechanism since peripheral processes are the likely origin that triggered cortical reorganization. Consequently behavioural mechanisms could be of value in reducing both the cortical disorder and the involuntary lack of coordination of movement.

Cross-modal representational plasticity

In regions in which different sensory representations are processed, cortical plasticity may lead to changes across the borders of a modality. Thus, visual deprivation results in an extension of the neighbouring non-visual regions which do not normally respond to visual processing [35]. Such intermodal plasticity may result from various types of neuronal mechanisms among which activation of silent input, axonal sprouting, or Hebb-like mechanisms have been discussed. In humans, suggestive evidence for intermodal plasticity has also been reported. Rösler, Röder and coworkers [49], for instance, compared event-related potentials in a haptic mental rotation task, which involved the tactile discrimination of letters, in blind people and blindfolded sighted subjects. While the tactile stimuli were encoded, blind subjects showed a pronounced occipital activity (a negative slow wave), while blindfolded, sighted subjects exhibited frontal predominance of activity. A similar frontal predominance of the negative slow wave occurred in blindfolded sighted subjects and a similar occipital predominance in congenitally blind subjects during the rotation task proper. Adventitiously blind subjects, however, exhibited a pronounced negative potential over both the frontal and the occipital-cortex. These results suggest that reorganization occurs rather quickly following the loss of vision. However, the temporal development



Fig. 3. Locations of the equivalent current dipoles (ECD) for D1-D5 projected onto a coronal MR-slice of one dystonic subject. Large symbols on the left (right hemisphere) indicate the range of locations for D1 and D5 for a group of 9 control subjects. The smaller symbols are those from one musician with focal dystonia of D2-D4 of the left hand. The representations of the dystonic digits are marked by asterisks. A fusion can be observed for the representation of the fingers of the dystonic hand.

seems to vary depending on the task (such as encoding or processing stimuli).

Cortical and behavioural plasticity following brain lesions

In the field of neurological rehabilitation, it is of great interest to examine the plasticity and functional reorganization following brain lesions in humans. More specifically, future MSI research should focus on the investigation of processes underlying recovery and plasticity of function, such as the organization and reorganization of cortical function in sensory and motor impairment following ischaemic or haemorrhagic infarct, and the impact of particular rehabilitation procedures on cortical reorganization. In several laboratories, for instance, constraint-induced facilitation of impaired movement is currently employed to overcome non-use of an affected upper extremity in patients subsequent to stroke. These studies employ the training procedure developed by Edward Taub [50] which involves massive practice of the affected extremity combined with restraint of the unaffected extremity. It is very likely that these massive altera-

tions of sensorimotor function are mediated by alterations in cortical reorganization.

So far, research on plasticity and reorganization following brain lesions has focused on the recovery of sensory and motor function. Brain damage such as that resulting from cerebrovascular accidents can lead to a variety of alterations, including: (a) complete destruction of a given brain structure combined with total loss of activity in this area; (b) remaining structural integrity, but decrease of brain activity; (c) disintegration of distributed cooperative activities, i.e., alteration of spatio-temporal patterning of brain activity secondary to focal damage. In all three cases it is important to gain detailed information about the extent of the necrotic centre versus the surrounding area of reduced perfusion (penumbra) and the outer oedematous zones in focal brain damage. In addition, it is important to obtain information about the functional status of each particular area. While the structural information can routinely be determined by MRI, procedures determining the status of function of the particular area remain to be further developed. Such methods can be based on MSI.

The assessment of functionality in areas directly affected by strokes and their neighbouring regions

can, for instance, be evaluated by dipole density of delta waves. The location of the estimated ECD was always in non-infarcted tissue, in the region of the somatosensory cortex.

Recovery of attention and language function is another field in which MSI offers interesting perspectives. Research on aphasia suggests that symptoms do not exclusively reflect impaired sensory input-related functions of the lesioned areas but are also consequences of impaired cognitive processes that are not directly linked to speech perception and language production.

In summary, recent studies suggest that brain lesions following trauma not only lead to impairment of sensory functions related to the particular area destroyed by the lesion, but also to impairment in higher cognitive functions related to input processing. It has further been suggested that reorganization, i.e. substitutional processes beyond compensation may take place following stroke and during rehabilitation. However the areas and the amount of reorganization either through spontaneous recovery or through training remain to be specified. Rules governing the different types of CNS reorganization need to be determined

Therapeutic approaches emerging from research on functional cortical reorganization.

The distinct association between cortical reorganization and clinical symptoms opens the possibility that behavioural treatments aimed at altering cortical reorganization might be effective in relieving previously untreatable conditions. For instance, we have argued [25] that the results by Recanzone et al. [37] could be used as a basis of a new therapeutic approach to tonal tinnitus. This research has shown that there is an increase in the representation of the frequencies involved in an auditory learning paradigm. Thus, by having patients attend to and discriminate some features of acoustic stimuli that are close to the tinnitus frequency, it might be possible to drive cortical reorganization of the non-tinnitus frequencies into the tinnitus representation, thereby reducing it. Masking sounds have been used extensively in the treatment of tinnitus, however, without reliable

success. The new approach would differ by creating a situation where the stimuli were behaviourally relevant and were adjacent to, not within, the tinnitus range. In a similar fashion, it is currently being tested (in the laboratory of H.F.) whether alteration of the disordered somatotopy in upper extremity amputees through massive and behaviourally relevant stimulation of the stump, might be used as treatment for phantom limb pain.

Candia et al. [51] suggested a treatment approach for focal hand dystonia that is based on the idea to separate functionally 'webbed' fingers. The digit exhibiting the main dystonic symptoms is unrestrained, while one or several of the other digits that are usually moved in concert are immobilized, and extensive practice is given in performing individual movements of the dystonic finger in coordination with movements of an unaffected finger. It seems to be favourable to carry out the movements on the individual's own musical instrument.

The data described here suggest that new intervention techniques designed to influence maladaptive alterations in cortical organization might be quite effective in relieving the symptoms of several so far untreatable disorders such as focal dystonia and phantom limb pain.

Acknowledgements

Research was supported by the Deutsche Forschungsgemeinschaft and the Volkswagen-Stiftung

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