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Topography of the perceptual improvement induced by repetitive somatosensory stimulation

Silvia Macchione

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Topography of the perceptual improvement induced by repetitive somatosensory stimulation

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Whatever can be said of what is tangible, can be said of touch, and vice versa.

- Aristotle, *De Anima*

Résumé en Français

L'**acuité tactile** est l'une des fonctions les plus sophistiquées du cerveau humain. Elle nous permet d'explorer les différentes formes et textures des objets avec lesquels nous entrons en contact quotidiennement. Un fonctionnement si bien développé est possible grâce à un complexe système de cellules nerveuses, qui commencent au niveau des récepteurs cutanés et convergent vers le cortex somatosensoriel primaire, où les stimuli sont codés de façon topographique dans des représentations corticales du corps, qui ensemble forment l'*homunculus* sensoriel. Une caractéristique désormais universellement reconnue du système somatosensoriel mammalien est que ces représentations corticales sont dynamiques et peuvent être modifiées par l'effet de la plasticité cérébrale. En fait, on appelle plasticité cérébral l'habilité du cerveau de changer à la suite d'événements extérieurs. Par exemple, une vaste littérature reporte qu'en particulier les représentations du cortex somatosensoriel primaire qui correspondent à la main et au visage montrent une incroyable plasticité, c'est-à-dire peuvent être modifiées par l'expérience. Parallèlement, au niveau perceptif, l'acuité tactile aussi est influencée par les changements plastiques qui ont lieu au niveau cortical. Ces changements peuvent conduire à une amélioration ou réduction de l'acuité tactile. Dans ce cadre, et à cause de son importance dans notre vie quotidienne, il devient fondamental de mieux comprendre les phénomènes qui mènent à une **amélioration** de l'acuité tactile. Chez l'homme sain, un gain dans l'acuité tactile peut être obtenu de différentes façons. Par exemple, plusieurs études montrent que l'acuité tactile s'améliore suite à plusieurs séances d'entraînement en une tâche particulière, ce qu'on appelle l'apprentissage perceptif. Toutefois, cette méthodologie demande beaucoup d'effort et attention par la personne. Une autre forme d'amélioration de l'acuité tactile, sûrement plus avantageuse car indépendante de l'entraînement, peut être obtenue grâce à une simple stimulation mécanique d'une petite région de la peau, appelée **stimulation somatosensorielle répétée** (RSS de l'anglais Repetitive Somatosensory Stimulation). La **RSS** consiste en une stimulation mécanique très légère qui perdure pendant 3 heures sur la peau du bout d'un doigt (notamment la pulpe de l'index droit). On pense que l'amélioration tactile serait amenée par l'activation simultanée et répétée de plusieurs récepteurs cutanés au niveau de la région stimulée. Cette activation

simultanée serait nécessaire à induire une plasticité de type Hebbian, c'est-à-dire un renforcement de l'efficacité synaptique, qui conduit à une amélioration transitoire de la performance psychophysique. Avant de commencer ce travail de thèse, il avait été montré que la RSS appliquée à la pulpe de l'index droit améliorait à la fois l'acuité tactile de ce même doigt, ainsi que celle du visage. Toutefois, aucune modification n'avait été observée sur le doigt homologue (index gauche), ni sur le doigt à côté (majeur droit). Il avait été montré donc que la RSS pouvait améliorer l'acuité tactile **localement** (sur le doigt stimulé) et aussi à **distance** (sur le visage) mais la topographie de l'amélioration tactile, notamment sur les autres doigts dans les deux mains, demeurait inconnue. Également, l'hypothèse d'appliquer la RSS sur une autre région du corps (notamment le visage) et vérifier ses effets à la fois locaux sur le visage, ainsi que à distance sur les doigts, n'avait jamais été investiguée. Le but de mon travail de thèse constituait donc à investiguer dans le détail la topographie de l'amélioration tactile induite par l'application de la RSS, spécifiquement '*au sein d'une même et entre*' plusieurs régions du corps. Pour répondre à cette question, deux différentes lignes de recherche ont été développées. En ce qui concerne la première ligne de recherche (**Étude 1**), l'hypothèse principale était que l'effet de la RSS dans la main n'est pas limité au doigt stimulé mais, au contraire, que la stimulation peut amener à une amélioration d'autres doigts dans les deux mains. En stimulant l'index de la main droite avec la RSS et en évaluant les changements de l'acuité tactile sur plusieurs régions non stimulées, mes résultats ont démontré que la RSS conduit à l'amélioration tactile du doigt stimulé ainsi que de deux doigts non stimulés dans la main controlatérale, spécifiquement le pouce et le majeur. Cette étude prouve pour la première fois que la RSS d'un doigt est capable d'induire une amélioration tactile locale ainsi qu'une amélioration tactile à distance entre les deux mains. En ce qui concerne la deuxième ligne de recherche (**Étude 2**), l'hypothèse principale était que le transfert d'amélioration tactile induit par la RSS d'un doigt vers le visage est bidirectionnel. En stimulant le côté droit de la lèvre supérieure par RSS et en évaluant les changements de l'acuité tactile de plusieurs régions du visage et des mains, mes résultats ont démontré que la RSS conduit à l'amélioration tactile de la lèvre stimulée ainsi que de deux régions non stimulées, spécifiquement le côté gauche de la lèvre supérieure et l'index de la main droite. Cette deuxième étude prouve que la RSS d'une région du visage est capable d'induire une amélioration tactile locale ainsi qu'une amélioration tactile à distance sur la main, en

démontrant que l'effet d'amélioration tactile entre la main et le visage est bidirectionnel. Dans leur ensemble, les données expérimentales constituent une contribution significative à l'étude de la topographie des changements perceptifs induits par la RSS. La **nouvelle topographie** montrée par mes études est beaucoup plus riche par rapport à la topographie décrite en précédente dans ce champ de recherche. Enfin, ces résultats pourront être utilisés dans une application clinique. L'identification de protocoles capables d'induire une amélioration de l'acuité tactile est en fait cruciale dans le traitement des déficits sensoriels en générale et, dans ce cadre, les résultats de cette thèse pourront être utilisés pour configurer des applications de la SSR dans un contexte de réhabilitation de plusieurs parties du corps.

Résumé

Le toucher joue un rôle prépondérant dans notre vie quotidienne. Il est connu depuis longtemps que l'acuité tactile peut être améliorée par effet de la plasticité cérébrale, suite à entraînement. Une autre forme d'amélioration, indépendante de l'entraînement, peut être obtenue grâce à une simple stimulation mécanique d'une petite région de la peau, appelée stimulation somatosensorielle répétée (RSS). Avant de commencer ce travail de thèse, il avait été montré que la RSS pouvait améliorer l'acuité tactile localement (sur le doigt stimulé) et aussi à distance (sur le visage) mais la topographie de l'amélioration tactile, notamment sur les autres doigts, demeurait inconnue. Également, l'hypothèse d'appliquer la RSS sur une autre région du corps (notamment le visage) et vérifier ses effets à la fois locaux sur le visage, ainsi qu'à distance sur les doigts, n'avait jamais été investiguée. Le but de mon travail de thèse constituait donc à investiguer la topographie de l'amélioration tactile induite par RSS *au sein d'une même et entre* plusieurs régions du corps. Une première étude a révélé que la RSS d'un doigt est capable d'induire une amélioration tactile locale ainsi qu'à distance entre les deux mains. La deuxième étude a prouvé que la RSS d'une région du visage est capable d'induire une amélioration tactile locale ainsi qu'une amélioration tactile à distance sur la main. De plus, l'effet d'amélioration tactile entre la main et le visage est bidirectionnel. Dans leur ensemble, les données expérimentales constituent une contribution significative à l'étude de la topographie des changements tactiles induits par la RSS.

Mots clés: acuité tactile, amélioration perceptive, plasticité corticale, stimulation sensorielle

Abstract

Touch plays a fundamental role in our daily activities. It has long been known that, thanks to brain plasticity, tactile acuity can be improved following training. Another form of tactile improvement, independent from training, can be achieved through a simple mechanical stimulation of a small region of the skin, called repetitive somatosensory stimulation (RSS). RSS of a finger was well-known to improve tactile acuity locally (on the stimulated finger) and also remotely (on the face). However, topography of tactile improvement, especially on other unstimulated fingers, was unknown. In addition, the hypothesis of applying the RSS to another body region (notably the face) and investigating the possible effects both in the face and fingers was not explored. The aim of this work of thesis was therefore investigating the topography of the RSS-induced tactile improvement *within and between* different body regions. One first study revealed that RSS of a finger induces tactile improvement both locally and remotely across fingers. The second study showed that, when applied on the face, RSS is able to induce tactile improvement both locally, on the face, and remotely, in the hand. This demonstrated that the tactile improvement between the hand and the face is bidirectional. Overall, the experimental data I provide constitute a significant contribution to the study of the topography of RSS-induced tactile improvement changes.

Key words: tactile acuity, perceptual improvement, cortical plasticity, somatosensory stimulation

Title:

Topography of the perceptual improvement induced by repetitive
somatosensory stimulation

Titre:

Topographie de l'amélioration perceptive induite par stimulation
somatosensorielle répétée

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Improvement at the finger transfers to the face. D. Muret, H. R. Dinse, <u>S. Macchione</u> , C. Urquizar, A. Farnè, and K. T. Reilly, “Touch improvement at the hand transfers to the face,” <i>Curr. Biol.</i> , vol. 24, no. 16, pp. R736–R737, 2014	159
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Table of Abbreviations

FA	Fast adapting
SA	Slowly adapting
RFs	Receptive fields
CNS	Central nervous system
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
BA	Brodmann's area
VPM	Ventral posteromedial nucleus
VPL	Ventral posterolateral nucleus
SSEPs	Somatosensory evoked potentials
2PD	Two-point discrimination
fMRI	Functional Magnetic Resonance Imaging
GOT	Grating orientation task
MI	Primary motor cortex
LTP	Long-term potentiation
NMDA	N-methyl-D-aspartate
TBS	Theta-burst stimulation
GABA	Gamma-Aminobutyric Acid
LTD	Long-term depression
STDP	Spike timing-dependent plasticity
ICMS	Intra-cortical microstimulation
APTS	Associative pairing of tactile stimulation
RSS	Repetitive Somatosensory Stimulation
FDT	Frequency discrimination task
RTs	Reaction times
MEG	Magnetoencephalography
BOLD	Blood-oxygen-level dependent
GM	Gray matter
iFC	Intrinsic Functional Connectivity
RSN	Resting-state network

General Introduction

Touch is the most extensive sense of our body. The use of the adjective 'extensive' in reference to touch has a double sense. When we think of touch, we immediately think of our hands since we recognize and manipulate objects with them, but touch is actually a sense belonging to all body parts. If other senses, like smell, taste, hearing, are limited to the head region, touch extends over the entire body surface. Thus, touch is the most extensive sense we have. The vastness of touch is also an expression of the variety of functions it performs. Thanks to tactile perception, we can search for our keys thrown into the bottom of our bag, perceive the texture of the clothes we wear, feel whether a cup of coffee is too hot or too cold, grasp this cup of coffee and place it near our mouth, distinguish whether a drop of coffee falls on our hand or on our arm as well as a plethora of other actions.

The importance of touch acuity is universally recognized. Without the ability to *feel* objects and their physical features we could not perform all the actions we perform every single day of our life. Tactile acuity is not only fundamental for feeling, but it also contributes to motor control. Indeed, the loss of tactile feedback can sometimes result in severe motor impairment. When our fingers touch an object we receive a lot of sensory information that is necessary to grasp and grip the object. If this sensory information is missing, then motor abilities become impaired, even in the absence of problem in the motor system. Because of the importance of tactile acuity, a large part of research in neuroscience has aimed at developing protocols to improve it.

Improvement in tactile performance is made possible by the reorganizational properties of our brain. Animal brains have an extraordinary ability to change, i.e. to learn new skills and adapt following perturbations in the external world. This phenomenon is called brain plasticity. The somatosensory system, in particular, is known to undergo a multitude of plastic changes following a variety of perturbations. Some of these perturbations can arise from injuries - for example in case of sensory loss at the upper limb - and bring to dramatic plastic changes both at neural and perceptive level. There is a massive literature showing how hand and face are two body regions particularly involved in this kind of plasticity following injury. Conversely,

other perturbations - which do not involve sensory loss - have been shown to sometimes reflect functional benefits. For instance, improvement of tactile acuity is one of the perceptual benefits we can achieve thanks to plastic reorganization of our brain, following controlled manipulations.

In the work contained in this thesis I will present a study investigating improvement of *tactile perception or acuity* (these two terms will be used interchangeably). In particular, I will show how improved tactile perception induced by a protocol of somatosensory stimulation transfers within and between different body parts: the hand and the face.

For the purpose of the work, I will firstly introduce some textbook notions on touch properties and somatosensory organization (Chapter 1). Then I will focus in more detail on the plastic changes that can occur in the somatosensory system, with particular attention to those changes associated with alterations in tactile perception, especially in the hand and face (Chapter 2). In a third chapter, I will describe in detail the literature relating to the stimulation protocol I used to investigate tactile improvement. Chapter 4 will describe the experimental contributions of this thesis, and Chapter 5 will provide a general discussion.

Chapter 1: Introduction to touch

Touch is our physical interface with the external world. Since skin covers our entire body, we can *feel* with any part of our body. Thus, it is as if we are entirely and continuously immersed in a stimuli-dense world. Given the extent of the touch apparatus and the massive amount of information that is constantly perceived via this apparatus, it is not surprisingly that touch is one of the most complicated and less known human senses. In this first chapter I want to give some general information about touch, zooming in on the way the brain encodes tactile information at the periphery and within the primary somatosensory cortex, which have the bigger relevance for the purpose of my thesis.

1.1 Structure of the skin

Skin is the organ of touch. The skin on the volar surface of the hand is glabrous, in contrast to hairy skin which is found on the dorsal surface. It consists of two major subdivisions: epidermis and dermis. The epidermis is the superficial layer, and is composed of five sublayers. The order from outer to inner layers is: stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum and stratum germinativum. The dermis consists of only two sublayers: the papillary (upper) and the reticular (lower). The epidermis and dermis are interconnected through a series of papillary folds.

When fingers interact with an object, tactile stimuli need to be coherently processed. The initial contact with the external objects occurs thanks to specialized neural structures called sensory receptors. The fundamental function of the sensory receptors is to transform stimulus energy into electrical energy, through a process called stimulus transduction. The sensory receptors are morphologically specialized to transduce specific forms of energy. In particular, skin includes three types of specialized cutaneous sensory receptors: mechanoreceptors (for mechanical stimuli), nociceptors (for pain) and thermoreceptors (for temperature). For the purpose of this thesis, I will exclusively describe the mechanoreceptors characteristics.

The mechanoreceptors sense the physical deformation of the skin when we interact with objects, then information is sent to the central nervous system for interpretation and most often subsequent action. Tactile perception of mechanical stimuli in hand glabrous skin relies into four different categories of mechanoreceptors: Merkel cells, Meissner's corpuscles, Ruffini endings and Pacinian corpuscles (Figure 1.1). Merkel cells are situated in clusters within the basal layer at the top of the deep epidermal folds that project into the dermis; Meissner's corpuscles are located more superficially at the epidermal-dermal junction; Ruffini endings are instead located deep within the connective tissue of the dermis; finally Pacinian corpuscles are multi-layered structures located in the subcutis.

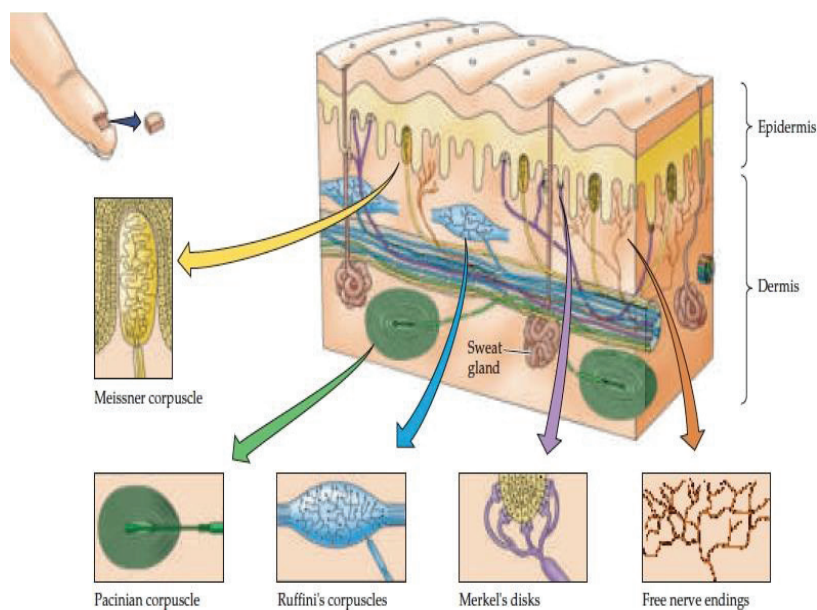


Figure 1.1 [Taken from Purves et al., 2004, after Darian-Smith, 1984]: Schema of the anatomical section of a small skin region in the finger. The skin includes a variety of morphologically distinct mechanoreceptors, situated at different depths within the dermis. A representation of the volar, glabrous skin is showed.

Mechanoreceptors are associated with different populations of afferent nerve fibres, whose function is to convey information along the ascending pathway. These tactile afferents are known as fast adapting (FA) I and II fibres and slowly adapting (SA) I and II fibres, according to the nature of their response to sustained indentation of the skin (Johansson and Vallbo,

1983; Vallbo and Johansson, 1984). While all of these populations respond to mechanical stimulation, they respond differently to features like spatial details or vibration, for example. Moreover, they are each associated with a specific type of mechanoreceptor.

- The SA I end in Merkel cells and they are densely distributed. They are highly sensitive to fine spatial detail (for example points, edges or curvatures) as opposed to overall indentation. Their receptive fields (RFs, see below for a detailed description) are relatively small, about 2-3 mm in diameter. Since SA I respond linearly to skin indentation, they also code curvature very well (Bisley, et al., 2000) and are highly sensitive to very low temporal frequencies of vibrotactile stimulation ranging from 0.4 to 3 Hz, which usually result in the sensation of pressure.
- FA I terminate in Meissner's corpuscles. They are even more densely distributed than SA I. Similar to SA I, their RFs are relatively small, around 3-5 mm in diameter. In contrast with SA I, and in terms of discriminative power, they do not perform as well for the discrimination of very fine spatial detail since they are insensitive to static contact. While these fibres respond very well to transient deformation, particularly to the low-frequency vibration occurring at the earlier stage of contact, i.e. when the hands interact with objects in relative motion (Johnson, 2001). Importantly, FA I are involved in grip control since they provide critical feedback for precise grip control (Westling and Johansson, 1987). For these reasons, FA I are thought to be sensitive at maximum to vibrotactile temporal frequencies ranging from 3 to 40 Hz, which produce the sensation of flutter (Talbot et al., 1968).
- SA II are associated with Ruffini endings. They are not as dense as SA I and FA I. Their RFs are about five times larger than those of SA I and their sensitivity to skin deformation is about six times poorer than that of SA I. Indeed, SA II are not good at detecting fine spatial details, on the contrary they are highly sensitive to vibrotactile frequencies ranging from 100 to 500 Hz and seem to produce the effect of buzzing. Interestingly, SA II are also much more sensitive than SA I to skin stretch.
- FA II terminate in Pacinian corpuscles. They are less widely distributed in the hand compared to SA I or even FA I. They have extremely large RFs, and consequently they are very poor at discriminating spatial details. On the contrary, they are highly sensitive to transient stimulation like vibration. FA II are very important for detecting

events like hand-held objects (Johnson, 2001). FA II are thought to be maximally sensitive to vibrotactile temporal frequencies ranging from 40 to 500 Hz, and they produce the sensation of vibration within that frequency range.

Hairy skin contains five main types of mechanoreceptors with large myelinated afferents. Two of them are slowly adapting and terminate in Merkel and Ruffini endings, while the other three are fast adapting and they include non-encapsulated hair-follicle receptors innervating hairs and Pacinian corpuscles. Their general characteristics are similar than those found in glabrous skin. In figure 1.2 the different distribution of mechanoreceptors in glabrous skin on the hand are displayed.

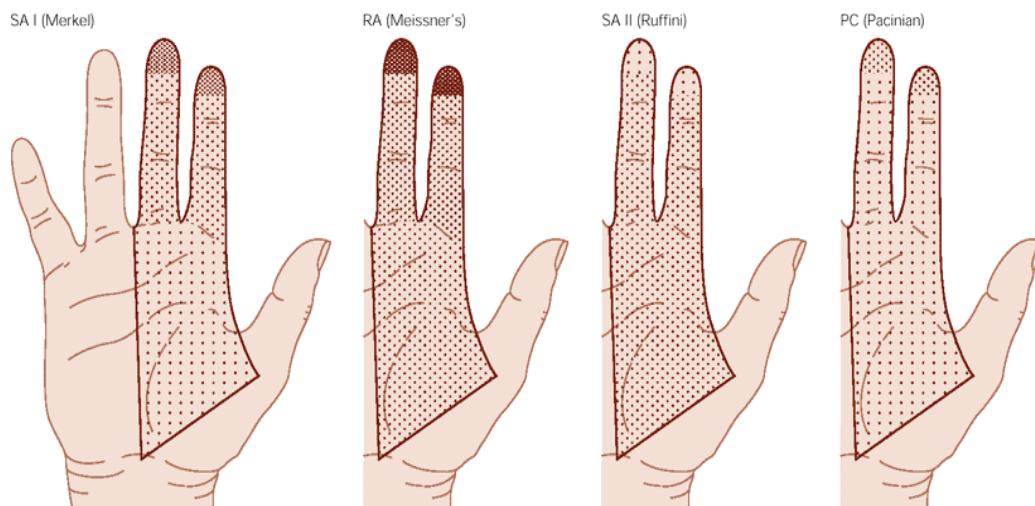


Figure 1.2 [Taken from Kandel et al., 2000, adapted from Vallbo and Johansson, 1978]: Distribution of mechanoreceptor types in human hand glabrous skin. The highest density of receptors is shown by the heaviest stippling. Meissner's corpuscles and Merkel disk receptors are distributed preferentially on the distal half of the fingertip. Pacinian and Ruffini endings are much less common and they are distributed more uniformly on the hand, indeed they show little differentiation of the distal and proximal regions. The fingertips are the most densely innervated regions of the skin in the entire human body. Fingertips receive approximately 300 mechanoreceptor nerve fibres per square millimetre.

The receptive field (RF) of a mechanoreceptor for touch is the region of skin that is directly innervated by the terminals of the mechanoreceptor's neuron. RF thus includes the entire area of skin through on a tactile stimulus can produce activity in a given neuron. Normally, each mechanoreceptor responds only to stimulation within its receptive field, so that a stimulus that affects an area larger than the receptive field of one neuron will activate adjacent mechanoreceptors. The size of a stimulus therefore influences the total number of receptors that are stimulated: a large object held between both hands will contact and activate more touch receptors than a pen grasped between the thumb and index finger.

RFs properties play a leading role in tactile perception. Size and density in particular are two fundamental properties of RFs which can modulate tactile perception. Indeed, tactile sensitivity of our skin dramatically changes according to these characteristics. The density of receptors in a given part of the body determines how well the sensory system can resolve the detail of stimuli applied to that area. A dense population of receptors for touch translates into bigger tactile sensitivity; conversely a more sparse population reflects smaller tactile sensitivity. For instance, tactile sensitivity is greatest on the glabrous skin on the fingertip (Figure 1.2), the palmar surface of the hand, the sole of the foot, and the lips. It is worth noting that touch perception involves different measures of tactile acuity (for example absolute tactile sensitivity, spatial discrimination, orientation discrimination) which differ across body parts and differently correlate between them (Ackerley et al., 2014).

The difference in size of the RFs of mechanoreceptors plays an important role in the functions of the mechanoreceptors. Meissner's corpuscle and Merkel disk receptors can resolve fine spatial differences because they transmit information from a restricted area of skin. As these receptors are smaller in diameter than the fingerprint ridges of glabrous skin, individual receptors can be stimulated by very small bumps on a surface. This very fine spatial resolution allows humans to perform fine tactile discrimination. Pacinian corpuscles and Ruffini, on the contrary, are poorly suited for accurate spatial localization or for resolution of fine spatial detail. The smallest RFs are located on the tips of the fingers (which display the biggest sensitivity). RFs are slightly larger on the proximal phalanges and even bigger on the palm. RFs on hairy skin also increase in area as stimuli are moved proximally from the wrist to the trunk. These variations in RF size reflect the density of mechanoreceptors in the

different regions of the skin. The spacing of mechanoreceptors is smallest on the fingertips and widens proximally on the palm, where receptors are less densely packed.

The size of the RFs in a particular region of skin defines the capacity to determine whether one or more points are stimulated. A sensory neuron innervating Meissner's corpuscles and Merkel disk receptors transmits information about the largest skin indentation within its RF. If two points within the same receptive field are stimulated, the neuron will signal only the larger indentation. But if the points are located in the receptive fields of two different nerve fibers, then information about both points of stimulation will be signalled. The farther apart the points lie on the surface, the greater the likelihood that the two active nerves will be separated by silent nerve fibers (Kandel et al., 2000).

In addition, mechanoreceptors also differ in sensory thresholds, i.e. the minimum intensity of stimulation required to generate an action potential in the nerve. For instance, fast adapting receptors have lower touch thresholds than slowly adapting receptors. The Pacinian corpuscle is the most sensitive mechanoreceptor. The Meissner's corpuscles are particularly sensitive to abrupt changes in the shape of objects that occur at the edges or corners and to small irregularities on the surface sensed during palpation by the hand. More salient bumps or edges are required to activate the slowly adapting Merkel disk receptors. In general, the strongest responses occur when sharp edges or punctate probes, such as a pencil point or a probe, contact the receptive field (Kandel et al., 2000).

1.2 Spatial acuity

Size of the RFs is fundamental to determine spatial resolution acuity. The spatial resolution on the skin can be measured in several different ways. One of the most traditional tests, known as the two-point discrimination threshold, measures the smallest gap between two points contacting the skin that are experienced as two separate tactile sensations. Indeed, stimuli on various regions of the skin can be quantified in humans by measuring their ability to perceive a pair of nearby stimuli as two distinct entities. The minimum detectable distance between two stimuli is called the *two-point threshold*. The two-point threshold varies for different

body regions (Figure 1.3). These variations are correlated with the size of sensory receptive fields and the innervation density of mechanoreceptors in the superficial layers of the skin. Normal threshold values tend to be around 2-4 mm on the fingertips and about 10-11 mm on the palm (Weinstein, 1968).

Of particular relevance for this thesis is the understanding of the way two distinct points touching the fingertip skin are actually perceived as distinct. To this regard, inhibitory interactions are particularly important for fine tactile discrimination. Indeed, the brain uses a physiological mechanism which in order to help spatial tactile acuity to be preserved and – under particular circumstance – increased. This mechanism is called *lateral inhibition*.

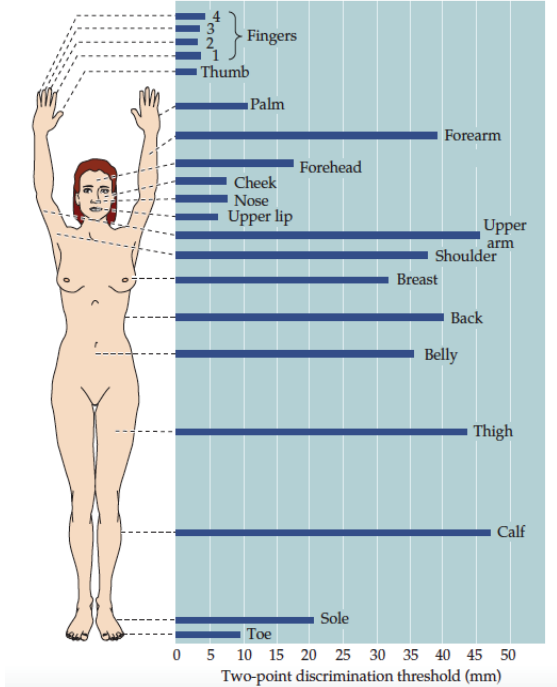


Figure 1.3 [Taken from Purves et al., 2008, adapted from Weinstein 1968]: Two-point discrimination thresholds are different throughout the skin surfaces. Two-point threshold is the minimum distance at which two stimuli are perceived as distinct. Note that thresholds vary for different body parts. Specifically, two-point threshold is low at fingertips (the lowest in absolute) and face, while is high at the rest of the body.

Basically, lateral inhibition reduces coexisting and ongoing activation present at the other locations of the cortical population. To understand how lateral inhibition plays a role in spatial

acuity, we have to consider two cases, the one where only one point is stimulated and the other where two points on the skin are stimulated (Figure 1.4). Stimulation of a single point activates only one population of cells in the cortex. Maximal activity is recorded in the centre of this population. These neurons are surrounded by a band of neurons whose firing rates are depressed below normal tonic levels by the actions of interneurons that form lateral inhibitory networks. Conversely, stimulation of two adjacent points activates two populations of receptors, each with a peak of activity. Normally, i.e. in absence of lateral inhibition effect, the coexistence and convergence of the two active populations in the central nervous system would result in a single large group of undistinguished inputs. Indeed, in this case the activity in the two populations would tend to overlap, and the distinction between the two peaks might become no longer clear but blurred (impaired spatial tactile acuity).

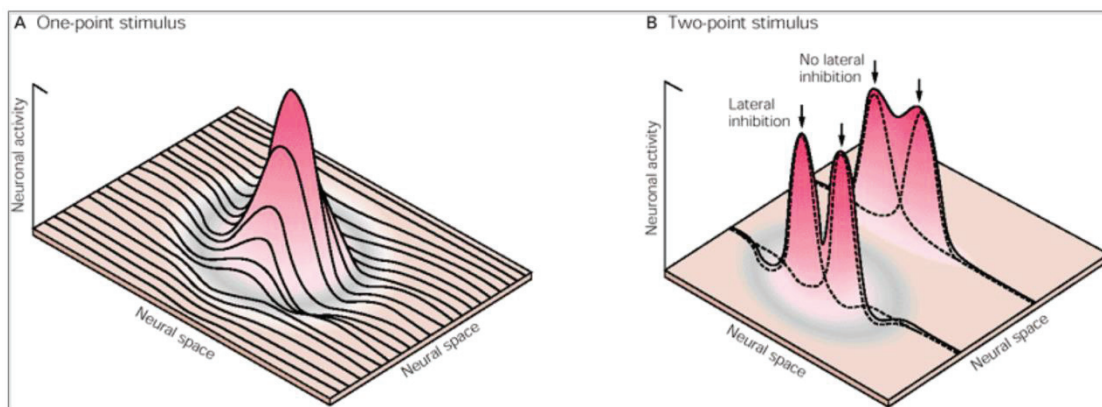


Figure 1.4 [Taken from Kandel et al., 2000, adapted from Mountcastle and Darian-Smith, 1968]: Model of action of lateral inhibition on two-point discrimination. Figure on the left shows the case where one single site on the skin is stimulated. The stimulation produces a peak of activity in the centre of the stimulated population, while surrounding neurons are depressed below normal tonic levels by the actions of interneurons that form lateral inhibitory network. Figure on the right shows the case where two distinct adjacent points on the skin are stimulated. Similarly, the stimulation produces two peaks of activation (displayed by dotted lines). In absence of lateral inhibition effects (in the background of the figure), the convergence of these two stimulated populations would result into a single huge excitatory input. On the contrary, lateral inhibition suppresses excitation of these neurons between the two peaks allowing

the development of bimodal response peaks indicative of an improved ability to perceive two closely neighboring stimuli apart.

However, lateral inhibitory networks suppress excitation of the neurons between the points, sharpening the central focus and preserving the spatial clarity of the original stimulus (improved spatial tactile acuity) (Kandel et al., 2000; see Isaacson and Scanziani, 2011 for review). Specifically, lateral inhibition allows the development of bimodal response peaks, which is indicative of an improved ability to perceive two closely neighbouring stimuli as distinct. To conclude, lateral inhibition would shape or sculpt the cortical activity in order to preserve the spatial distinction between the two stimuli.

1.3 From skin to maps

From mechanoreceptors in the skin, sensory information is conveyed to the central nervous system (CNS) through several ascending pathways that run in parallel through the spinal cord, brainstem and thalamus to finally reach the somatosensory cortex. Then, cortex projects in turn to the primary motor cortex and to higher-order associative cortices located in the parietal lobe, and back to the subcortical structures involved into the processing of mechanosensory information. Tactile information involving spatial discrimination are carried through two different pathways. Information arising from the body are carried through the dorsal-medial lemniscal pathway and those arising from the face through the main sensory trigeminal pathway. The various pathways that carry somatosensory information to the CNS will not be described in this thesis (see Kandel et al., 2000 or Delhaye et al., 2018 for recent overview).

More relevant for the scope of the thesis is instead describing the way information is conveyed to the primary somatosensory cortex: i.e. in a somatotopic way. Indeed, at each of the processing stages involved into the ascending sensory pathways, the arrangement of the tactile inputs preserves the spatial relations of the receptors on the body surface. At the final step of the processing, i.e. in SI, the maintenance of this topographic constancy thus creates a cortical map of the body surface so that neighbourhood relations are preserved: information

from receptors that are close to each other in the skin is conveyed to neighbouring neurons in the cortex. As result, SI contains a body map which is somatotopically organized.

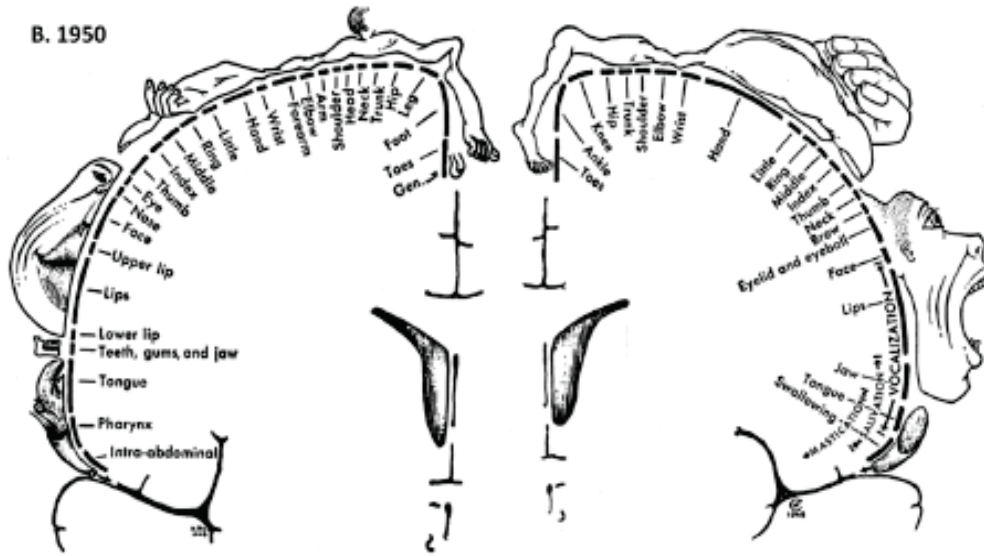
1.3.1 Primary somatosensory cortex

Sensory information processing culminates in the cerebral cortex, classically divided into primary and secondary somatosensory cortices. The contralateral primary somatosensory cortex (SI) is thought to process and encode type and intensity of the sensory inputs, whereas the bilateral secondary somatosensory cortex (SII) is believed to perform higher-order functions including sensorimotor integration, integration of information from the two body halves, attention, learning and memory. These two areas are reciprocally connected via cortico-cortical connections (Burton, 1986; Jones, 1986). Moreover, left and right SII cortices have reciprocal connections and the majority of SII neurons display bilateral RFs (Burton, 1986; Caminiti et al., 1979; Jones, 1986; Manzoni et al., 1989). Furthermore, SII is reciprocally and somatotopically connected to contralateral SI (Jones, 1986).

SI in humans is located in the parietal lobe along the posterior bank of the central sulcus (i.e. in the post-central gyrus). It is made up of Brodmann's areas (BA) 3a, 3b, 1, and 2 (in rostro-caudal order). BA3b corresponds to the anterior bank of the post-central gyrus, for this reason some authors in the past considered only area BA3b as primary somatosensory cortex (Merzenich et al., 1978). Experiments conducted by Powell and Mountcastle (1959) revealed that the distinct areas BA3a, BA3b, BA1 and BA2 should be considered as distinct functional entities. Indeed, they demonstrated that neurons in BA3b and BA1 respond primarily to contralateral low-threshold tactile stimuli. This is due to the fact that BA3b receives SA and FA cutaneous input, while BA1 receives FA vibratory sensation. On the other side, BA3a responds primarily to stimulation of proprioceptors, while BA2 respond to both tactile and proprioceptive stimuli. Another important finding on the functional structure of SI is that each BA area contains a somatotopic representation of the body surface. Consequently, SI contains 4 separate and complete representations of the body surface (Merzenich et al., 1978; Kaas et al., 1979; Jain et al., 2001). Since most of the projections arising from ascending pathways reach BA3b, cortical processing of tactile discrimination takes place in this area. In humans, the first observations in this regard were made by direct stimulation of the brain in awake

patients undergoing brain surgery for epilepsy. These famous experiments were conducted by Penfield and Boldrey over a period of almost 10 years. The stimulation of different regions of SI elicited tactile sensations that were located in specific parts of the body. As a consequence, a complete map of the body surface was detected in SI. Penfield and Boldrey collected data from 163 patients and the result of their study were published in 1937 in the celebrated book 'Brain' (Penfield and Boldrey, 1937). To make the description easier, all the verbal observations and schematic charts were illustrated into a unique drawing: the sensory *homunculus* (Figure 1.5A, left panel). Literally, homunculus means 'little man'; indeed it is basically the transposition of the body surface on the cortical surface. As previously anticipated, the homunculus' striking characteristic is that each body part is represented in a topographical manner, so that fingers are represented adjacent each other and the hand is represented close to the forearm, etc. Strikingly, the face and hand are not close anatomically but are closely represented in the homunculus. The leg is represented most medially at the crown of the skull, followed by the trunk, arms, face, and finally, most laterally (near the ear), the teeth, tongue, and esophagus.

A



B

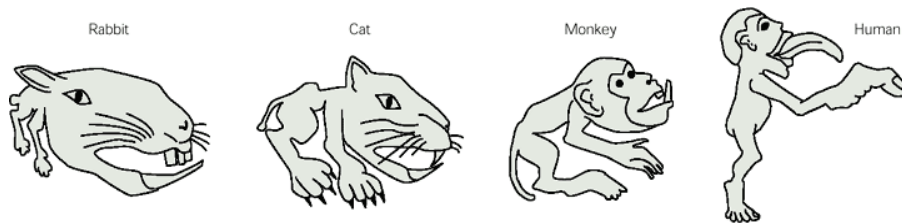


Figure 1.5: Penfield's homunculus and comparison with other species. Figure A shows the representation of the sensory (left) and motor (right) homunculus as described by Penfield and Boldrey in 1937. First, note the different proportions across body parts: hand and face, which are close each other, have the biggest representations. The length of each bar drawn on the cortical surface is indicative of the relative size. Then, note that hand and face are represented close to each other, with the thumb in between, even if these two regions are anatomically distant. [Adapted from Penfield and Boldrey, 1937] Figure B shows differences in cortical magnification across different animal species. Note that these representations are created following functional needs, i.e. different species adapt the stored somatosensory information according to the body parts which are used the most. On the right another way to represent the human sensory homunculus is displayed. [From Kandel et al., 2000]

In addition to the location-based somatotopic organization, another fascinating characteristic of the homunculus map is that the actual size proportions of the body parts are not preserved. The face is larger compared with the back of the head, the thumb is gigantic compared with the other fingers, and the torso has the smallest area of all. On the one hand, this distortion reflects differences in innervation density in different areas of the body I described above. On the other hand, the different innervation densities reflect functional differences arising from a differential use of each body part. In this context, hand and face are the two body parts we use mostly for our daily activities (working, manipulating objects, eating, speaking just to provide some example), thus the ones with highest magnification at cortical level. Similar function-based distortions are observed in the body representations of other animals. In rabbits, for example, the face and snout have the largest representation because they are the primary way a rabbit explores its environment (Figure 1.5B).

To sum up and simplify what I previously described, the somatosensory system seems to be perfectly organized like in a loop: different mechanoreceptor densities on the skin reflect the different levels of acuity across body parts; according to the different mechanoreceptor densities the cortical maps are differently represented, so that a low density translates into a small representation; finally, the cortical magnification reflects the use we make of our body parts in a functional manner.

As for SII, its somatotopy is less fine-grained than that in SI. Indeed, a somatotopic map is also present in SII, but the point-to-point correspondence between body-parts and neural areas, where they are represented, is not as precise as in SI (Del Gratta et al., 2000; Disbrow et al., 2000; Ruben et al., 2001; Simões et al., 2001). It is important to also note that the organization of the somatosensory maps in SI is similar to another somatotopic map, the motor homunculus (Figure 1.5B, right panel) found in the precentral gyrus (Penfield & Rasmussen, 1950). The two maps are incredibly similar. The areas responsible for the perception of touch on the hands in the somatosensory homunculus, for example, are located mostly in front of the areas responsible for hand movements in the motor homunculus. This close somatotopic correspondence between these two maps suggests the existence of close sensory-motor functional relationships.

Several more recent studies using imaging techniques support the somatotopic organization of SI first reported by Penfield (Baumgartner et al., 1991; Nakamura et al., 1998; Del Gratta et al., 2000; Iannetti et al., 2003; Nguyen et al., 2004; Nevalainen et al., 2006; Jamali and Ross, 2013). In particular, one of the few studies investigating numerous body parts together reported a detailed somatotopy of the body, as shown in Figure 1.6 (Nakamura et al., 1998). In fact, the majority of studies focused one single body part. In particular, a lot of studies investigated the hand, reporting a particular high magnification of the tips of the thumb and index fingers (Shoham and Grinvald, 2001), and a large overlap between finger representations (Iwamura et al., 1980; Shoham and Grinvald, 2001). In particular, the biggest overlap was found between middle, ring and little fingers.

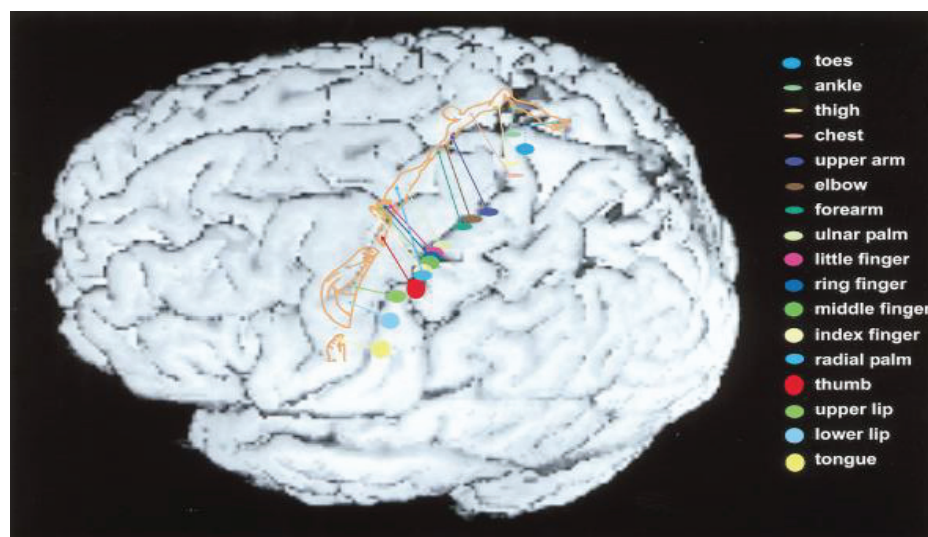


Figure 1.6 [from Nakamura et al., 1998]: Somatotopy of the body recorded in a MEG study. This figure shows the detailed somatotopic localization of all body parts as recorded from a human participant in a MEG, then displayed on MRI image. Note the similarity of the body drawn on the left (in orange) with the homunculus obtained in Penfield's studies (displayed above).

Chapter 2: Somatosensory Plasticity

2.1 Concept of Plasticity

The term 'plasticity' is derived from the Greek word πλαστός (plastos), which means molded. Over the past several decades, this term has been adopted by the neuroscience field. Today, one of the fundamental concepts of modern neuroscience is that the brain is not a static organ, as was thought in the past. On the contrary, its connections are dynamic and can be continuously modified and shaped by experience. Plastic changes are expressed both in functional and structural terms. Pascual-Leone et al. (2005, page 377) gave this definition of plasticity:

'Plasticity is an intrinsic property of the human brain and represents evolution's invention to enable the nervous system to escape the restrictions of its own genome and thus adapt to environmental pressures, physiologic changes, and experiences'.

Brain plasticity is obvious in the maternal womb during fetal life, when the brain is not yet completely developed, and it continues throughout childhood. It was long thought that the adult brain was not able to undergo plastic changes. When the first evidence started to show that the brain is actually able to change in an adaptive way based on new experiences, it focused the attention of many researchers interested in investigating this fascinating phenomenon.

The somatosensory system in particular represents a striking example of neural plasticity, which has become one of the most investigated models of plastic changes in the brain. There are two major reasons that somatosensory plasticity has been so widely investigated: on the one hand, the somatosensory cortex lends itself to investigation because it contains well defined and ordered cortical maps. On the other hand, the perceptual consequences in response to experience are so salient that researchers were motivated to clarify the mechanisms underlying the associated processes. For instance, somatosensory plasticity due

to experience translates into the extraordinary ability to (i) adaptively respond to injuries occurring throughout life and (ii) learn and improve tactile skills. In the first case, the consequences associated with injuries have been particularly well described at cortical level, i.e. in terms of cortical reorganization in SI. In the latter case, the consequences associated with learning have most often been described at the behavioural level, i.e. in terms of improved acuity of the sense of touch in the hands. Thus, the somatosensory plasticity is not a single process leading to a unique output, on the contrary it involves so many different forms and levels and consequences that no general principle can be fixed for it.

Despite years of intensive study, the rules governing plasticity, somatosensory plasticity in particular, are far from being fully understood. One possible way of approaching this complexity is to classify the different forms of changes using different criteria. Firstly, one could classify the somatosensory plasticity based on the different level of analysis at which it has been observed and described: *synaptic, representational and behavioural*. Trying to figure out the principal actors linking the three components of the triad has guided much of the work in the field of modern neuroscience. Indeed, one major goal was and continues to be to correlate changes in synaptic efficacy between two neurons to changes in cortical representations, and these latter to changes in behaviour. However, the reality of experimental evidence is far from this ideal situation and is much more complicated. In fact, if on the one hand it is well-known that changes in synaptic efficacy are one of the substrates for learning, for example, on the other hand it is also true that changes in behaviour are not always directly correlated with cortical changes. Thus, what is established is that somatosensory plasticity is often expressed at different levels but the underpinnings of the changes occurring at each level and the causal relationships between them are far from being understood.

A second way one could classify somatosensory plasticity is considering which kind of stimulus brings to a given process. According to this, one can generally distinguish between plasticity following a *decrease* and plasticity following an *increase* of stimuli. The first one includes the circumstance in which there is permanent or temporary interruption of the afferent signals along the sensory pathway, and it refers to the well-known cases of peripheral or central injury. In contrast, the latter includes circumstances in which there is an increase in the amount of sensory stimuli along the pathway, and it refers to the cases of both restoration

in the damaged brain and perceptual learning in the intact brain. Thus, depending on whether there is a decrease or an increase of sensory inputs, the brain adapts differently to these changes, often with negative or positive perceptual consequences, respectively.

Indeed, some authors refer to negative or *maladaptive* plastic processes those that bring about functional (behavioural) impairment (following amputation or brain damage for example), and as positive or *adaptive* those processes that lead to functional benefits (following sensory training for example). However, since this distinction could appear superficial if one considers the difficulty in classifying all the possible individual perceptual consequences simply as positive or negative, its use is often debated. For this reason, this classification will not be used here. For the scope of this thesis, in this section I will give an overview of the different plastic changes which take place within the somatosensory system, trying to describe where possible the underlying processes and the consequent effects at synaptic, cortical or perceptual levels, depending on the case. Schematically, I will first describe the circumstance when the brain has to adapt following a decrease of inputs, then the opposite circumstance of increase of inputs. Finally, I will describe a form of plasticity which is of particular interest for the scope of this thesis: Hebbian plasticity.

2.2 Plasticity following decreased inputs

Most of the knowledge we have regarding changes in the somatosensory cortex when a source of inputs is missing come from studies on amputation or deafferentation. The first studies investigated these changes in animals by experimentally inducing severe peripheral lesions at the level of the upper-limb. Similarly, cortical changes were investigated in humans following amputation of the upper-limb. SI contains well-ordered and detailed maps of all the body parts, so that physically adjacent parts are represented next to each other resulting in topographic maps of the body. After the loss of peripheral input, the most impactful consequence within the cortex is that this well-ordered topographical representation is partially changed in favour of dynamic reorganizational changes. Indeed, the *normal* cortical topography undergoes a *reorganization* of the maps in order to adapt to the altered external conditions. As I will describe in this section, this reorganization was at first considered as a

loss of the original topography in favour of a new topography. However, recent evidence reversed this theory by showing that the original topography actually *persists* despite the reorganizational changes. Moreover, first studies described this reorganization as taking place into the cortex, whereas recent evidence highlighted the major contribution of other brain structures for producing such reorganizational changes. This section will briefly review some of these studies investigating cortical reorganization.

2.2.1 Animal studies

The first evidence of reorganizational changes came from primate somatosensory cortex studies conducted by Merzenich and colleagues (1983a,b). They performed transection of the median nerve, thus removing inputs from the glabrous (ventral) portion of fingers D1, D2 and D3. Immediately after transection, there was *unmasking* of inputs from dorsal skin areas, the volar palm, and the bordering zones on D3 and D4 in a limited area of the cortex which previously represented the glabrous surfaces of the D1-D3 fingers. This unmasking was thought to arise from existing horizontal connections or thalamocortical inputs that were previously suppressed by inhibitory circuitry (Merzenich et al., 1983a). A complementary study investigating the time course of these changes over several weeks (Figure 2.1) revealed that the representations of the bordering glabrous skin surfaces progressively expanded to occupy larger and larger portions of the former median nerve area, producing a progressive reorganization (over several weeks) of the previous somatotopic maps. Then, 2-9 months after the nerve transection, these reorganized cortical areas developed a progressively more refined spatial representational resolution and topographic order, until median nerve area took its former territory (Merzenich et al., 1983b). Following the same line of research, in subsequent experiments, Merzenich and colleagues (1984) examined the effects of the amputation of one or two fingers in monkey (finger D3, or D2 and D3). The result was that 2-8 months after amputation, most of the cortical areas that originally responded only to the skin surfaces corresponding on the amputated fingers became responsive to inputs from adjacent fingers or the palm. However, although the cortical area representing the fingers significantly expanded, representational changes were relatively local since there was no significant increase of the representation of more distant fingers, for example D5 (Merzenich et al., 1984).

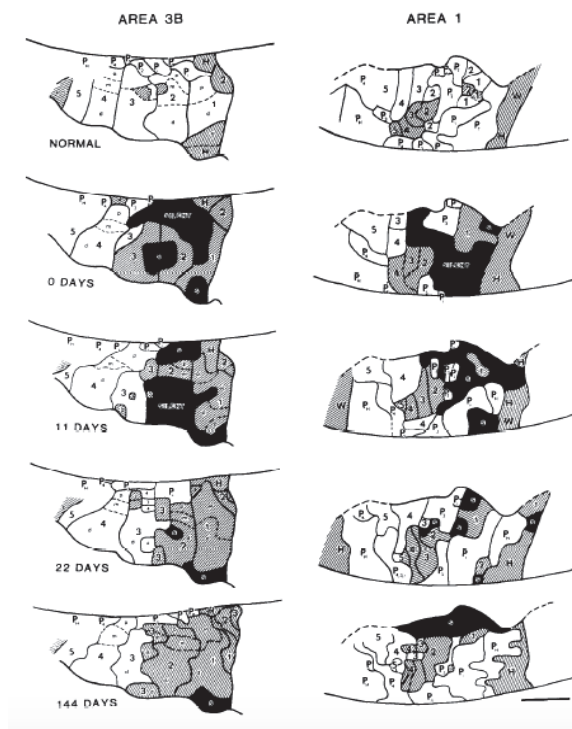


Figure 2.1 [From Merzenich et al., 1983b]: Temporal progression of the reorganization of the cortical map following median nerve transection. Somatotopic representation of the hand in area 3b (right) and 1 (left) from a single monkey before (up, normal), immediately after (0 days), and different times (11, 22 and 144 days) after transection of the median nerve. Numbers 1-5 represent the fingers, while letters p, m, and d represent the proximal, middle, and distal portion of each finger. Hatched areas represent the dorsal surface of the hand, and black represents silent areas. Note that, immediately after transection, much of the cortex remained silent, while some areas exhibited responses to the dorsal surface of D1-D3. Silent cortex reduced over time (11-22 days), and 144 days after transection very little cortex remained unresponsive, while novel responses to the dorsal surface of D1-D3 emerged.

These experiments demonstrated that somatosensory cortical map of fingers in adult monkey changes following sensory deprivation from this body part. Most of the changes involved the representation of the intact and immediately adjacent fingers, since the cortical area which was unresponsive immediately after the lesion came to be excited by inputs from neighbouring skin surfaces. Several similar examples of reorganization in adult

somatosensory cortex in response to denervation or amputation were reported later. In particular, Calford and Tweedale (1988) investigated the time course of receptive field properties after finger amputation in flying fox. They found that RFs which were originally restricted to the amputated finger had immediately enlarged 20 hours after finger amputation. Besides these RFs which enlarged to include parts of the remaining metacarpal, similarly enlarged RFs were also found at sites where the field initially crossed the line of amputation. Importantly, already by the third day after amputation the area containing these RFs was noticeably reduced, and this reduction continued for the following 7-8 days. Thus, one week after finger amputations the enlarged RFs shrank completely until only small RFs remained. Similar to the previously described experiment (Merzenich et al., 1983a), these effects were thought to be due to the reduction or removal of *inhibitory interactions* which before amputation prevented the expression of existing but silent inputs. Indeed, Calford and Tweedale suggested that removing one digit containing RFs of a cortical locus also removes the dominant inhibitory stimulus, and this would explain the immediate expression of the new enlarged RFs they observed. However, the fact that RFs progressively shrank over several days, suggested that if expansion is given by a removal of inhibition then shrinking implies a gradual changes in the excitatory/inhibitory balance (Calford and Tweedale, 1988).

The studies described above reported evidence of plastic reorganization in cortical maps following sensory deprivation. This reorganization was often expressed as local since changes were limited to the deprived and adjacent areas, and short-term since changes were restricted to the period immediately following the manipulation. However, later studies provided evidence that the extent of reorganization can be far greater than previously reported, and that changes in the cortical maps can be also found on a larger -scale (physically) and on a longer-term (temporally). One of these studies investigated SI activity in four monkeys after deafferentation of an upper-limb more than 12 years before the recording time (Pons et al., 1991). Remarkably, they found that the deafferented cortical area (which included the maps of the fingers, palm, remaining upper-limb, neck and occiput) responded to stimulation of the face. Specifically, not all the face but stimulation of only a relatively small portion of the face (from the chin to the lower jaw) was found to elicit neural activation in the deafferented zone. Moreover, the pattern of reorganization in this new enlarged representation of the face was highly specific, with the midline of the face which was represented caudally and the lateral

parts of the lower jaw which were instead represented in more rostral parts. Figure 2.2 (modified from Pons et al., 1991) shows how the face area representation enlarged toward the former, now deafferented, upper-limb area representation, in a sort of *invasion* between adjacent areas. The mechanisms underlying such extraordinary reorganization were not clear at that time and are still not completely understood even today (see below Kambi et al., 2014). The extent of the cortical reorganization reported by Pons and colleagues (1991) was substantially bigger than the reorganization previously reported following median nerve transection (Merzenich et al., 1983a,b) or amputation (Merzenich et al., 1984). In the first case the extent was around 1-2 millimetres, in the latter case the cortical invasion spanned over 1-2 centimetres (an order of magnitude greater). Thus, it is highly unlikely that similar mechanisms accounting for such local changes (Merzenich et al., 1983a,b; 1984) might also account for such long-range changes (Pons et al., 1991).

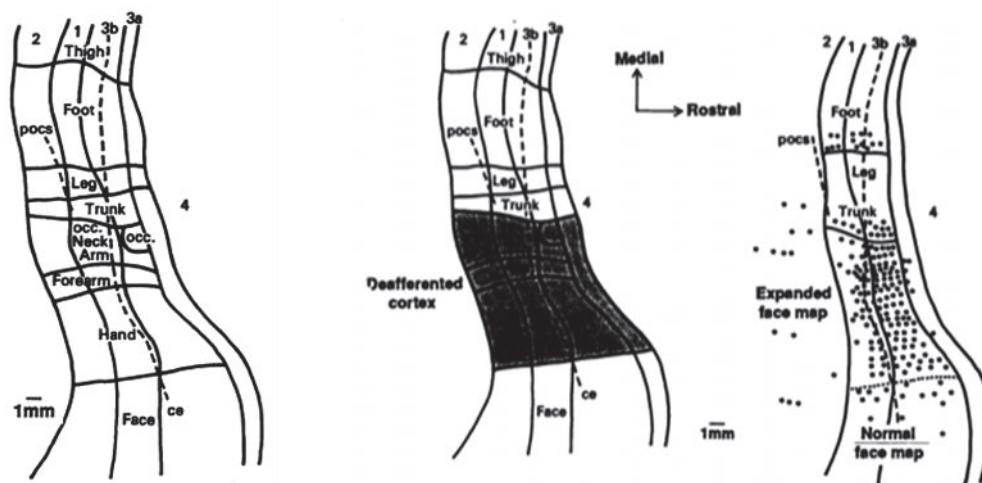


Figure 2.2 [Modified from Pons et al., 1991]: Face cortical representation invades the deafferented cortex. The figure shows the flattened map of monkey SI, before (left) and after (middle and right) deafferentation. The large black zone in the middle figure represents the deafferented cortex, corresponding to the former representations of the fingers, palm, remaining upper-limb, neck and occiput. The figure on the right shows the recording site density. Since this area responded to stimulation of the face, the face was thought to invade the deprived area.

One hypothesis suggested by the authors, as an alternative to the unmasking of pre-existing thalamo-cortical or cortico-cortical projections, was the sprouting of new projections across the deafferented area, thus crossing the face/hand border. Similar evidence of cortical reorganization between one invading and one invaded area corroborating the hypothesis of a sprouting of cortical connections accounting for this process was provided in a subsequent anatomical tracing study conducted by Florence and colleagues (1998). Their aim was to determine whether the growth of new connections plays a leading role in the reorganization of somatosensory cortex following deprivation in peripheral somatosensory inputs. To this purpose, the distribution of thalamic and cortical connections was investigated in four monkeys with long-standing, accidental trauma to the forelimb. Similar to previous findings, they found that regions that normally responded to sensory stimulation of the hand after upper-limb amputation became responsive to the face. More importantly, injections of tracers in area 1 of these monkeys revealed normal patterns of thalamo-cortical connections, but markedly expanded lateral connections in areas 3b and 1. Thus, this finding strengthened the hypothesis that the growth of intra-cortical but not thalamo-cortical connections could account for much of the reorganization of the sensory cortical maps (Florence et al., 1998, but see below Kambi et al., 2014). Florence's study provided evidence of widespread expansion of lateral connections in the sensory deprived area, likely driven by intra-cortical sprouting. According to the available data, sprouting could arise from both new and pre-existing connections. In this latter case, sparse widespread cortical connections that normally exist in the hand representation of somatosensory cortex could be unmasked by the injury, similar to the other unmasking previously described (Merzenich et al., 1983a). However, this hypothesis is in contrast with an earlier study showing that regions of deactivated cortex can remain silent for months after denervation (Garraghty et al., 1994). On the contrary, if widespread lateral connections are normally present, they should be able to reactivate cortex relatively rapidly after sensory deprivation, without the need for long recovery periods where connections can grow and become effective (but see below Chand and Jain, 2015).

The studies I described above show that following loss of peripheral inputs coming into the sensory pathway from the upper-limb there is a massive cortical reorganization, with the deprived cortical area of the upper-limb being *invaded* by the cortical area of the adjacent face. However, some studies also provide evidence of the opposite circumstance, i.e. of the

cortical reorganization occurring following loss of inputs from the face. Of particular interest for the aim of this thesis is a study in rodents conducted by Kis et al., 1999, where the physiological consequences of a unilateral infraorbital nerve lesion were investigated. Immediately following nerve crush, the deprived cortical vibrissal representation started to respond to stimulation of the forepaw digit and not to stimulation of the face. This invasion of the forepaw area toward the area of the face was still present even a few weeks after nerve crush. Interestingly, the two representations returned to their normal extent 60 days after nerve crush (Figure 2.3). Even if found in different species, this finding and the studies previously mentioned (Pons et al., 1991; Florence et al., 1998) demonstrate that the invasion between the cortical representation of the hand and face is bidirectional, i.e. that face invades the hand and vice versa. This suggests that lateral connections cross the cortical border between the two areas in both directions, allowing changes arising in one part to affect the other (but see below Fang et al., 2002). In addition, these results demonstrated that temporary infraorbital nerve lesion not only resulted in a transient disappearance of the contralateral vibrissa-evoked responses from the barrel cortex, but also produced an expansion of the neighbouring representation area of the digits of the contralateral forepaw (Kis et al., 1999).

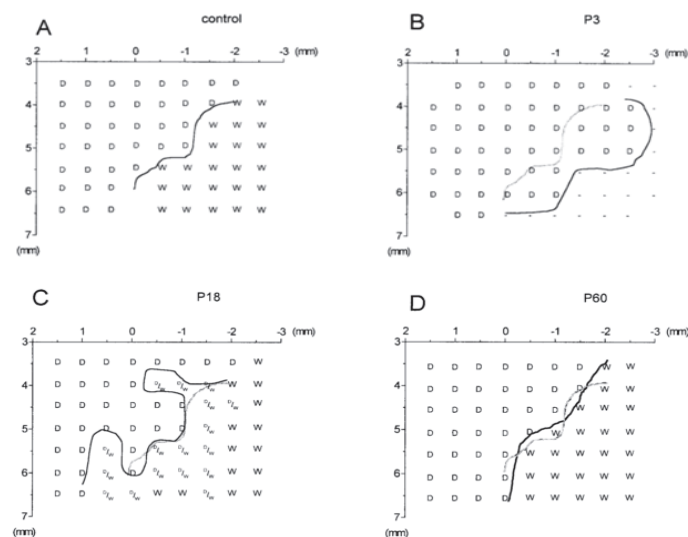


Figure 2.3 [Modified from Kis et al., 1999]: Reorganization in cortical maps of rodent digit and whisker representations induced by unilateral infraorbital nerve lesion. Figure A shows the posterolateral border of the normal representation of fingers

2, 3, and 4. **Figure B** shows that following unilateral nerve crush there was a large area unresponsive to whisker deflection, but stimulation of the digits evoked responses in the enlarged representation. The grey line indicates the original border between the fingers and whisker regions, the black line the posterior border of the enlarged digital representation. The shift in digital representation was observed within minutes/hours after the nerve crush. **Figure C** shows the expanded digital representation and the reappeared whisker responses resulting in an overlapping zone between the pure digital (D) and the vibrissal (W) cortical areas. The grey line indicates the original border between D and W areas, black line posterior border of the pure digital area. Finally, **Figure D** shows that 60 days after nerve crush, the representational maps of the digits and vibrissae in the primary somatosensory cortex returned to their normal size.

So far, I described some studies showing extensive cortical reorganization of the topographic maps following sensory loss from, in particular between the hand and face regions. This reorganization was described at cortical level, so that possible interpretations accounting for such plastic changes involved the unmasking of pre-existing thalamo-cortical or cortico-cortical projections and/or in alternative the sprouting of new projections across the deafferented area, thus crossing the face/hand border. However, these interpretations did not find confirmation in subsequent studies investigating the possible substrates of the changes. Indeed, a more recent body of literature quite completely reversed the hypothesis that reorganizational changes displayed at cortical level arise from the involvement of intrinsic cortico-cortical and/or thalamo-cortical connections, demonstrating that reorganizational changes are rather due to different subcortical contributions.

A first important study conducted by Fang and colleagues (2002) labelled the intrinsic connections of the face and hand portions of area 3b in several species of New World monkeys to determine whether these two regions are interconnected. Results showed that the intrinsic connections in either the hand or face representations were almost completely confined to their respective representation, and very few neurons projected across the border. Thus, these connections cannot account for the more extensive reactivations of hand and forelimb cortex that have been demonstrated after the loss of most or all of the afferents from the forelimb. The extensive reactivations do not seem to depend on the distributions of thalamo-cortical connections either. Indeed, neurons in the somatosensory thalamus labelled

by injections in either face or hand representations were confined to either VPM, representing the face, or the hand subnucleus of VPL, but not to both subnuclei. To conclude, this study suggested that the reactivation of hand cortex by face stimulation (for example Pons et al., 1991) does not depend on a previously existing network of intrinsic cortical connections across the hand-face border, or mismatched thalamo-cortical projections (Fang et al., 2002).

Evidence that intra-cortical projections across the hand-face border are few, confined to the immediate vicinity of the border, were confirmed by Chand and colleagues (2015). In addition, this study showed that in monkeys with long-term unilateral lesions of the dorsal columns at cervical levels and subsequent expanded chin representation, (i) intra-cortical intrinsic connections do not sprout across the hand-face border; and (ii) thalamo-cortical connections from the hand and face representations in the ventro-posterior nucleus to area 3b also remained unaltered after injury. Thus, this study corroborated the hypothesis that sprouting of intrinsic connections in area 3b or the thalamo-cortical inputs does not contribute to large-scale cortical plasticity (Chand et al., 2015). Apparently, the mechanisms that lead to brain reorganization have to operate at a different level. This level might have been clarified by the work of Kambi and colleagues (2014). They demonstrated that selective inactivation of the cortex does not block the emergence of the observed hand-face reorganization, while selective inactivation of the cuneate nucleus completely abolishes the plastic reorganization. Indeed, the results unequivocally showed that expansion of face inputs into the deafferented hand region of area 3b is due to changes taking place in the brainstem nuclei, whereas if the information flow from the reorganized cuneate nucleus of the brainstem is interrupted, the reorganized cortex becomes silent (Kambi et al., 2014). These evidence clearly put forward the main involvement of the cuneate nucleus as substrate for the observed hand-face plasticity, despite large evidence showed that representational changes are expressed at cortical level.

2.2.2 Human studies

Large-scale reorganizational changes following sensory deprivation have also been reported in humans. Because of their perceptual consequences, changes crossing the hand/face border in particular have been extensively described as they are one of the most fascinating examples

of somatosensory plasticity (Elbert et al., 1994, 1997; Flor et al., 1998; Birbaumer et al., 1997; Karl et al., 2001). Beside small differences in the extent of reorganization and some methodological differences across studies, all these studies reported that loss of peripheral sensory inputs at the hand resulted in an enlarged representation of the face area, which expanded into the hand and sometimes arm areas, so that stimulation of the face evoked activity in the area formerly occupied by the representation of the hand. Elbert and colleagues (1997) for example showed that following upper limb amputation the “missing” cortical area became responsive to stimulation on the lip and corner of the mouth. Interestingly, an increase in the representation of the intact hand was also reported, in the hemisphere *ipsilateral* to the injury (Figure 2.4). The authors suggested that two separate plasticity mechanisms were occurring: one in the injured hemisphere accounting for the invasion of the face area toward that of the deprived hand, and another in the intact hemisphere accounting for the enlarged representation of the intact hand (Elbert et al., 1997).

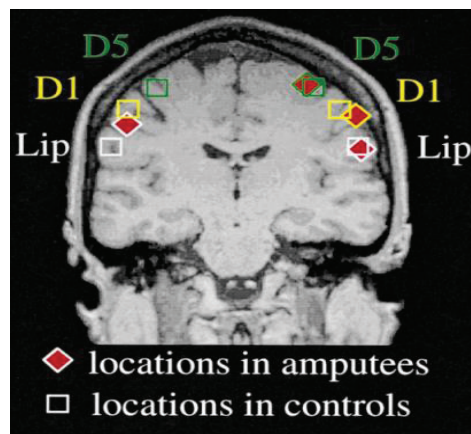


Figure 2.4 [From Elbert et al., 1997]: Localization of the equivalent current dipole for D1, D5 and Lip stimulation in controls (open squares) and amputees (filled diamonds). For the amputees, the left side of the figure (contralateral to the affected hand) shows the shift of the Lip area toward the D1 area, while the right side (contralateral to the intact hand) shows the expansion of the intact hand as a result of the shift of the D1 area away from the D5 area.

From a functional point of view, the enlarged representation of the intact hand could be considered as an adaptive plasticity process between the two hemispheres, where the loss of inputs into a given area results in loss of inhibition between this area and its homolog in the opposite hemisphere. Similar findings were reported by Calford and Tweedale (1990) in adult flying foxes and monkeys, where immediately following denervation produced by amputation or local anaesthesia enlarged receptive fields were found in the representations of the unaffected fingers. This suggested that inhibitory mechanisms are involved in the maintenance of the balance between homologous cortical areas, and that when this inhibitory input is lost, as appears to be the case in sensory deprivation, adaptive plastic changes occur.

Altogether these studies show that a plastic remodelling clearly occurs in the somatosensory cortex in response to loss of inputs. According to some evidence, remodelling was first thought to be triggered by pre-existing (albeit) sparse widespread cortical connections in the somatosensory representations that are unmasked by the injury. Specifically, following elimination of input from the limb, lateral projections from face to limb representations could either sprout or become unmasked, leading to the observed reorganization. However, as previously described, mechanisms accounting for this remodelling as well as the involvement of subcortical contributions and the exact time-course and extent of changes still represent a challenge for researchers.

But, why would the cortex operate in this way? Is there a functional benefit for such a salient reorganization? In the recent past, probably with the scope to assign a positive implication to the observed reorganization, some changes involving invasion of cortical areas were considered as adaptive (Nava and Röder, 2011). On the opposite side, other changes were considered maladaptive (Flor et al., 2006), since this did not bring any benefit but rather a malfunction.

The positive connotation of cortical reorganization is debated and studies are often contradictory. So far, no definitive evidence of direct perceptual gains due to input loss have been observed. On the contrary, some study clearly suggested the opposite. For example, albeit one could think that increased representation of a given body part should in turn lead to increased acuity for this party, evidence reported that finger amputation in humans does not

result in lower detection thresholds or improved spatial acuity on the remaining fingers (Vega-Bermudez and Johnson, 2002).

In this same line, the most striking example of maladaptive plasticity following severe sensory loss is *pain* (Flor et al., 1995; Birbaumer et al., 1997). In particular, when reorganizations occur across the hand/face border, most patients report experiencing intense phantom limb pain (PLP) (Flor et al., 1995; Karl et al., 2001). Distorted *phantom sensations* following amputation are the most extensively documented and striking consequence related to amputation. Many studies report the dramatic experience of amputees who, even decades after injury, have a continual (often painful) sensation of the missing limb (Flor et al., 2006). These phantom sensations can be as vivid and as natural and span a range of qualities, including for example pressure, temperature, tingling, itch, movement and pain (Ramachandran and Hirstein, 1998; Raffin et al., 2012). In a famous series of studies conducted by Ramachandran (1993) three amputees reported experiencing precise correspondence between touch applied on their face and referred sensations perceived on the phantom hand. Importantly, the reported referred sensations from the face to the hand were topographically organised, so that neighbouring sites on the face elicited sensations on neighbouring fingers. This behavioural evidence corroborated the electrophysiological recordings described above (Pons et al., 1991) showing that following upper-limb amputation some areas normally responding to hand stimulation became responsive to stimulation on the face. Thus, important behavioural consequences are associated with the invasion of the face representation toward the missing hand representation. The topographic pattern of the sensations referred to the missing limb after touching the face strengthened the hypothesis that reorganization is taking place in the cortex, since the cortical topography, i.e. the proximity of the face and hand representations in SI, is predictive of the perceptual remapping. However, some authors are not in agreement with the hypothesis that referred sensations result from SI reorganization, suggesting on the contrary that referred sensation would not respect the cortical topography. In a recent work Makin and colleagues (2017) reviewed some studies displaying referred sensations (Figure 2.5) and showed that some referred sensations could be triggered by touch applied on multiple body parts (for example feet, chest, and neck) whose representations are not cortical neighbours of the hand area. Interestingly, referred sensations were even reported when touch was applied to body parts contralateral to the missing hand.

Contrary to the classical hypothesis that massive functional cortical reorganisation observed in SI following sensory deprivation was thought to result from widespread sprouting of intracortical connections (Pons et al., 1991; Florence et al., 1998), Makin and colleagues agreed with the more recent evidence (Kambi et al., 2014; Chand et al., 2015) which report how much of the reorganisation following nerve injury takes place in the brainstem, and not necessary in the cortex (see Makin et al., 2017 for further discussion).

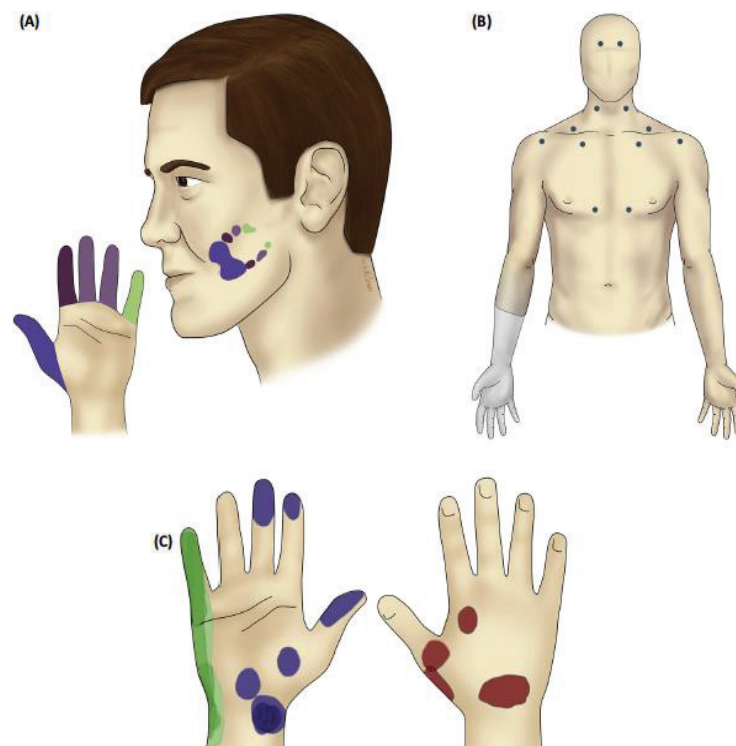


Figure 2.5 [From Makin et al., 2017]: Referred sensations. **Figure (A)** is adapted from Ramachandran and Hirstein (1998). Note the perfect topographical mapping observed between the location of the trigger region on the face and the location of the referred sensation on the left phantom hand. D5 (green) is localized close to the ear, while D1 is localized closer to the mouth. In between, the topographically ordered sensations on the other fingers. **Figure (B)** is adapted from Knecht et al., (1996). Touch on different parts of the body (indicated with blue dots), which are not cortical neighbours of the deafferented limb, were found to evoke referred sensations on the missing limb. **Figure (C)** is adapted from (Tan et al., 2014). Electrical stimulation of the residual

somatosensory nerves evokes perception on the missing right hand. The coloured patches indicate locations of consistent perceived sensations on the phantom hand over the course of 2 months, during stimulation through different electrodes located on the median (blue), ulnar (green), and radial (red) nerves.

Indeed, perceptual consequences of cortical reorganization following sensory deprivation, in particular following upper-limb amputation, are extremely complex and heterogeneous, probably the trickiest phenomenon related to somatosensory plasticity. Moreover, studies often refer to single case reports, then it becomes difficult to generalize and discover common underlying mechanisms accounting for all the different perpetual consequences observed in the literature. The experimental evidence that I reviewed in this section suggests that SI is involved in brain plasticity taking place following sensory loss, at least as site where reorganizational changes are displayed. It is likely, however, that other subcortical mechanisms (Kambi et al., 2014; Jain et al., 2000; Makin et al., 2017) mainly contribute to the remodelling of the brain and the subsequent perpetual consequences.

Evidence of short-term plastic changes in the somatosensory system, which are interesting for this thesis, comes from studies of *anaesthesia*. One study investigating both the hands showed rapid improvements in tactile spatial acuity and changes in cortical processing for the left hand during cutaneous anaesthesia of the right hand (Werhahn et al., 2002a). Interestingly, right hand anaesthesia did not elicit changes in grating orientation task (GOT) thresholds at the lip, as well as and right foot anaesthesia did not modify GOT thresholds at the left index finger, but significant perceptual improvement was found only at the left hand after anaesthesia of the contralateral right hand. Similar specific results were replicated in somatosensory evoked potentials (SSEPs) recordings: after anaesthesia of the contralateral right hand, the stimulation of three fingers in the left hand displayed and increase in the differential amplitude between SSEPs components. Moreover, the evidence that the deafferentation of one hand's representation enhances processing in the contralateral homologous representation is consistent with the previously described hypothesis that deafferentation of a cortical representation influences the homotopic representation in the opposite hemisphere (Calford and Tweedale, 1990; see also Werhahn et al., 2002b). In this

context, according to the authors, the anatomical and functional substrates for such interactions do exist and are thought to be predominantly inhibitory.

Similar inhibitory interaction between hands were reported in a subsequent study by Bjorkman and colleagues (2004a) who investigated changes in MI and SI during and after tourniquet-induced anaesthesia of the right hand. They found changes in sensory as well as motor functions in the contralateral hand. Specifically, they found an improvement in spatial tactile discrimination assessed by the two-point discrimination (2PD) task, and this improvement remained for 15 min following the temporary deafferentation. They also found increased perception of touch (assessed through von Frey's hair), but in slight contrast with 2PD values this measurement showed a rapid return to baseline 15 min after release of the tourniquet. On the contrary, grip strength improvement was still present 15 min after release of the tourniquet, and this was reflected in the increased activity in the right primary motor cortex (ipsilateral to the anaesthetised right) found in the fMRI investigation. All these results are shown in Figure 2.6 (modified from Bjorkman et al., 2004a).

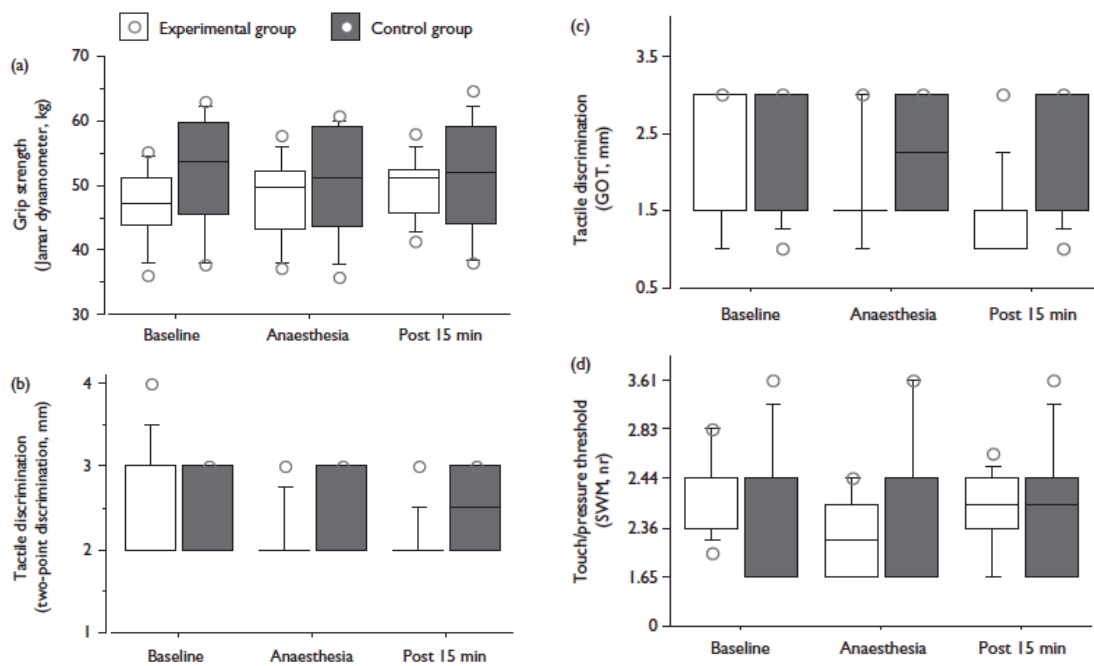


Figure 2.6 [Modified from Bjorkman et al., 2004a]: Tactile and motor performance before (baseline), during and 15min after tourniquet-induced anaesthesia of the

right hand. In each graph results from experimental (white) and control (grey) groups are shown. Grip strength in the left hand **(a)**, measured with Jamar dynamometer, increased significantly during anaesthesia and the improvement remained 15min after anaesthesia. Tactile discrimination in the left index finger **(b)**, measured with 2PD task, improved significantly during anaesthesia and the improvement also remained 15min after. In contrast, tactile discrimination in the left index finger **(c)**, measured with GOT, showed no significant changes in the experimental group. Finally, perception of touch in the left index finger **(d)**, measured with von Frey's filaments, improved significantly during anaesthesia but it came back to the baseline value 15min after anaesthesia.

Surprisingly, since opposite evidence was reported in Werhahn's study (2002), in this study no significant change in contralateral hand was reported for GOT thresholds. Thus, these data are slightly discordant with those reported by Werhahn. Following anaesthesia of one hand, the both studies reported increased tactile acuity of the contralateral hand and increased cortical activity of the ipsilateral hemisphere, but only in Werhahn's study an improvement in GOT performance was found. This discrepancy, together with the difference in latency of touch perception and tactile discrimination improvement, might arise from different cortical processing of stimuli related to touch perception and tactile discrimination. In a subsequent study by Bjorkman and colleagues (2004b), local skin anaesthesia was performed on the forearm. The result was a rapid significant improvement in both tactile discrimination and perception of touch in the ipsilateral hand. This improvement remained for at least 24 hours after the anaesthesia. However, in contrast to the experiment just described with tourniquet-induced anaesthesia (Bjorkman et al., 2004a), changes in hand tactile acuity were found only in the ipsilateral hand. Indeed, no change was found in the left, contralateral hand, nor in motor function of the ipsilateral hand. This lack of improvement transfer to the contralateral hand might be due to the type of manipulation, which might not have been sufficient to induce changes in both hemispheres.

Altogether these studies investigating changes immediately following anaesthesia suggest that plastic dynamics between the hemispheres may result in functional changes in the ipsilateral or contralateral hand depending on the changes conditions. Indeed, homotopic regions of SI are linked in a such way that cortical changes induced in one hemisphere in the form of receptive field expansion produced by limited peripheral denervation, are immediately

mirrored in the contralateral hemisphere (Calford & Tweedale, 1990; Werhahn et al., 2002a,b). Consequently, deafferentation of one hand resulting in improved tactile discrimination in the contralateral hand may be due to rapid redistribution of cortical resources to recruit cortical areas to serve sensory and motor functions in the contralateral hand, in a sort of behavioural compensatory gain (Werhahn et al., 2002b).

Interestingly, similar deprivation-induced plasticity has also been associated with distorted perception at the face. For example, Gandevia and Phegan (1999) reported that following anaesthesia of the thumb either by nerve block or cooling there was enhanced perceived size of the lips. On the contrary, the perceived size of the adjacent index finger was not affected. Another study reported both cortical and behavioural consequences following abolishing sensation from the radial and medial three-quarters of the hand by pharmacological nerve block of the radial and median nerves (Weiss et al., 2004). Magnetic source imaging showed that the cortical representation of the little finger and the skin beneath the lower lip, whose intact cortical representation zones are adjacent to the deafferented region, had moved closer together, presumably because of their expansion across the deafferented area. In addition, in the side ipsilateral to the blockade, decreased two-point discrimination threshold near the lip, increased absolute touch threshold in fingers and mislocalization of touch of the intact ulnar portion of the fourth finger to the neighbouring third finger whose nerve supply was blocked were reported (Figure 2.7).

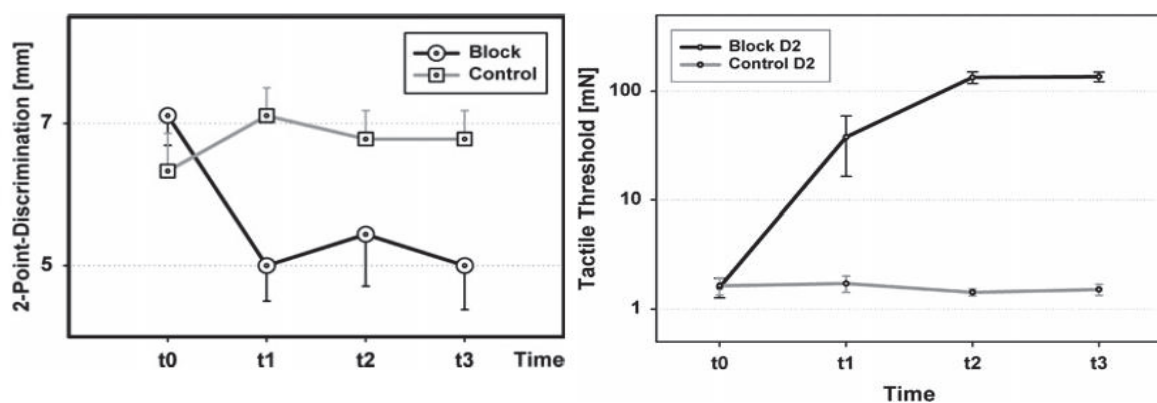


Figure 2.7 [Modified from Weiss et al., 2004]: Two-point discrimination threshold at the lower angle of the lip (left) and absolute touch threshold at the index finger (right) before, during and 15min after tourniquet-induced anaesthesia of the right hand. Two-point discrimination and absolute thresholds were measured over time in the

control session (diamonds) and following nerve blockade (circles) at: t0, 45 min before treatment; t1, 30 min after treatment; t2, 90 min after treatment; t3, 150 min after treatment. Note the decrease of threshold discrimination for lip and the increase of absolute threshold at the index finger.

One likely explanation for the observed invasion of the dipoles of D5 and lip into the cortical representations of the deafferented fingers following pharmacological block could be the unmasking of previously silent neural connections (Merzenich et al., 1984; Pons et al., 1991; Sanes and Donoghue, 2000). Since further data from paired-pulse TMS procedure revealed a motor cortex disinhibition for two muscles supplied by the unaffected ulnar nerve, the authors suggested that disinhibition within the somatosensory system could account for not only the invasion but also for the observed behavioural correlates of the nerve block.

To sum up, in the first part of the chapter I described how following abolition of sensory input to the central nervous system from a portion of the body, notably the upper-limb, tactile stimulation of adjacent parts of the body whose sensory supply is intact produces evoked responses not only in the cortical regions of SI representing the intact body parts, but in the deprived cortical zone as well. The representation zone of the deafferented or amputated limb was said to be invaded. In particular, this form of plasticity has been found across the hand-face border, with the face area invading the former hand area. As I described, this cortical reorganization does not seem to bring any particular perpetual benefit. Rather, the most frequent consequence of this plasticity relates to painful sensations referred to the missing limb. Concerning the mechanism accounting for the cross-border hand-face plasticity, if in the past the sprouting of cortical lateral projections from face to limb representations was the favourite candidate, more recent evidence would rather suggest that plastic changes occur into the cuneate nucleus of the brainstem. Sensory deprivation can also be experimentally induced through anaesthesia. Similar to amputation cases, both cortical and perceptual changes were reported in this case, but their amount was obviously reduced since sensory deprivation produced by anaesthesia is typically temporary and less dramatic than amputation. In particular, the functional consequences are not negative as is the case in amputees, instead some cases of *improved* tactile acuity has been reported. Also given the rapid nature of the changes, it is likely that unmasking of previously silent connections take place to induce the

observed changes. In all cases, sensory loss induces a dramatic unbalance into the physiological balance of inputs required to ensure the correct functioning of all the body parts, and the changes I described are only a small part of the brain changes that operate to adapt to this unbalance.

2.3 Plasticity following increased inputs

Opposite to the case of interruption of inputs discussed above, is the circumstance of increased amount of peripheral inputs along the somatosensory pathway. This second category is equally heterogeneous, as it includes both reports of patients who have undergone surgical transplantation following amputation and more natural cases where the input increase is achieved following sensory learning. For the purpose of the thesis, in this section I will focus more in detail on changes produced by activity-dependent plasticity, which can be found both in everyday life activities, i.e. in naturalistic cases, and in controlled training, i.e. in a laboratory.

2.3.1 Restoration-dependent plasticity

As previously described, deprivation-induced plastic changes involve a huge rearrangement of the somatosensory cortex to adapt to the modified input following a lesion. This demonstrates that cortical maps are not static, but instead undergo drastic reorganizational changes. Nevertheless, not even these new plastic changes are permanent. In fact, a growing number of studies report how deprivation-induced plastic changes are actually reversible following restoration of the missing sensory inputs (Giraux et al., 2001 in MI; Frey et al., 2008 in SI). Frey and colleagues (2008) reported the first evidence that the representation of a transplanted hand can actually recapture the pre-amputation S1 hand territory. The unilateral hand transplant was performed 35 years after traumatic amputation of the right hand. They saw that the palmar tactile stimulation delivered 4 months post-transplant evoked contralateral SI responses. In addition, no evidence for persistent intrusion of the face representation within the representation of the transplanted hand was found, although such intrusions are commonly

reported in non-transplanted amputees. Thus, the importance of this study was crucial as it clearly suggested that even decades after complete deafferentation, restoring afferent input to S1 leads to reestablishment of the hand representation within its original territory. Such finding attests to the great ability of the brain to *continuously* change and shape according to external modifications in the sensory pathways. In addition, the finding also suggests how the original maps are actually persistent, even after extreme injury and reorganization. Evidence in favour of map stability was reported by Reilly and colleagues (Gagné et al., 2001; Reilly et al., 2006) in the context of motor plasticity in hand amputees. Recently, this concept has been extended to sensory map stability (Makin and Bensmaia, 2017), in the light of new studies in amputees (Frey et al., 2008; Kikkert et al., 2016). The deprivation of sensory inputs from a given body part would not lead to abolishment of the corresponding cortical representation. Instead, the original cortical representation would keep its own territory, even if the functional processing is lost. In this context, Makin and Bensmaia (2017) suggested that mechanisms of synaptic plasticity may be not sufficient to form *completely* new sensory representations and that descending input from other cortical regions may serve to maintain the original somatosensory topographies (see Makin et al., 2017 for discussion).

2.3.2 Activity-dependent plasticity: naturalistic cases

Practice makes perfect. This is a very old proverb which completely matches the idea I want to develop in the next two sections. Our tactile abilities, and more generally all our sensory abilities can be improved through exercise and practice. Perceptual learning is the ability of the sensory system to improve following repeated exposure to stimuli (Gibson 1969). The classical example comes from musicians or athletes. If we want to learn how to play music, or how to improve in a sport, we have to practice our abilities in that given task. With respect to tactile acuity, this concept may not seem as intuitive as the majority of tasks we perform with our hands involve both somatosensory and motor contributions. However, there are some specific cases showing that tactile acuity can be improved in a naturalistic way, i.e. in daily activities. Similar to the previous evidence reported in case of sensory deprivation, both cortical and behavioural changes have also been found in cases of increased input. In particular, activity-dependent plasticity was found to be related to representational expansion.

Thus, the cortex can dynamically allocate area in a use-dependent manner to different differentially engaged inputs throughout life. Unfortunately, to the best of my knowledge, activity-dependent plasticity in human is poorly documented in literature, at least at imaging level. However, I will provide some experimental evidence.

For example, studies in string players showed that the cortical representation of the fingers of the left hand (which is particularly stimulated to coordinate movements on the strings) are enlarged compared to fingers of the right hand (which are less stimulated in this specific task) and also compared to non-players (Elbert et al., 1995). These results were confirmed by a subsequent study also in string players (Hashimoto et al., 2004). Another, if possible more “pure” tactile example is that of Braille readers. Pascual-Leone and Torres (1993) showed that the right index finger of Braille readers had a larger sensorimotor representation than the left (non-reading) finger and compared with non-Braille readers. In a more recent study, Gindrat and colleagues (2017) investigated somatosensory cortical electrical activity evoked from the fingertips of touchscreen phone users and nonusers. They found that touchscreen users had larger cortical potentials in response to tactile stimulation of the three fingertips involved in touchscreen phone use (thumb, index and middle fingers) compared to nonusers. Furthermore, the amplitude was directly proportional to the recent phone-use history quantified using battery logs built into the touchscreen phones. This study represents an extraordinary example of activity-dependent plasticity, i.e. how tactile activities we perform everyday with our fingers can induce changes in cortical organization. Moreover, results provided another intriguing finding. Indeed, authors hypothesized that the increased cortical activity associated with individual fingertips in touchscreen users may affect the inhibitory interactions between fingers. Gandevia and colleagues (1983) reported that when neighbouring fingertips are simultaneously stimulated, the magnitude of the evoked potential is smaller than the arithmetic sum of signals from the corresponding individual stimulations (Figure 2.8A) because of lateral inhibitory interactions between the neighbouring fingers (Gandevia et al., 1983). To investigate this hypothesis in Gindrat’s study, the difference between the predicted and real evoked potentials in response to simultaneous stimulation of the thumb and index fingertips was measured. Results showed that the measure of inhibition was significantly enhanced in touchscreen users compared to the nonusers (Figure 2.8B), suggesting that

increasing the lateral inhibition between the neighbouring fingertips may have contributed to the larger amplitude potentials reported in touchscreen users (Gindrat et al., 2015).

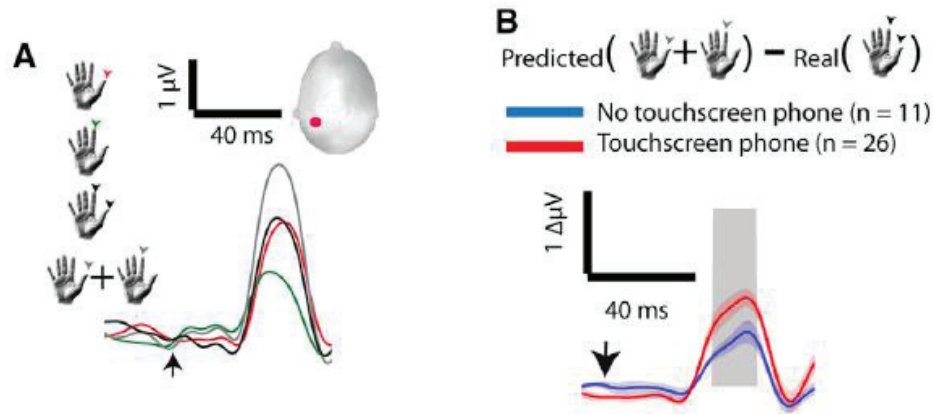


Figure 2.8 [Modified from Gindrat et al., 2015]: Sensory integration from two adjacent fingers in touchscreen users and nonusers. Figure (A) shows that the predicted (linear sum) signal magnitude (in grey) is larger than the real response evoked by simultaneous stimulation (in black) of the thumb and index finger. Figure (B) shows that the difference between the predicted and real response magnitudes was enhanced in touchscreen phone users (in red) compared to nonusers (in blue).

Further evidence of activity-dependent plasticity comes from animal studies. For example, Xerri and colleagues showed that natural stimulation of the skin surface results in an expansion of the cortical representation of that surface (Xerri et al., 1994). They found an almost twofold expansion of the cortical representation of nipple-bearing skin in lactating female rats compared with non-lactating female rats, as well as a concomitant decrease in receptive field size. Similar findings were reported in subsequent studies, where rats housed for more than three months in an enriched environment exhibited substantial enlargement of the cutaneous forepaw representation, associated with smaller receptive fields. Compared to the hairy skin representation, the glabrous skin (more stimulated) had the highest cortical magnification (Xerri et al., 1996).

2.3.3 Training-dependent plasticity

The term training-dependent plasticity refers to behavioural and/or cortical changes occurring after a period of experimentally controlled practice or exercise. The underlying principle is the same than previously described for the naturalistic cases of activity-dependent plasticity, i.e. the ability to improve thanks to perceptual learning. The difference is that now changes are experimentally induced by training.

Related to the previous evidence of activity-dependent plasticity in Braille readers, some studies investigated both behavioural and cortical changes of training-dependent plasticity but this time in sighted people, using Braille reading as a model. In a first study, participants were trained in Braille reading at one hand over 3 weeks (Debowska et al., 2016). After training, Braille character discrimination performance was significantly improved compared to before the training session. Following training, the strongest activation increase observed in fMRI was found in SI, while no functional effects were found within SII. Surprisingly, they reported a robust bilateral activation of SI during the unimanual tactile discrimination task, suggesting that this may be a result of increased interhemispheric communication between homotopic regions. These results are in contrast to those reported by Sathian and colleagues (2013), where no effect of tactile learning in Braille reading (still in sighted people) was found. However, some procedural differences could account for this discrepancy. Interestingly, another Braille study where sighted participants were trained over 9 months did not find any change in somatosensory cortex at the end of the training period (Siuda-Krzywicka et al., 2016). Instead, an increased activation was found in the left fusiform gyrus. Similarly, some procedural difference could account for this discrepancy. Specifically, the fact that the training period was so different between the two studies (3 weeks in Debowska's study versus 9 months in Siuda-Krzywicka's study) could account for the different pattern of results. Indeed, some investigations on learning-related plasticity at multiple time points (Lövdén et al., 2013) would suggest that Braille learning has different stages. Specifically, during the initial stage of Braille learning, the somatosensory cortex might display an increased response to Braille words. Then, after a certain period of training, as the effects of early sensory learning consolidate in the somatosensory cortex, the cortical focus of learning might shift elsewhere, for example into the ventral visual stream (Siuda-Krzywicka et al., 2016).

Moving away from studies investigating the possible neural correlates of training-dependent changes in tactile perception, there is a massive literature which instead investigated the way these changes transfer across different fingers. More in specific, these studies investigated the transfer of tactile improvement from a trained finger to other non-trained fingers, i.e. the topography of the training-dependent tactile learning. For instance, Sathian and Zangaladze (1997) trained participants over several sessions and observed improved acuity on several fingers that were trained. They reported global transfer of tactile learning, that is, across all fingers. Other studies replicated this global and non-specific transfer across all fingers (Sathian and Zangaladze 1998; Spengler et al., 1997). These observations were taken as complete transfer, implying that the learning was not topographically restricted. Thus, in early investigations no particular topographical pattern was found in tactile learning. In contrast, in 2001 Harris and colleagues demonstrated that improvements in tactile roughness discrimination transferred almost completely to the adjacent and homologous fingers, and partially to a topographically non-relevant finger, suggesting a topographic transfer gradient. In particular, the limited range of transfer was the following: tactile learning transferred to the first adjacent of the trained finger and to the finger symmetrically opposite the trained one, but not to the second adjacent of either the trained finger or the homologous finger on the other hand. A complete topographical transfer of tactile learning was achieved by Harrar and colleagues (2014). In this study, performance improved not only at the trained finger but also at its adjacent and homologous fingers, following training. Although these fingers were not exposed to training, they nevertheless demonstrated similar levels of learning as the trained finger. Conversely, the performance of the finger that was neither adjacent nor homologous to the trained finger was unaffected by training. This suggested that tactile learning transfers across fingers following a topographical organization. Specifically, this pattern of transfer was consistent with the topography of primary somatotopic brain areas, which contain somatotopic representations of fingers. Thus, these effects of tactile perceptual learning might be due to plastic changes in neuronal populations with RFs spanning multiple fingers (Harrar et al., 2014). Indeed, tactile RFs in SI often span multiple digits, both within the hand (Thakur et al., 2012) and across the hands (Iwamura, 2000). In contrast, the organization of RFs in the secondary somatosensory cortex (SII) is more complex and often not somatotopic (Iwamura et al., 2002). In addition, a recent study in humans revealed that SI (as well as SII)

integrates somatosensory inputs across homologous fingers (Tamè et al., 2012), thus accounting for the observed bilateral changes.

Further investigation into the topography of training-dependent tactile learning also provided evidence that learning transfers differently (in terms of timing and amount of improvement) to two fingers that are both physically and cortically adjacent to the trained finger (Dempsey-Jones et al., 2015). Specifically, they found that following training of the middle finger tactile learning transfers to the homologous contralateral finger and to the two adjacent index and ring fingers (Figure 2.9). However, the amount of the transferred improvement was different between the adjacent fingers, i.e. bigger at the index compared to the ring finger. In addition, improvement was immediate at the index finger, but delayed at the ring finger. They suggested that different use patterns between these fingers could account for these differences. Specifically, the middle finger is used more frequently with the ring than with the index finger, and this should lead to greater representational overlap between the former than the latter pair. Furthermore, this difference in overlap could be reflected in differential learning transfer from the middle to index and from the middle to ring fingers. Expanding representation of the trained finger would recruit cortical territory from the two adjacent fingers and this might have different immediate effects on these fingers due to differences across them. An alternative explanation for the differential transfer effects from the trained middle finger to its adjacent fingers could be the result of diverse excitatory and inhibitory synaptic plasticity in horizontal intra-cortical connections (Hickmott and Merzenich, 2002; Paullus and Hickmott, 2011). In this case, the middle and ring finger representational zones should have a greater number of continuous connections between them than the middle and index finger representations because of differential use patterns.

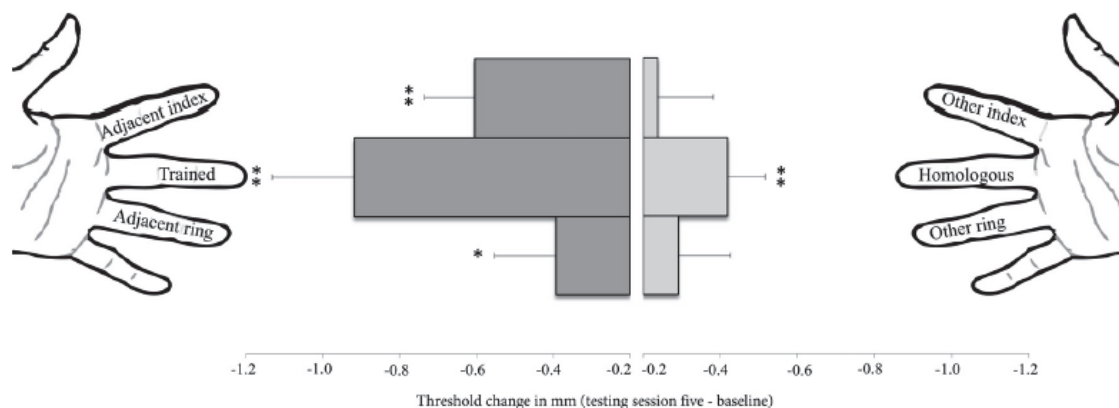


Figure 2.9 [From Dempsey-Jones et al., 2015]: Topographic transfer of training-dependent learning. Bars graph show the threshold changes at 6 fingers following training of the middle finger. Larger negative values (i.e., larger bars) reflect greater improvement in tactile acuity. Note that changes in the tactile threshold were significant at the trained, adjacent index, adjacent ring, and homologous fingers following training.

2.4 Hebbian plasticity

As I wrote at the beginning of this chapter, trying to find the missing link between synapses and cortex, and between cortex and behaviour, in a very simplistic categorisation of levels, is the goal of a huge number of neuroscientists. So far, very few incontrovertible - if such a definitive term can be used in science, where nothing is definitive - evidence have been provided in this field.

Concerning the cortical reorganization found in adult animals, exclusively in a context of increased inputs, one theory in particular represents a leading underlying candidate for some changes found in cortical representations. This particular form of plasticity is generally called *Hebbian plasticity* or *Hebbian learning*, from the name of the neuroscientist Donald O. Hebb who first put forward this theory. Hebbian theory attempts to provide a basic mechanism to explain synaptic plasticity, in which simultaneous activation of cells leads to pronounced increases in synaptic strength between those cells, and provides a biological basis for learning. Since at the synaptic level Hebbian theory refers to increases in synaptic strength between neurons that fire together, and decreases if they are activated separately, this method of

learning is also called “associative learning”. This principle is best expressed by the following statement (Hebb, 1949, page 62):

When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.

The expression is commonly referred to as “Hebb's law” and is often paraphrased as:

Neurons that fire together wire together.

This simple postulate is thought to play a crucial role in cortical reorganization of the adult brain. However, the first studies showing the effectiveness of *associative* or *pairing* plasticity were conducted at the synaptic level. Specifically, it was described for the first time in hippocampal neurons after the identification in 1973 of a mechanism called long-term potentiation (LTP).

In 1973 Timothy Bliss and Terje Lomo discovered that a brief high-frequency train of stimuli (called tetanus) to any of the three major synaptic pathways increases the amplitude of the excitatory postsynaptic potentials in the target hippocampal neurons of the anaesthetized rabbit. This facilitation was called *long-term potentiation* (LTP) (Bliss and Lomo, 1973). Later, some studies investigated the effect of LTP on the Schaffer collateral pathway, which connects the pyramidal cells of the CA3 region of the hippocampus with those of the CA1 region. It was found that LTP in the Schaffer collateral pathway typically required activation of several afferent axons together, a feature they called *cooperativity*. This feature derives from the fact that the NMDA receptor-channel (N-methyl-D-aspartate receptor is one of the three types of ionotropic glutamate receptors) becomes functional and conducts Ca^{2+} only when two conditions are met: (i) glutamate must bind to the postsynaptic NMDA receptor and (ii) the membrane potential of the postsynaptic cell must be sufficiently depolarized by the cooperative firing of several afferent axons to expel Mg^{2+} from the mouth of the channel. The finding that LTP in the Schaffer collateral pathway requires simultaneous firing in both the postsynaptic and presynaptic neurons to adequately depolarize the post-synaptic cell (a feature nowadays called *associativity*) provided direct evidence for *Hebb's rule* previously described

and quoted. Basically, the simultaneous pre- and postsynaptic activity results in the strengthening of the synaptic connection. Thus, to implement Hebb's rule, neurons must possess a coincidence receptor able to record the co-occurrence of pre- and post-synaptic activity. NMDA receptor fulfils this role, since in the presence of glutamate and postsynaptic depolarization, the NMDA receptors permit the influx of Ca^{2+} , which is a critical early step in the induction of LTP. As in the hippocampus, subsequent studies showed that LTP can also be induced in the cortex, in both cortical slices and in vivo. For instance, Baranyi and Fehér (1981) first demonstrated associative synaptic plasticity in the cortex with intracellular recordings from cat motor cortex in vivo by pairing synaptic input from the ventrolateral nucleus of the thalamus with stimulation of a second pathway or intracellular depolarization.

Concerning cortical LTP, three protocols have been used to induce it: (a) tetanus (b) theta-burst stimulation (TBS) and (c) through pairing, in which intracellular depolarization of the postsynaptic cell is paired with low-frequency afferent stimulation. In general, blocking GABAergic inhibition or removing Mg^{2+} seem to increase the probability of inducing LTP (see Bear & Kirkwood 1993), since the basic hypothesis is that manipulations that decrease inhibition or increase the NMDA current result in more robust LTP.

Associative long-term depression (LTD) has also been described. Specifically, if LTP is a form of activity-dependent plasticity which results in a persistent enhancement of synaptic transmission, LTD is the complementary process, in which the efficacy of synaptic transmission is reduced. Furthermore, more recently also the concept of spike timing-dependent plasticity (STDP) has been developed following the important observation in other in vitro preparations that the timing of pre- and post-synaptic action potentials (spikes) determines the polarity of synaptic change. Repeated activation of a presynaptic spike followed by post-synaptic spike, within a brief time window of approximately 50 ms, leads to LTP, while the reverse order leads to LTD (Markram et al., 1997; Bliss and Cooke, 2011).

A further step in Hebbian plasticity investigation was made with intra-cortical microstimulation (ICMS) experiments, which are approaches in the middle between synaptic plasticity (just described) and cortical map plasticity (described below) experiments. In vivo experiments in sensory cortex of rats and monkeys consisted of repetitive electrical pulse trains intra-cortically delivered via a microelectrode (Dinse et al., 1993, Recanzone et al.,

1992b, Spengler and Dinse 1994). As result of this procedure, experiments showed transient changes in the somatotopic map in area 3b. In particular, expansion of the cortical representation over a cortical zone several hundred microns across (Recanzone et al., 1992b; Spengler and Dinse, 1994), changes in RFs location and size (Recanzone et al., 1992b) and also increased correlation in activity in neuron pairs separated by long distances (Dinse et al., 1993) . For instance, Recanzone's study, one of the pioneering studies in this field, displayed that the largest RFs were found in the centre of the zone representing the behaviourally engaged skin, but larger RFs were also found in adjacent zones, with resulting increased overlapping of RFs in the cortical zone representing the trained skin. All these changes (enlarged representation, increased size of RFs and increased overlapping) were not observed into the representation of the *untrained* hands. In contrast to studies in which stimuli applied in behaviour engaged the finger with significant trial-by-trial variability in stimulus location (Xerri et al., 1994), in these monkeys the RFs representing the trained skin were enlarged and not smaller. Remarkably, this was interpreted as a consequence of the fact that, according to the Hebbian postulate (which will be described below), any input into the cortex driven from the invariantly stimulated skin location would be integrated into a necessarily larger receptive field. In contrast, when stimuli are delivered to random skin locations (as in Xerri et al., 1994), each small sector of skin is an effective source of competitive input for the Hebbian network, and receptive fields therefore shrink in size as the zones of representation of the engaged skin surface grow in size. Recanzone's studies showed that the improvement in frequency discrimination was accounted for by a learning-induced change in the temporal coherence of the response in the engaged cortical population. Altogether these results demonstrated that ICMS, i.e. a protocol following Hebb's rule, is able to induce substantial changes in cortical representations, notably expansion of the stimulated area and changes in RFs size.

This evidence was confirmed from a number of animal studies, demonstrating how the temporal coincidence of neural events and thus the characteristics of the input statistics play a key role for the induction of changes in synaptic excitability and thus for cortical reorganizational changes (Clark et al., 1988; Mogilner et al., 1993; Diamond et al., 1992; Wang et al., 1995).

The rationale of these experiments was as follows. The topographical organization of cortical maps arises from temporally coincident events. Thus, according to the Hebbian theory, if it is true that the correlation between neighbouring skin surfaces can be experimentally changed, then it is also true that modifications in the cortical maps should be observed. The hypothesis was first tested in 1988 by Clark and colleagues. They artificially changed the normal correlations between monkey skin surfaces by surgically connecting the skin surface of two fingers (i.e. the formation of syndactyly) or by translocating patches of innervated skin across the hand. The rationale of the study was that receptive fields derive not from rigid anatomical connections, but by the selection of a subset of a large number of inputs. Thus they proposed that inputs are selected on the basis of temporal correlation. Several months after finger fusion, results showed that the manipulation increased the correlation of inputs from skin surfaces of adjacent fingers. The striking discontinuity between the zones of representation of adjacent fingers on the somatosensory cortex, i.e. the somatotopic boundaries between the fused fingers, disappeared and many cortical units had double digit receptive fields (Figure 2.10). The opposite approach was used in a subsequent study, where Mogilner and colleagues (1993) investigated the effect of the reversal of a congenital finger syndactyly. Before finger separation, input sources from adjacent fingers strongly overlapped each other. A few weeks after the surgery, finger representations rapidly moved apart in the cortical representation, relating with the new functional status of the separated fingers. These experiments showed that, following the induction of new temporal neighbourhood relationships, new representations of skin surfaces emerged at new cortical locations. This was consistent with the hypothesis that Hebbian plasticity underlies cortical map formation and alteration.

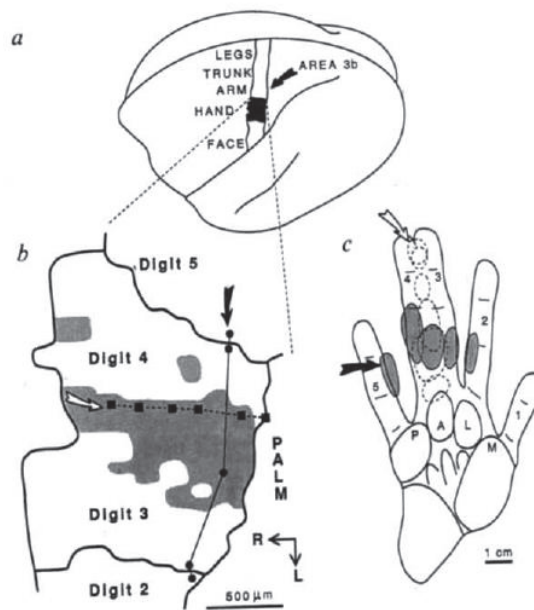


Figure 2.10 [From Clark et al., 1988]: Monkey cortical representation of WHAT after cutaneous fusion of fingers 3 and 4. a) Dorsolateral view of adult neocortex with the representation of the contralateral skin surface including that of the hand (black). **b)** Reconstruction of the cortical representations of fingers 3 and 4, five and a half months after surgical fusion of these fingers. The shaded area marks the cortical region of double-finger representation following finger fusion. **c)** Contralateral hand to that which underwent syndactyly.

To conclude, these latter studies, altogether with studies previously described in activity-dependent plasticity, showed that changing the pattern of input statistics at the level of the periphery, notably at the hand, results in rapid reorganizational changes in cortical representation of the stimulated area. In these studies the Hebbian, i.e. associative, plasticity has been often emphasized as a mechanism underlying cortical map formation and reorganization.

Chapter 3: Repetitive Somatosensory Stimulation-induced Plasticity

3.1 Introduction to Repetitive Somatosensory Stimulation

(RSS)

In the previous chapter I described how the coincidence of temporal inputs is thought to be the fundamental factor for the induction of plastic changes within the somatosensory cortex. Indeed, a number of cellular studies examining long-term potentiation (LTP) and long-term depression (LTD) and more recently spike-timing-dependent plasticity (STDP) have led to the idea that these processes lead to activity-dependent plasticity. The main limitation of these studies is that their experimental approach in animals is relatively invasive, since the plastic changes are generally achieved through procedures performed intra-cortically in vivo and/or in slice preparations. For obvious reasons, this has prevented researchers from performing these same procedures in humans, and consequently hindered them from directly evaluating the impact of this kind of protocol in human behaviour. In other terms, what was missing was a link between animal studies demonstrating that correlated inputs play a key role in the induction of activity-dependent plastic changes, and a procedure based on the same principles as animal studies and which could be applied in human in an analogous way.

The turning point in the activity-dependent literature and more generally in the frame of somatosensory plasticity occurred in 1996 in the form of a study published by Godde and colleagues. The basic idea of this study was to translate the principles used to induce synaptic plasticity at a cellular level into a peripheral sensory stimulation protocol that could be performed in a totally non-invasive and passive way in human subjects. For this purpose, they conceived a protocol of associative pairing of tactile stimulation (APTS), totally non-invasive, where mechanic stimuli would have been continuously delivered on the skin.

Before going into a detailed description of the protocol, some precisions are requested to make the reading more clear. First, it is necessary to specify that, depending on the laboratory and context where it was used, this stimulation protocol, first called APTS, has also been named differently over the past twenty years. The various names include terms like, for example co-activation, exposure-based learning, training-independent learning, sensory learning or repetitive somatosensory stimulation. To avoid any possible confusion coming from the use of several terms, in this thesis I will only use the term Repetitive Somatosensory Stimulation and its abbreviation - RSS. It is also worth noting that different variants of the protocol have been used by authors (for example low/high stimulation frequency and single/multi finger stimulation), but the conceptual characteristics of each protocol remain the same as the original paradigm. For the purpose of this thesis, I will describe with particular emphasis the low-frequency (1 Hz on average) and single-digit RSS protocol, which is the same procedure used for the experimental contributions reported in the following chapters.

The basic idea underlying RSS is the Hebbian theory of plasticity. According to this, one typical RSS protocol is characterized by several hours of simultaneous and repetitive stimulation of several receptive fields on the skin, and it follows two basic assumptions. First, the extensive stimulation of several sites on the skin results in synchronous co-activation of several neural afferents and, shortly after, several interconnected cortical neurons. Second, the co-activation of a large number of receptive fields on the skin leads to synchronous neural activity that is instrumental in driving plasticity in the form of changes in neural response and cortical topography. Moreover, because of the induced plasticity, brain changes translate into behavioural changes at the level of tactile perception. Indeed, studies conducted over the past two decades have reported that RSS-induced plasticity is associated with changes at both the cortical and behaviour levels in humans, as shown by improved tactile perception. In this chapter, I will first review the main features of RSS, starting with the very first studies in the literature. I will then describe both the perceptual and cortical effects that have been found following RSS. Finally, I will report on the spatial distribution of the perceptual effects across several body-parts (hereafter, topography), which is a crucial matter for the scope of this thesis.

3.2 General Overview on RSS main features

As mentioned above, the study that revolutionized the literature on activity-dependent plasticity was published in 1996 by Godde and colleagues. This study includes two different but complementary experiments, one in animals and one in humans. First, in intact rat brains they investigated the correlates of cortical reorganization elicited by a protocol of associative tactile stimulation or RSS applied to two separate skin locations (two non-overlapping receptive fields) on the hind-paw of adult rats. The protocol they used systematically varied the input statistics which, as described in the previous chapter, are hypothesized to play a crucial role in the induction of cortical plasticity. Normally, maps of the hind-paw representation within the somatosensory cortex of adult rats are characterized by small, low-threshold, cutaneous receptive fields located on single digits, pads or parts of the heel. After 6-15 hours of stimulation on two digits or on one digit and one pad, expansions of the respective cortical skin representations, emergence of new skin fields in cortical zones formerly not responding and changes in size (i.e. increase) of the receptive fields were observed (Figure 3.1).

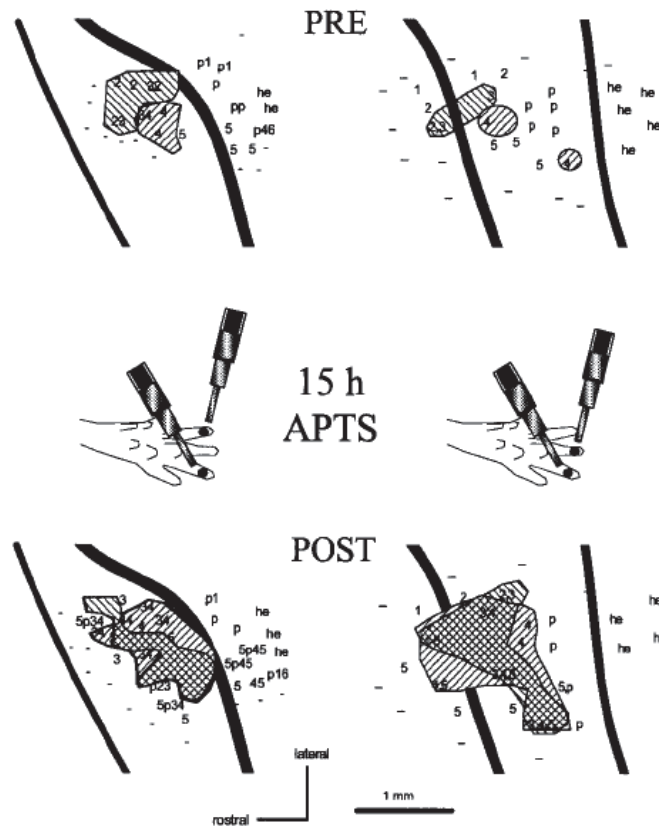


Figure 3.1 [From Godde et al., 1996]: Cortical reorganization after RSS. The figure shows on the top the maps of the rat hind paw representations in SI under normal conditions, and on the bottom the same maps after application of 6-15 hours of tactile stimulation on digits 2 and 4 (left) and on digits 3 and 4 (right). After stimulation, the border region and the central hind paw representation were remapped, with a huge expansion of the former maps and newly emerged skin representations containing the stimulated skin fields. The different hatchings displayed in the bottom section correspond to different cortical areas representing the stimulated skin fields. A substantial overlap of the cortical representation of the simultaneously stimulated skin fields was found.

Importantly, when the authors investigated the effects of a so-called single point tactile stimulation (SPTS), where stimulation was applied to one single site only, no changes were found. These results showed that it is necessary to simultaneously activate several sites on the skin to induce plasticity, which is the underlying principle of RSS.

Secondly, Godde and colleagues (1996) explored whether application of the same tactile RSS protocol that led to cortical reorganization in the rats could produce changes in human tactile

perception. To this purpose, they compared tactile acuity, measured as spatial discrimination thresholds, of the stimulated fingertip (specifically the right index, from now on called right-D2) before and after 2 or 6 hours of 1 Hz stimulation protocol analogous that that used in the electrophysiological rat experiments. The results of this parallel human study showed a significant improvement in tactile perceptual performance of the stimulated finger, as indicated by the decrease in its two-point discrimination thresholds. To the best of my knowledge, this was the first study showing that the same protocol of tactile, passive and associative stimulation of a small skin area, based on variation of the input statistics, can induce plastic processes resulting in (i) cortical reorganization in rat brain and (ii) behavioural changes in humans. Interestingly, both types of effects were not permanent but reversed after a certain time. In all human participants, thresholds were reduced immediately after the end of the stimulation and returned to baseline values the following day. The same was also for the electrophysiological reorganizational changes in rats. The similarity of the time courses in the rats and humans suggests that the processes underlying the plastic changes might be similar. Despite the reversibility of these RSS-induced changes, the study showed that fast plastic changes based on variation of the input statistics have perceptual consequences, suggesting on the one hand the significance of adapting a protocol of repetitive stimulation to humans and on the other hand, the primary role that such a protocol, and its associated functional improvements, could play in improving tactile performance.

The reversibility of the RSS-induced tactile improvement was shown in a subsequent study (Godde et al., 2000), where the time course of the recovery of tactile performance of the stimulated right-D2 was evaluated two, four, six, eight and twenty-four hours after two hours of RSS. They found that tactile improvement was still present four hours after RSS, but this was no longer the case at after six hours (Figure 3.2). Suggesting that duration of behavioural effects of a two-hour RSS protocol is within 4-6 hours.

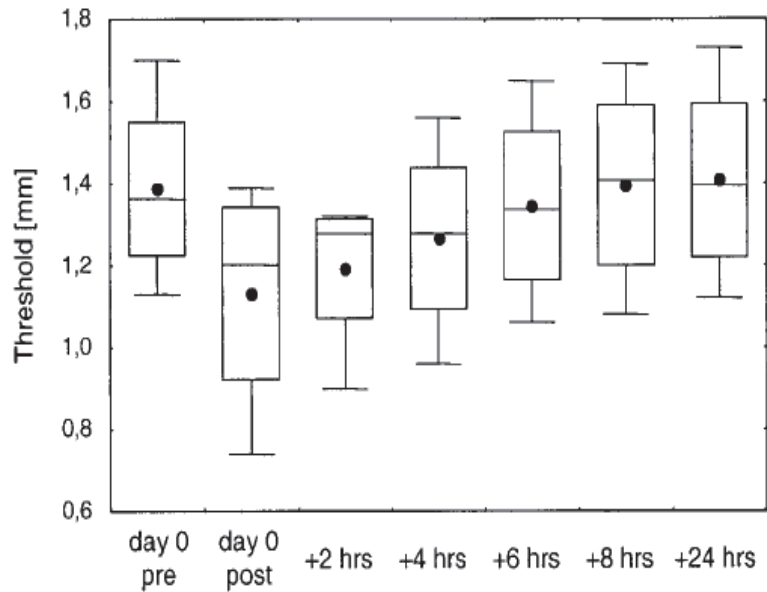


Figure 3.2 [from Godde et al., 2000]: Recovery of RSS-induced effects. Tactile performance evaluated at different times before and after two hours of RSS on right-D2. Note that tactile threshold was significantly reduced immediately after the end of the stimulation (post) and was still reduced after four hours, even if the effect size decreased over the time. After six hours, threshold value was back to the baseline (pre).

In addition to investigating the time-course of the effects on tactile acuity, this study also investigated the minimal duration of stimulation sufficient to elicit changes in tactile performance. They found that 30 minutes of RSS on the right-D2 were not sufficient to evoke significant changes in the acuity of this finger, whereas changes became significant after two hours of stimulation and remained present up to six hours after stimulation. Interestingly, although one might expect that a longer duration of stimulation might reveal a bigger effect size, the amount of tactile improvement was relatively similar after two or six hours. Moreover, when the RSS protocol was applied for longer, or even over consecutive days, changes were of similar amplitude to those observed after shorter stimulation periods. Interestingly, however, the prolonged application of RSS over three consecutive days resulted in a delayed return to baseline, probably indicating stabilization of the tactile improvement over time (Figure 3.3).

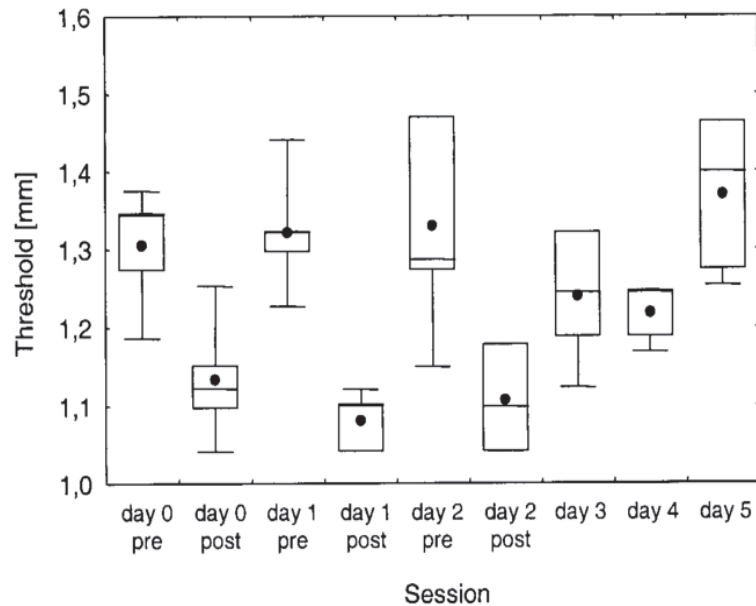


Figure 3.3 [from Godde et al., 2000]: Cumulative RSS-induced effects. Tactile performance evaluated before (pre) and after (post) two hours of the RSS protocol applied on three consecutive days (day0, day1, day2). Tactile performance was further evaluated on the three days following the final RSS application (day3, day4, day5). Note that repeated applications of RSS did not increase the magnitude of the threshold changes but affected the time course of recovery. Indeed, thresholds did not return to normal on day 3, or 4 but remained at an intermediate level for 2 consecutive days, indicating a longer lasting effect.

As mentioned above, the idea underlying RSS is that *co-activating a large number of receptive fields* on the right-D2 fingertip in a Hebbian-like manner induces plastic changes in the nervous system that in turn induce behavioural changes. For this reason, in a typical RSS protocol the tactile stimuli are transmitted through a solenoid moving a small diameter membrane (typically, eight millimetres). Thus, the solenoid can co-activate several cutaneous receptive fields found within this surface area on the fingertip. To demonstrate that co-activating a large number of receptive fields is instrumental in driving perceptual improvement, one study compared the effects of a typical RSS protocol with those induced by

a modified version, the so-called single-site stimulation (Pleger et al., 2003). This modified version consisted of a small single stimulation site instead of one large area (0.8 mm^2 single-site stimulation *versus* 50 mm^2 RSS), in which only a small “point-like” skin area was stimulated (Figure 3.4).

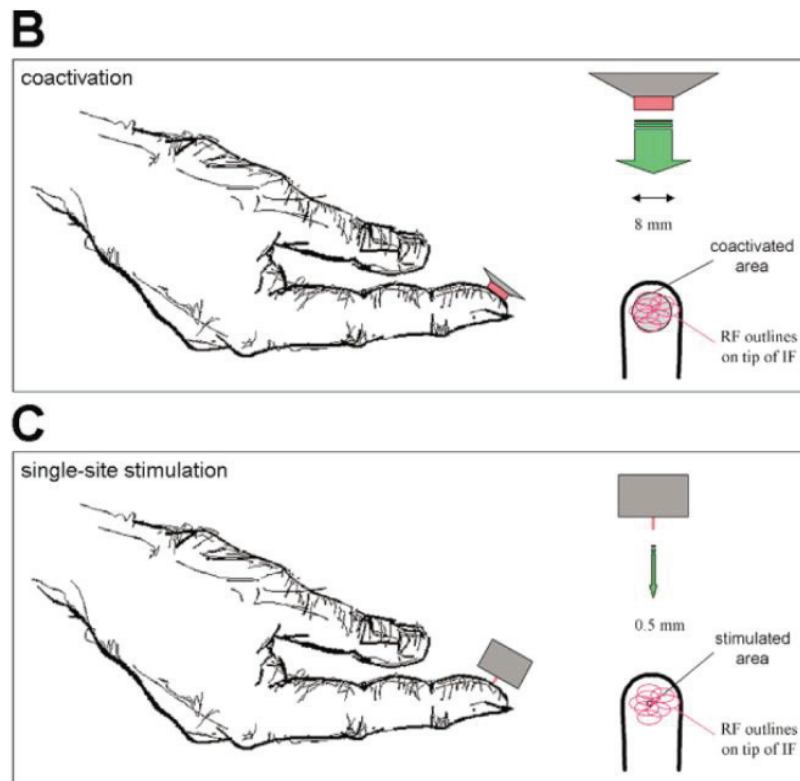


Figure 3.4 [modified from Pleger et al., 2003]: Comparison between RSS and single-site stimulation. Figure B shows the application of a typical RSS protocol: a small solenoid with a diameter of 8 mm was mounted on the right-D2 tip and was used to transmit tactile stimuli to the skin. The *co-activated* area was large - 50 mm^2 . Figure C shows the application of single-site stimulation: a small device consisting of only one tiny stimulator with a diameter of 0.5 mm was mounted on the right-D2 tip to stimulate a single “point” on the skin. The stimulated area was very small - 0.8 mm^2 .

Stimulation frequency (1 Herz on average) and duration (3 hours) were the same. Pleger and colleagues (2003) reported that when this modified single-site protocol was applied for three hours to the tip of the right-D2, no effect in tactile performance on this finger was found. This

same study also investigated the consequences at the cortical level of both RSS (50 mm²) and single-site stimulation and found that single-site stimulation did not lead to any reorganizational changes in cortical maps, while RSS (50 mm²) did (see below for a detailed description). This finding provided solid evidence in favour of the importance of simultaneously activating several receptive fields in order to drive plastic changes. Moreover, the lack of both perceptual and cortical effects after the single-site stimulation ruled out the possibility that other unspecific mechanisms, like attentional enhancement for example, could account for the changes previously attributed to RSS.

3.3 RSS-induced changes and synaptic plasticity

Together with the necessity to simultaneously activate several receptive fields on the skin to elicit these effects (Pleger et al., 2003), other evidence coming from other subsequent studies account for the Hebbian-like plasticity of RSS. First, similar to LTP and LTD in cellular studies, two different in-vitro protocols of high- and low-frequency RSS reported respectively improvement and impairment of tactile acuity (Ragert et al., 2008). This study indicate that Hebbian-like mechanisms of synaptic plasticity are most likely to account for RSS-induced plastic changes and that these latter are controlled by neuromodulatory system.

Other studies investigated the hypothesis that RSS-induced effects rely on the induction of synaptic plasticity. First, a study conducted by Dinse and colleagues (2003a) revealed that RSS-induced effects are N-methyl-D-aspartate (NMDA) receptor dependent. NMDA is a receptor known to be involved in synaptic plasticity (Bliss and Collingridge, 1993; Nicoll and Malenka, 1995), which can be blocked by the administration of memantine (Parsons et al., 1999). The authors applied RSS to two groups of participants, one of whom received memantine, and investigated changes in both tactile performance and cortical representation of the stimulated right-D2. The memantine group showed no RSS-induced improvement in acuity and in parallel, no changes in somatosensory evoked potentials (SSEPs). Thus, blocking the NMDA receptors also blocks the RSS-induced effects (Dinse et al., 2003a). Yet another study found evidence that RSS-induced synaptic plasticity processes rely on GABAergic mechanisms (Dinse et al., 2003b). GABA plays an important role in maintaining

of the balance of excitation and inhibition and its action is enhanced in the presence of its agonist lorazepam. Authors showed that a single dose of the GABA agonist lorazepam completely annulled the improvement of tactile acuity. These pharmacological studies suggest that RSS-induced effects are most likely controlled by glutamatergic and GABAergic receptors, which are well-known to play an important role in synaptic plasticity.

RSS-induced effects also appear to be dependent on cholinergic mechanisms (Bliem et al., 2008). Previous studies have shown that the cholinergic system modulates behavioural learning and LTP (Everitt and Robbins, 1997), and that the cholinergic system can be impaired/perturbed by administering scopolamine, an acetylcholine antagonist (Sawaki et al., 2002). Similar to the protocol followed in the memantine study, Bliem and colleagues (2008) investigated the effects of scopolamine on RSS-induced improvement. They found that following three hours of RSS on the right-D2, acuity of this finger not only did not improve, but was actually impaired.

3.4 Perceptual correlates of RSS-induced changes

Improvement in tactile acuity of the right-D2 following RSS of this same finger was the first effect described in the RSS literature (Godde et al., 1996). Tactile acuity was evaluated using a spatial discrimination task, i.e. the two-point discrimination (2PD) task. Following that very first study, tactile improvement as evidenced by lowered two-point discrimination threshold has been replicated in numerous subsequent studies (Godde et al., 2000, 2003; Pleger et al., 2001; 2003; Höffken et al., 2007; Dinse et al., 2003a,b; Bliem et al., 2008) and has become the most investigated perceptual correlate of RSS. As I will describe in the last section of this chapter, the topography of this improvement - within and among different body parts - has instead received much less attention. Instead, some authors have investigated the specificity of the RSS-induced perceptual improvement, i.e. the hypothesis that changes in tactile acuity could be found assessing other different measures, of both spatial discrimination acuity and touch perception.

First, it is worth noting that tactile spatial acuity changes following RSS have also been observed in the form of threshold changes on the grating orientation task (GOT) (Hodzic et

al., 2004). Some studies also investigated absolute touch threshold and tactile localization. Even if the results are controversial and less defined compared to the continuously proven improvement in two-point spatial acuity, some evidence suggests that absolute touch threshold is not affected by RSS (Bliem et al., 2008; Dinse et al., 2003b; Kalisch et al., 2007). On the contrary, the localization of tactile stimuli among different fingers in the same stimulated hand seems to be influenced following synchronous multiple-fingers RSS (Pilz et al., 2004; Kalisch et al., 2007). However, studies investigated the tactile location after RSS of the five finger of one hand, so caution should to be used when comparing these results to RSS of a single finger. For instance, Kalisch's study showed that synchronous multifinger RSS of all fingers on a hand leads to improved tactile acuity (i.e., diminished two-point discrimination thresholds) and changes in typical mislocalization behaviour (i.e., decreasing numbers of mislocalizations with increasing distance from the stimulated finger), while asynchronous RSS did not bring to any change (demonstrating the importance of temporally coherent inputs to drive Hebbian-like RSS plasticity, as previously reported).

Moving away from purely tactile features, some findings also investigated changes in temporal processing. In one study, both spatial and frequency discrimination abilities were evaluated before and after RSS on the right-D2 (Hodzic et al., 2004). This study found opposite patterns for the two modalities: spatial discrimination acuity assessed by GOT was improved, while frequency acuity assessed by a frequency discrimination task (FDT) was impaired. On the one hand, this finding suggests that RSS-induced effects might be specific only for spatial features. On the other hand, the evidence that frequency discrimination was *impaired* is contradictory, suggesting that perhaps some competitive mechanisms might play a role in promoting some cortical processes and inhibiting some others (Hodzic et al., 2004). An element supporting instead the non-specificity of the RSS- induced effects for spatial features comes from a more recent study investigating decision making (Wilimzig et al., 2012). This study reported that following RSS of the middle finger, reaction times (RTs) in a tactile multiple-choice RT task (that required selecting a given finger out of all 10 fingers on both hands) were significantly shortened for this finger compared to RTs of other fingers. It is important to note that under normal conditions RTs strongly differ among individual fingers, displaying an inverted trend in which the RTs for the middle finger (from now on called D3) are significantly slower than those of other fingers (Figure 3.5,A). Wilimzig and colleagues

(2012) reported that, on the contrary, the stimulated right-D3 showed the fastest response following RSS (Figure 3.5,B). Wilimzig’s study demonstrates that applying RSS on a finger results in significant speeding up of RTs for this finger, not only in improved spatial discrimination acuity, thus corroborating the non-specificity of RSS effects for spatial acuity.

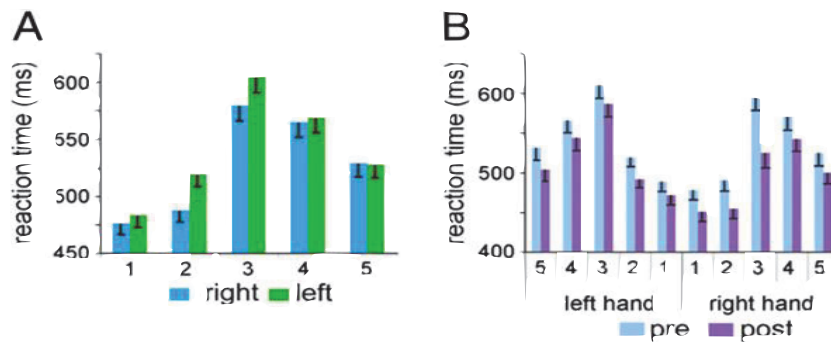


Figure 3.5 [modified from Wilimzig et al., 2012]: RSS-induced effects on reaction times (RTs). **Figure A** shows RTs for all fingers (D1-D5) of the left (green) and right (blue) hand. Note that RTs differ among fingers, with D3 being slowest and D1 being fastest. **Figure B** shows RTs of all fingers (D1-D5) of the left and right hand before (light blue) and after (magenta) RSS on the right-D3. RTs on right-D3 were significantly faster after application of RSS, as shown by the huge reduction of the corresponding bar. On the contrary, changes in RTs of other fingers were not significant.

To sum up, despite the still open debate between specificity and non-specificity of RSS-induced effects, the most relevant finding that these studies attest to is that RSS alters human perception by improving skills like tactile acuity in a similar way to that observed after training-dependent learning (as discussed in the previous chapter). I mentioned at the beginning of this chapter that some authors used to refer RSS as training-independent learning. The explanation for this terminology can be found in the fact that RSS-induced perceptual effects are actually comparable to those achieved following intense practicing and perceptual learning (Gibson, 1969). Note that the two terms differ only for the central word - *dependent* or -*independent*. In the first case, to develop an improved skill, learning is achieved by intensively and protractedly practicing the task, i.e. training for several days. In the second

case, improvement is achieved by simply applying RSS on a finger for a short period of 2-3 hours, without involving either attention or training. Thus, even if the behavioural outputs appear to be the same, the processes required to get this output are undoubtedly different.

However, even the use of the term learning to refer to RSS is not totally accepted by all researchers. If we consider (i) that processes involving modification of synaptic plasticity are recognized as neural substrates for learning and (ii) that RSS is thought to involve Hebbian-like mechanisms of synaptic plasticity (as suggested by the above reported studies), then one might associate RSS and learning (for review see Beste and Dinse, 2013). Anyhow, the question is trickier than this rational simplification. Indeed, even if there is evidence that both modalities share similar perceptual correlates, other points argue against a definition of RSS as learning. One crucial element of debate is the topography of RSS-induced changes, which seems to be totally different to that of the topography of changes observed after training-dependent learning. For example, while training-dependent learning effects transfer among different body parts (as described in the previous chapter), RSS-induced perceptual effects do not. Since topography is also crucial for the scope of this thesis, it will be discussed in detail in the last section of this chapter.

3.5 Neural correlates of RSS-induced changes

Several studies using different approaches have investigated the relationship between RSS-induced perpetual changes in behaviour and changes in brain organization. For instance, changes in cortical map representations have been found, with convincing evidence that these brain changes directly correlate with behavioural changes. In 2001, Pleger and colleagues were the first to combine the assessment of spatial tactile discrimination performance with measurements of somatosensory evoked potentials (SSEPs) in human participants. To study changes in the SI representation of the stimulated finger they calculated the N20-dipole locations before and after three hours of RSS on right-D2. They observed that the spatial discrimination threshold of right-D2 was lowered and that its representation was changed. After RSS the Euclidean distance between the dipole Pre- and Post-RSS was significantly greater in the left hemisphere (contralateral to the stimulated finger) than in the right

hemisphere and the polar angle of the N20-dipole for the right-D2 increased after RSS. These results indicate a lateral and inferior shift on the left post-central gyrus representation of the stimulated finger, but no changes on the right hemisphere (ipsilateral to the stimulation). To verify whether changes were delimited at the stimulated right-D2 only, they also measured SSEPs at the adjacent right-D1, by showing that the location of the N20-dipole of this finger did not change. This conclusion should be interpreted with caution, however, as data were collected for right-D1 in only 5 participants. Nevertheless, this evidence suggested that cortical shift was specific not only for the stimulated hemisphere but also for the stimulated finger. I previously mentioned that Godde and colleagues (2000) reported that perceptual improvement in discrimination tactile acuity was not a permanent effect, but reversed within 6-8 hours. In order to investigate whether dipole changes were reversible, SSEP measurements were repeated 24 hours after RSS. The N20-dipole distance values observed were in the same range as for the Pre session, indicating that RSS-induced changes of the N20-dipole locations are fully reversible and thereby parallel changes in discrimination improvement. Importantly, in addition to being the first study to show cortical plastic changes in human SI following RSS, this study also revealed that improvement in tactile discrimination was significantly correlated with cortical reorganization, by showing that the smaller the improvement in tactile discrimination the smaller the shift in dipole location. Similarly, those subjects who showed a large cortical reorganization (in the form of large dipole shifts) also had the lowest thresholds. It is worth to highlight that this correlation was found in all the participants. The importance of this finding is twofold. First, it demonstrated that improvement in perceptual performance is closely associated with cortical changes, which makes a strong link between perceptual and cortical changes. Second, the fact that perceptual gain is associated with cortical change means that we can relatively safely infer that in the presence of behavioural changes we might also predict the amount of cortical organization.

A subsequent magnetoencephalography (MEG) study (Godde et al., 2003) showed that three hours of RSS on right-D2 induced a shift of that finger's magnetic dipole in the left SI laterally along the post-central gyrus. As this shift in dipole source made 'closer' the D2 and D1 representations, it was interpreted by authors as an expansion of the representation of the stimulated finger towards D1. Interestingly, the same sort of attraction between the stimulated

D2 and the adjacent D1 was also found also in the SSEPs study (Pleger et al., 2001). Indeed, the expansion of the right-D2 representation was asymmetric, relatively shifted to D1 only. Psychophysical measurements confirmed that cortical reorganization was paralleled by a decrease in tactile discrimination.

RSS-induced cortical reorganization is not limited to SI. Changes have also been found in SII. Using functional magnetic resonance imaging (fMRI), Pleger et al., 2003 found that the stimulated finger (right-D2) had a larger activation area and a stronger BOLD signal in both SI and SII in the hemisphere contralateral to the right-D2. In both SI and SII these changes in BOLD signal were reversed 24 hours after RSS (Figure 3.6).

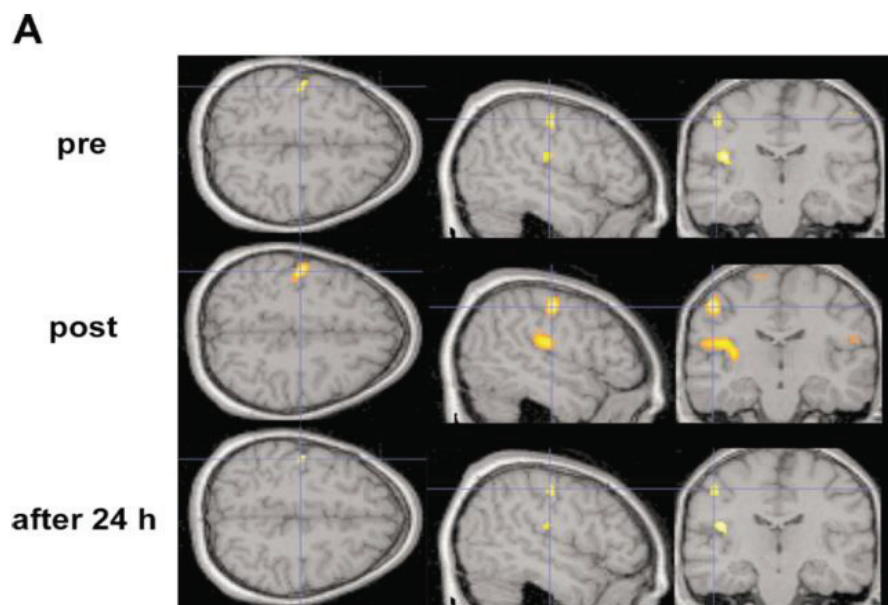


Figure 3.6 [modified from Pleger et al., 2003]: BOLD signal detected in SI and SII Pre, Post, and 24 hours after three hours of RSS on right-D2. Activations are shown on axial (left), sagittal (middle), and coronal (right) T1-weighted, normalized MRI slices. Note that after RSS there was an enlarged and increased activation of BOLD signal, in both left SI and left SII - contralateral to the stimulated right-D2. Note also that this increased activation totally recovered after 24 hours, when the BOLD signal returned to baseline.

Despite cortical changes in these two somatosensory areas, perceptual improvement in tactile discrimination was found to correlate exclusively with cortical changes in SI. However, the less defined and consistent somatotopic organization of SII (Ruben et al., 2001; Simões et al., 2001) might account for the lack of correlation at this level. Nevertheless, changes in SII suggested that RSS might involve some effects at levels of somatosensory processing beyond SI. Finally, it is worth noting that changes in BOLD signal were observed in either SI or SII when right-D2 was stimulated by single-site stimulation, a finding that is consistent with the lack of behavioural change after single-site stimulation that I described above.

In all the studies I have described above, the neural correlates of RSS-induced tactile improvement have been investigated extensively within the somatosensory cortex. In contrast, little is known about possible changes associated with RSS at other levels of brain organization, for instance in structural properties and functional connectivity. One very recent study provides some evidence that RSS also produces structural changes in brain morphology, specifically an increase in regional gray matter (GM) volume in the left somatosensory cortex (Schmidt-Wilcke et al., 2018). In addition, in an investigation of the intrinsic functional connectivity (iFC) in the resting-state network (RSN) of the sensorimotor system local up-regulations in iFC were found for brain regions primarily receiving somatosensory input, or regions recruited during tactile discrimination (Heba et al., 2017). However, further exploration in future studies about the effective connectivity and the relationship between functional and structural connectivity is needed to have a more complete overview of RSS-induced changes at this level.

3.6 RSS-induced changes and intra-cortical inhibition

A body of literature reported that RSS would produce some change in intra-cortical inhibition. One first approach to this argument involved the use of a paired-pulse stimulation protocol and SSEPs recordings (Höffken et al., 2007). The authors reported a significant reduction in paired pulse suppression (of the second response) of the stimulated right-D2 as recorded by SSEPs in left SI. In line with previous findings, these effects returned to baseline 24 hours after termination of RSS (Figure 3.7). In addition, the improvement in spatial discrimination

ability and the individual-level reduction in paired-pulse suppression were significantly correlated. Höffken and colleagues suggested that the reduced suppression of the second response in paired-pulse stimulation following RSS might be interpreted as a reduction of intra-cortical inhibition, probably due to activation of the intra-cortical GABAergic inhibitory system, which is thought to be involved in RSS-induced plasticity (Dinse et al., 2003b).

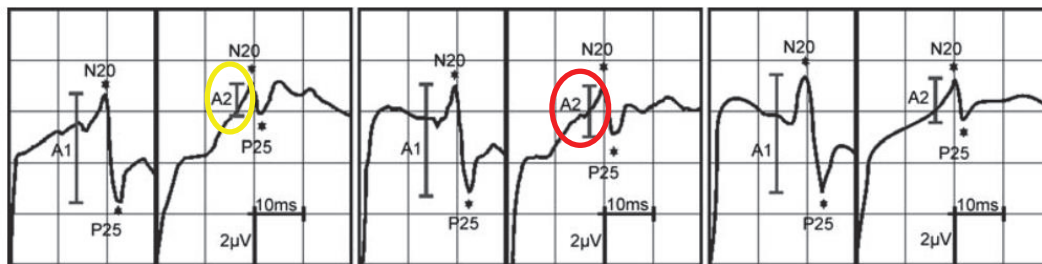


Figure 3.7 [from Höffken et al., 2007]: Individual cortical response to paired-pulse electrical stimulation on the median nerve with interstimulus intervals of 30 and 100 ms before (left), after (middle) and 24 hours after (right) 3 hours of RSS protocol on right-D2. Peak-to-peak amplitudes of the N20-P25 response component generated in S1. Paired pulse suppression was expressed as a ratio ($A2/A1$) of the second (A2) to the first response (A1). Note the significant reduction of the second response paired-pulse suppression after RSS (red circle) compared to pre-RSS (yellow circle). On the contrary, the observed change recovered to baseline 24 after termination of the stimulation.

A reduced inhibition could be interpreted as increased cortical excitability, and this was actually the interpretation given by Höffken and colleagues (2007). However, considering the physiological role of lateral inhibition in spatial discrimination (see Chapter 1) this appears to be at odds with the evidence just described referring a coupling between *reduced* intra-cortical inhibition and *improved* performance (Höffken et al., 2007). Indeed, an increased cortical excitability leads to *worsened* performance, and this was not the case.

Subsequent studies tried to disentangle this contradiction by computing a model of the underlying processes. This model was based on a Mexican-hat-type interaction characterized by recurrent excitation and lateral inhibition (Amari, 1977). According to this model (Pleger et al., 2016), RSS of several skin sites on the fingertip would weak the strength of inhibitory

interactions, possibly resulting in (i) the simultaneous activation of an increased number of cells, in turn leading to (ii) a finer spatial discrimination and (iii) a larger representation of this finger. From a practical point of view, especially those distances close to discrimination threshold would be perceived as separate (two peaks response) following RSS, and not as a single point (single peak response) as prior to RSS. A schematized example of this model is displayed in Figure 3.8 (Dinse et al., from Chapter 4 in *Human Haptic Perception Basics and Applications*, Grunwald, 2008).

For instance, it was used in a study investigating age-related tactile degradation (Pleger et al., 2016), where it was found that following RSS of the right-D2 tactile spatial discrimination of this finger resulted improved and SI BOLD response (contralateral to the stimulated right-D2) increased, and in the already described Wilimzig's study (2012), where it was found a significant speeding up of RTs for the stimulated finger. In particular, the graded RTs displayed in this study (i.e. higher RTs at the adjacent compared to non-adjacent fingers) were suggested to be function of lateral inhibitory connections between adjacent fingers. Indeed, since lateral inhibition is constrained by the cortical distance between fingers, the graded RTs reflected inhibitory effects larger for adjacent and weaker for more distant fingers.

In addition, this model would account for the opposite RSS-induced effects in tactile spatial discrimination (improvement: for example Godde et al., 2000; Pleger et al., 2001 2003; Muret et al., 2014, 2016) and localization (impairment: Pilz et al., 2004). Indeed, decreasing lateral inhibitory interaction within a finger would result in two peaks response for distances which before RSS elicited only single peaks, thus improving spatial discrimination; on the contrary, for localization, decreased inhibition would allow bigger fluctuation of peak position, thus impairing localization (Dinse et al., from Chapter 4 in *Human Haptic Perception Basics and Applications*, Grunwald, 2008).

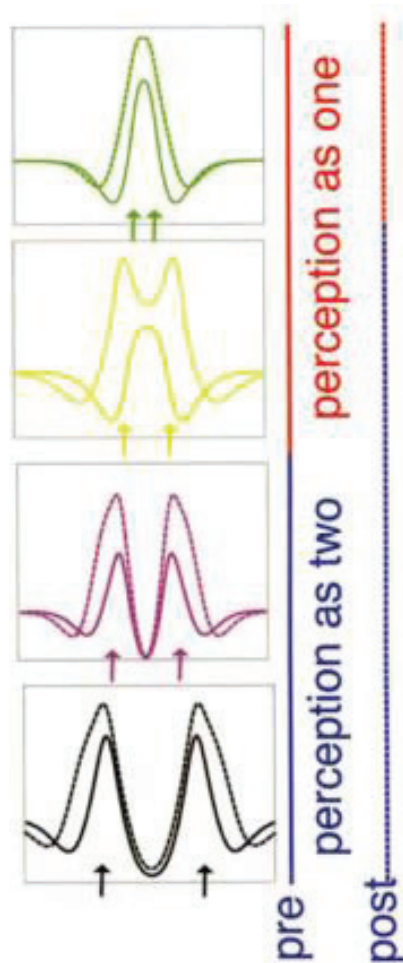


Figure 3.8 [Adapted from Grunwald, 2008]: RSS-induced increased lateral inhibition within the stimulated finger improves its tactile spatial discrimination. Graphs shows four different circumstances of two-point stimulation (simultaneous stimulation at two finger sites), where the spatial separation between the two points or *stimuli* (depicted by the arrows on the down of each graph) is bigger on the down and smaller on the top of the figure. Perception of these different spatial separations changes before (solid line: pre) and after (dashed line: post) RSS. Blues ranges indicate when two stimuli are perceived as two and red ranges when two stimuli are perceived as one. Before RSS, two spatially very close stimuli evoke single peak response (green and yellow solid lines) which corresponds to the perception of one stimulus. For larger distances (magenta and black solid lines) a two peaks response is evoked, corresponding to the perception of two stimuli. After RSS (dashed lines), a reduction of inhibitory connections within the stimulated finger does not change the perception of very close

(green) or very distant stimuli (black). Conversely, reduced inhibition has effect on the intermediate spatial separation (yellow), allowing the emergence of a two peaks response, which means perception of two stimuli.

3.7 Body-parts topography of RSS-induced changes

An important aspect of RSS-induced changes, which has been sometimes mentioned above but which I decided to discuss separately considering the relevance for the scope of the thesis, is the spatial distribution of the RSS changes over non-stimulated body-parts (i.e., its topography).

First, in parallel to the exploration of changes induced by RSS at the level of the stimulated finger (generally, the right-D2), several studies have also investigated possible changes at the level of other *non-stimulated fingers*. Concerning this point, no evidence has ever been reported that tactile improvement transfers from the stimulated right-D2 to the homologous left-D2 (Godde et al., 2000; Pleger et al. 2001, 2003; Dinse et al., 2003), neither to the adjacent right-D3 (Godde et al., 2000) nor to the left- or right-D5 (Muret et al., 2016). Based on this evidence, RSS does not appear to improve either the homologous finger on the contralateral hand or an adjacent finger on the same hand. Note, however, that the data concerning right-D3 were drawn from a very small group (n=7) so further investigation are needed to confirm this conclusion. Concerning the possible cortical effects, no study has ever reported any cortical change at the homologous left-D2 (Pleger et al., 2001, 2003; Dinse et al., 2003; Godde et al., 2003; Hodzic et al., 2004; Höffken et al., 2007) nor at the adjacent right-D1 (Pleger et al., 2001).

Taken together, these studies confirmed the assumption that RSS-induced changes are specific to the stimulated finger and that changes are limited to the cortical representation of this finger, without involving any transfer to other body parts. Concerning this issue, I would like to specify that the term '*transfer*' will be used frequently in this thesis to refer to transfer of perceptual improvement. I am aware that for certain readers this use might appear inappropriate as the *transfer* I refer to may not involve any physical transfer. Despite this, I have chosen to use this term as it is readily conveys the concept that a given effect (in this

case, the improvement of tactile spatial acuity) can appear (transfer) at a site that was not stimulated.

The *local* specificity of RSS-induced changes contrasts strongly with the well-documented transfer of perceptual improvement reported by studies on training-dependent learning. Indeed, as I described in the previous chapter, a number of studies showed that training a finger on a given task leads to improved acuity for this finger but also for other non-trained fingers (Sathian and Zangaladze, 1997, 1998; Harris et al., 2001; Harrar et al., 2004; Dempsey-Jones et al., 2015). This suggests that that two different procedures (RSS and training) can elicit similar improvements in tactile acuity at the stimulated or trained finger, but different transfer patterns to other body sites topography (no transfer in the case of RSS and a transfer in the case of training). One possible explanation for the presence of specificity in one case and generalization in the other could be that the two protocols call upon two different processing mechanisms to respond to the increased tactile input coming from the stimulated/trained finger. For training, transfer of tactile perceptual learning has been suggested to occur following plastic changes in neuronal populations with RFs that span multiple fingers, as a function of overlap in inter-finger representations (Dempsey-Jones et al., 2015; Harrar et al. 2014; Harris et al., 1999). In contrast, for RSS inhibitory interactions between fingers might be the leading candidate for the lack of improvement at non-stimulated fingers. As previously described, RSS of a finger results in the expansion of the cortical representation of this finger (Pleger et al., 2003). Therefore, one possible explanation for the lack of improvement at the adjacent right-D3 (Godde et al., 2000) might be that the increased cortical representation leads to the strengthening of lateral inhibitory connections across adjacent fingers (Hoechstetter et al., 2001; Simões et al., 2001; Tanosaki et al., 2002a; Severens et al., 2010; Cardini et al., 2011). Regarding this, it is important to remember that the sample tested in Godde's (2000) study was very small ($n=7$), so caution needs to be used when discussing these results. In contrast, the lack of improvement at the left-D2 after right-D2 stimulation has been widely demonstrated in bigger samples (Godde et al., 2000; Pleger et al. 2001, 2003; Dinse et al., 2003). As hypothesised above for adjacent fingers, inhibitory interactions between fingers (in this case inter-hemispheric interactions) might be the leading candidate for the lack of improvement on left-D2. Inter-hemispheric inhibitory interactions

between homologous cortical areas (Krubitzer et al., 1998; Henry and Catania, 2006) might play an important role in the latter case.

Contrary to the widely acknowledged *local* topography of RSS-induced perceptual improvement, a study investigating RSS-induced perceptual consequences on the face, published in 2014 by Muret and colleagues, on which I collaborated, completely called into question the idea of local specificity of effects after RSS. In this study, we demonstrated that RSS-induced tactile improvement is not only local but can also induce *remote* tactile improvement at a non-stimulated body region. We found that three hours of RSS on the right-D2 improves tactile acuity, measured as a lowering in the two-point discrimination threshold, not only at the stimulated finger, but also at the level of the face, specifically at both sides of the upper-Lip and at the right-cheek (Figure 3.9) (Muret et al., 2014, see Annexe 1 for the article).

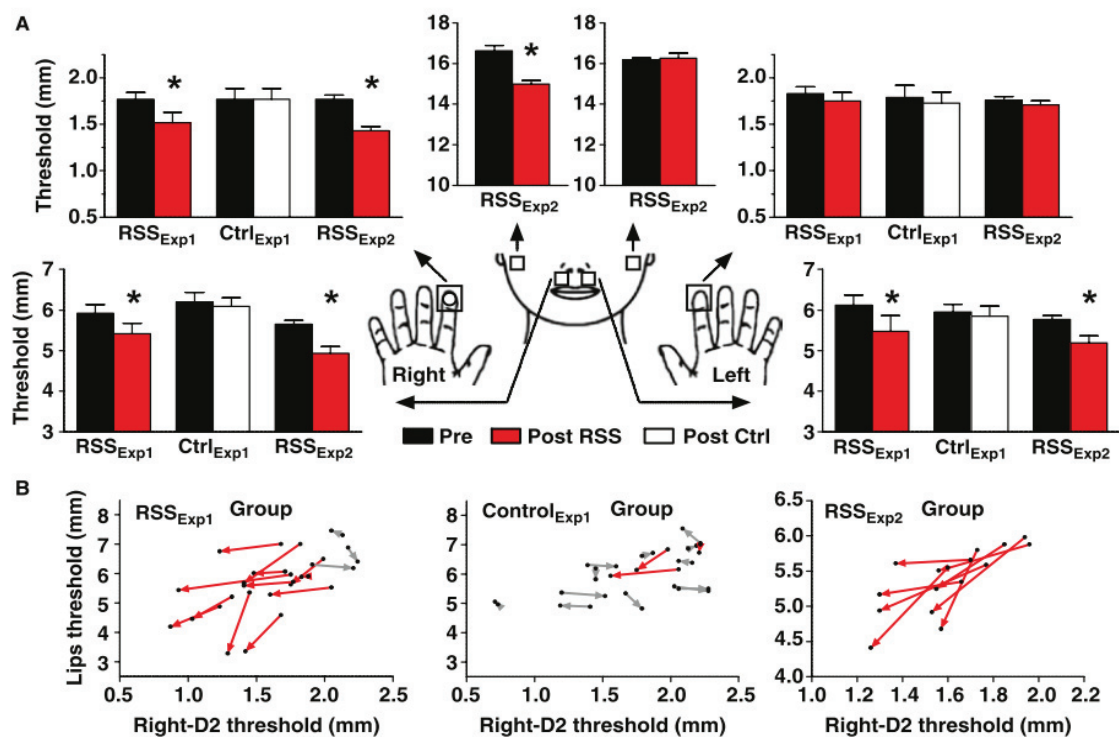


Figure 3.9 [from Muret et al., 2014]: Improvement of tactile acuity transfers from the finger to the face. Panel A shows spatial discrimination threshold Pre-

(black) and Post- (red) RSS applied to the right-D2 (RSS: red; Control: white), assessed at right/left-D2, right/left-Lip and right/left-Cheek. Note that, as shown by significant reduction of threshold, RSS improved tactile acuity on right-D2, both sides of the upper-lip, and right-Cheek in the RSS groups only. In contrast, no change was found in either the Control group or on the homologous left-D2 or left-Cheek in the RSS group. **Panel B** displays vectors showing the consistent relationship between threshold changes at the lips and right-D2 for each participant in the RSSExp1 (left panel), ControlExp1 (central panel) and RSSExp2 (right panel) groups. The starting and ending points of the vectors represent Pre- and Post-session thresholds respectively. Red vectors indicate parallel threshold decreases at both right-D2 and lips, whereas grey vectors illustrate other combinations of threshold changes.

Considering the proximity of these two body parts' representations within the sensory homunculus (Penfield and Rasmussen, 1950), we hypothesised that this transfer of tactile improvement arose from a spread of plastic changes from the right-D2 somatosensory representation into the face region via long range horizontal intracortical connections that cross the hand-face border (Muret et al., 2014). As described in the previous chapter, the hand-face border is a site at which plastic changes are commonly observed following sensory deprivation (Pons et al., 1991; Florence et al., 1998), with striking consequences on human perception (Ramachandran, 1993; Ramachandran and Hirstein, 1998). Our study suggested that by using the opposite approach, i.e. increasing tactile stimuli to the hand instead, can also results in changes in tactile perception that likely involve plastic changes across the hand-face border.

On the basis of this hypothesis our group conducted a neuroimaging study using MEG study (Muret et al., 2016) to investigate the neural correlates of the hand-face transfer. This study revealed changes in the representation of those body sites that showed improved tactile acuity after right-D2 RSS. Namely, an increased distance between the Lip and D2 dipoles in SI, which is consistent with the previously reported enlargement of the cortical representation of right-D2 (Pleger et al., 2003). In addition to replicating the behavioural findings in the 2014 study, this study provided information about the topography of the cortical changes.

Interestingly, changes were not limited to the left hemisphere, but were also observed in the right hemisphere, ipsilateral to the stimulated right-D2, suggesting that RSS induces cortical changes in both hemispheres. This idea goes against previously evidence describing the absence of any cortical change in the right hemisphere (no cortical change at the left-D2: Pleger et al., 2001, 2003; Dinse et al., 2003; Godde et al., 2003; Hodzic et al., 2004; Höffken et al., 2007), but it is important to note that right-hemisphere changes were only investigated for the left-D2 – a finger that shows no behavioural change after right-D2 RSS. In contrast, we observed changes in the right hemisphere that involved the lip representation – a body part that shows improved tactile acuity after right-D2 RSS (Muret et al., 2014; 2016). In view of the model of RSS as being local and therefore side-specific, upon observing a perceptual improvement in the left hemi-body we first thought that it was due to the bilateral representation of lip in SI (Disbrow et al. 2003; Nevalainen et al. 2006). However, the finding of bi-hemispheric changes suggests that the transfer of improvement to the ipsilateral hemisphere might be accounted for either intra-hemispheric or inter-hemispheric.

These latter studies (Muret et al., 2014, 2016) showed that the pattern of changes is more complex than previously thought. In addition, the conceptual meaning of the evidence they reported is twofold. Indeed, from the one hand these studies demonstrated that RSS-induces tactile improvement transfers across different body parts, therefore it is no longer local. From the other hand, they suggested that RSS-induces changes could occur not only in the hemisphere which is ipsilateral to the stimulation, but also ipsilaterally.

The pattern of changes induced by RSS becomes even more complicated by considering some very new evidence, reporting that when RSS was applied on the right-D2 no transfer of improvement to the forearm was found. This means that by stimulating a finger through RSS brings to improved tactile acuity on the anatomically far face but not on the close forearm, suggesting a preferential relationship between hand and face (Muret and Dinse, 2018).

Summary and Aims of the Thesis

In the previous chapters I developed some fundamental arguments necessary to introduce the aims of my thesis. First, I described how the somatosensory system, devoted to the sense of touch, displays an incredible plasticity, which results in changes at both neural and behavioural levels. These changes can be induced either following a decrease of sensory stimuli to the hand, as happens in case of amputation for example, or following an increase of sensory stimuli, as happens in case of training or RSS. In the first case I highlighted the close cortical and functional relationship that emerges between the hand and the face, while in the second I highlighted the fact that acuity of our hands is an ability we can improve through (i) training and learning or (ii) protocols of repetitive somatosensory stimulation (RSS).

RSS is of particular interest for the scope of this thesis since I used this procedure to provide the experimental contributions I will show in the next Chapter 4. As previously described in detail, RSS is a method able to improve finger tactile acuity without involving any training, practice or attentional process, but just through the application of a solenoid delivering mechanic stimuli on the skin. The fact that RSS is able to improve tactile acuity passively and quickly is an enormous advantage compared to the longer and harder procedures of training-dependent learning. For instance, this makes RSS an eligible method for improving tactile acuity in sensory deficits population. RSS-induced plasticity is well-known to induce reorganizational changes at cortical level and also behavioural changes in tactile performance. However, despite the plethora of studies conducted in the past two decades in order to characterize the RSS-induced effects, the topography of these changes is far from being totally understood. In particular, the topography of the improvement in tactile acuity needs to be further investigated since several fundamental points are still debated.

The experimentally-induced perceptual improvement in tactile acuity has been thought for a long time to be *local and specific* to the stimulated region because of the plethora of studies referring no transfer. However, this statement is in striking contrast (i) on the one hand with the evidence reported in training-dependent perceptual showing inter-fingers transfer of tactile

improvement and (ii) on the other hand with new evidence reported in RSS literature showing that RSS-induced tactile improvement transfers to the non-stimulated face.

The aim of this work of thesis is to investigate the topography of tactile improvement after RSS on the right-D2. The first goal is to investigate the question of whether RSS-induced tactile improvement is only local to the stimulated finger or transfers to the other fingers. To do this, a “mapping” of the tactile changes following RSS of right-D2 was carried out in both hands. The second goal is to further explore the newly discovered transfer of tactile improvement from the hand to the face. Specifically, I was interested in investigating whether this hand-face coupling is bidirectional, i.e. whether RSS applied on the face also improves tactile acuity at the hand.

These two lines of research together provide new information about the topography of RSS-induced tactile improvement. Specifically, the studies described in this thesis help understand how tactile improvement induced by RSS transfer within and between different body parts.

Chapter 4:

Experimental Contributions

Study 1: Topographical patterns of remote tactile improvement

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Introduction

Humans have the extraordinary ability to perceive and distinguish various types of somatosensory information with their hands. Given the importance of hand perception in everyday activities as well as the dramatic impairment that occurs after somatosensory loss [1][2], much research has been aimed at developing techniques to augment tactile perception at the fingers [3][4]. While it is possible to improve tactile spatial perception, most approaches require strenuous and prolonged training and are frequently incompatible for use with patient populations. One notable exception is repetitive somatosensory stimulation (RSS), which after a few hours of passive and unattended mechanical stimulation can improve tactile acuity [5][6].

RSS has long been thought to produce only local effects, with perceptual improvement limited to the stimulated region, most often the tip of the right index finger (right-D2). So many studies have demonstrated the absence of any change at the left index finger (left-D2), that left-D2 has become the canonical control in RSS studies [7][8][9][10][11][12]. The two studies that investigated whether RSS on the right-D2 affects a body part physically close to the stimulated finger found no change ([8] right-D3; [13] right-D5). In sharp contrast, recent works from our group revealed that the perceptual improvement induced by RSS can transfer to remote, non-stimulated regions of the skin, notably the face [13][14]. The coexistence of

both local and remote effects makes it clear that the topography of RSS-induced effects is far from fully understood.

Investigations into the neural substrates underlying tactile spatial acuity changes after RSS suggest a key role for plastic changes within the area of the stimulated finger in SI [9][10][13][15]. Our finding of an improvement at the face, together with the localization of the thumb's somatosensory representation between the stimulated index finger and face [16], suggest that right-D2 RSS might affect tactile spatial acuity on the right thumb (right-D1). Furthermore, since the perceptual improvement observed on the face was associated with cortical changes in *both* the left and right SI [13], right-D2 RSS might also affect tactile perception of fingers on the left hand. While this is clearly not the case for left-D2 [7][8][9][10][11], there is strong evidence from other tactile training protocols that tactile improvement can transfer to both homologous and non-homologous fingers [17][18][19][20].

Here we report two behavioural psychophysical experiments aimed at mapping the effects of right-D2 RSS on body parts with cortical representations close to that of the index finger: the thumb and middle finger. We examined both the left and right sides of the body and found that RSS on right-D2 improves tactile spatial acuity at both the left thumb and middle finger, but does not alter tactile acuity at the right thumb or middle finger. These findings reveal that the topography of tactile improvement following RSS is more complex than previously thought, and we propose a mechanistic model that attempts to account for both local and remote improvements in touch perception.

Results

Using the two-point discrimination (2PD) task we evaluated changes in tactile acuity on several body regions before and after 3 hours of RSS on the right-D2 fingertip. In the 2PD task a small part of the skin is touched with one or two probes at different distances between them, and the participant is asked to report if they feel 'one' or 'two' points. For each participant, and for each tested region, we calculated the detection threshold (i.e. the probe separation corresponding to 50% detection of two probes), and threshold change (i.e. the difference between Pre- and Post-RSS thresholds as a percentage of the Pre-RSS threshold, see Methods section). Thresholds Pre- and Post-RSS were compared using repeated measures

ANOVAs. When significant interactions were observed, the highest significant source of variance is reported in detail.

Experiment 1. Right-D2 RSS: 2PD task on left and right D1, D2, D3. We investigated whether right-D2 RSS affects tactile acuity at adjacent fingers on the stimulated and non-stimulated hands. To do this, we measured 2PD tactile acuity Pre- and Post-RSS at six sites: D1, D2 and D3 of each hemi-body. An omnibus three-way rmANOVA with the factors Region (D1, D2, D3), Side (right, left) and Session (Pre-RSS, Post-RSS) revealed significant main effects of Region [$F(2,28) = 649.97$; $p < 0.001$] and Session [$F(1,14) = 29.11$; $p < 0.001$], but not Side [$F(1,14) = 0.41$; $p = 0.532$], and a significant Region x Side x Session interaction [$F(2,28) = 43.49$; $p < 0.001$]. Post-hoc Bonferroni analyses showed that rD2-RSS decreased 2PD thresholds at the right-D2 [$p < 0.001$], left-D1 [$p = 0.047$] and left-D3 [$p < 0.001$], but not at the left-D2, right-D1 or right-D3 (Figure 1A). The threshold change analysis revealed a similar result: the percentage of threshold change was significantly different from zero for right-D2 [$t(15) = -12.345$, $p < 0.001$], left-D1 [$t(15) = -4.179$, $p < 0.001$] and left-D3 [$t(15) = -5.73$, $p < 0.001$] (Figure 1B). These findings suggest that rD2-RSS improves left-D1 and left-D3 tactile acuity.

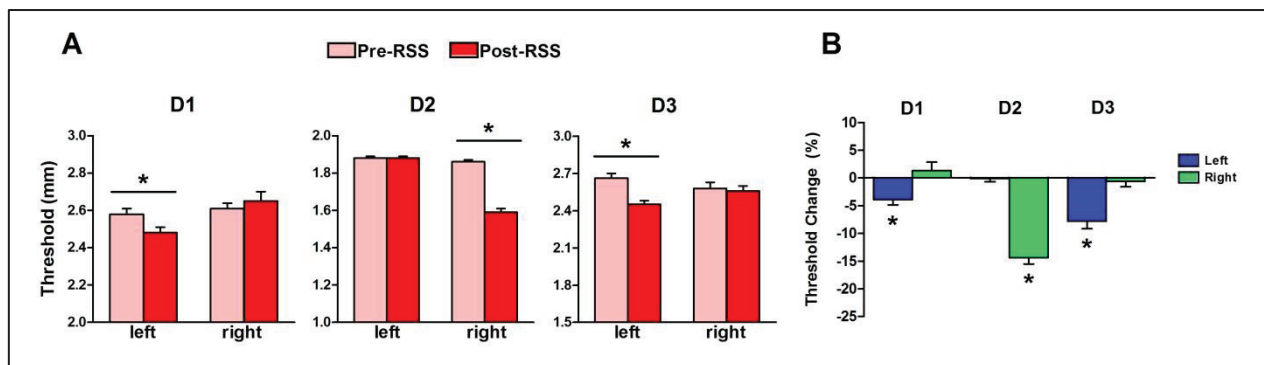


Figure 1: Effects of right-D2 RSS on tactile acuity in Experiment 1 participants (n=15). (A) Mean two-point discrimination threshold pre (pink) and post (red) RSS applied to the right-D2, assessed at right/left D1, D2, and D3 (mean \pm SEM). rmAnova and Bonferroni post-hoc tests revealed significant threshold decreases after RSS ($*P_{\text{Bonf}} < 0.05$) at right-D2, left-D1 and left-D3. (B)

Threshold changes at the six tested regions. T-tests revealed that threshold changes were significantly different from zero ($p < 0.05$) at left-D1, right-D2 and left-D3.

Experiment 2. Double-blind assessment: right-D2 RSS and sham control: 2PD task on left and right D1, D2, D3. To further investigate the transfer of RSS-induced tactile improvement from one hand to the other we conducted a second experiment with two major changes to our design. First, Experiment 2 was conducted double-blind (to prevent any possible participant/experimenter bias, see Methods section). Second, we tested both an experimental (canonical RSS) and a control group, the latter being exposed to a previously-piloted active sham stimulation. The Sham stimulation differed from canonical RSS in the number and temporal distribution of the somatosensory stimuli (see Methods section). Two groups of 20 participants received either canonical RSS (EXP2-RSS) or sham stimulation (EXP2-Sham) on the right-D2. Similar to Experiment 1, 2PD task was assessed on right/left D1, D2 and D3. An omnibus four-way rmANOVA with the factors Region (D1, D2, D3), Side (right, left), Session (Pre-RSS, Post-RSS) and Group (RSS, Sham), revealed a significant quadruple interaction [$F(2,76) = 8.336; p < 0.001$]. Bonferroni post-hoc analyses showed that 2PD thresholds decreased significantly only in the EXP2-RSS group and only at the right-D2 [$p = 0.042$], left-D1 [$P < 0.001$] and left-D3 [$P < 0.001$]. Thresholds were unchanged at left-D2, right-D1 and right-D3 (Figure 2A). Again, when tested against zero, threshold changes were significantly different only in the EXP2-RSS group and only for right-D2 [$t(20) = -3.014, p = 0.007$], left-D1 [$t(20) = -4.3202, p < 0.001$] and left-D3 [$t(20) = -4.7862, p < 0.001$] (Figure 2B). No significant threshold changes were observed in the EXP2-Sham group. The results from this double-blind experiment provide strong support for the conclusion that RSS on right-D2 improves tactile performance on the non-stimulated left-D1 and left-D3. Moreover, since an additional experiment reported in the Supplementary section demonstrates that tactile improvement at the lip and at left-D1 can be observed in the same subjects, we conclude that RSS on right-D2 remotely improves tactile performance on the non-stimulated lip, left-D1 and left-D3. Individual changes at each body part in both Experiments are reported in Figure S1 in the Supplementary section.

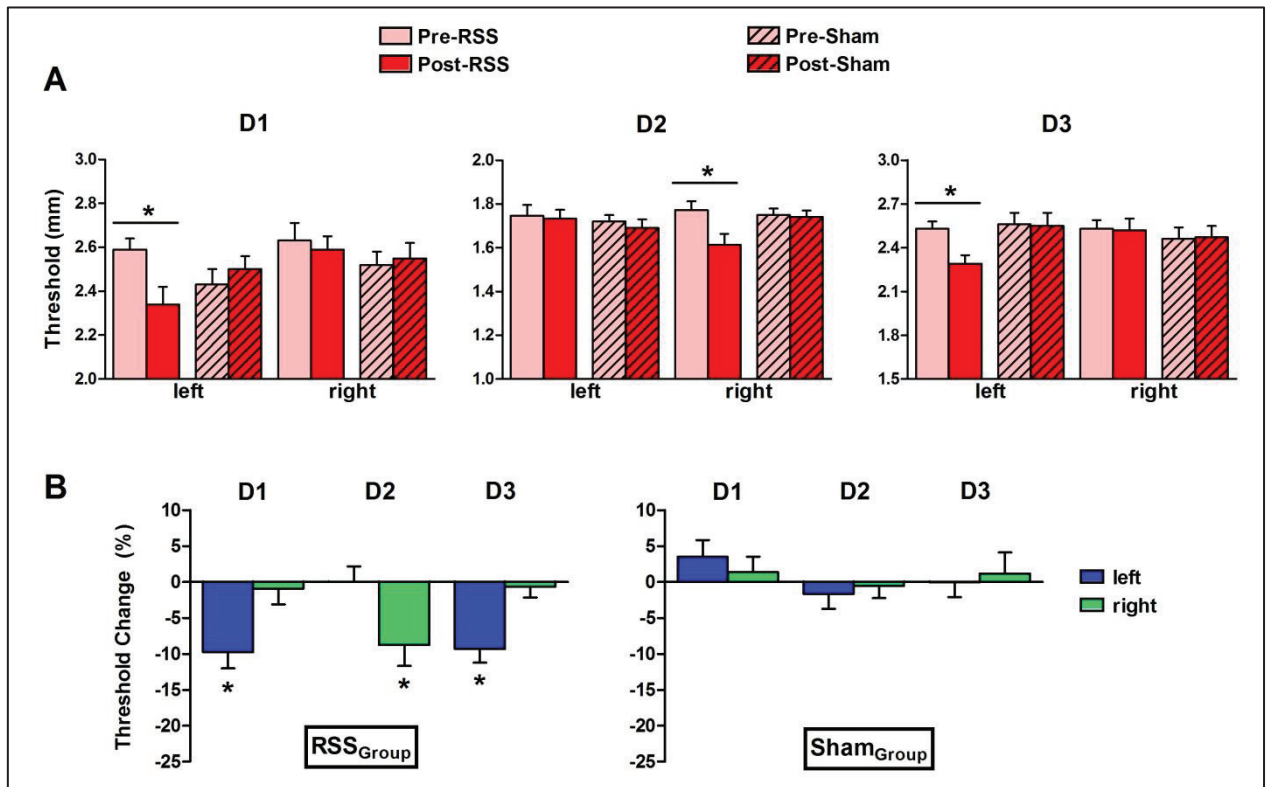


Figure 2: Effects of right-D2 RSS on tactile acuity in Experiment 2 participants (n=40). (A) Mean two-point discrimination threshold pre (pink) and post (red) RSS applied to the right-D2 (RSS: solid bars; Sham: striped bars), assessed at right/left-D1, -D2, and -D3 (mean \pm SEM). rmAnova and Bonferroni post-hoc tests revealed significant threshold decreases ($*P_{\text{Bonf}} < 0.05$) at right-D2, left-D1 and left-D3 in the EXP2-RSS group only. (B) Threshold changes at the six tested regions in EXP2-RSS group (left panel, n=20) EXP2-Sham group (right panel, n=20). T-tests revealed that threshold changes were significantly different from zero ($p < 0.05$) at left-D1, right-D2 and left-D3 in the EXP2-RSS group only.

Correlations. We tested whether the three significant effects reported following rD2-RSS (i.e. local improvement at right-D2 and remote improvement at left-D1 and left-D3) correlated with each other by combining all participants who underwent the RSS procedure (for a total n of 35: n = 15 from EXP1 and n = 20 from EXP2-RSS). We found that threshold

changes were significantly correlated between right-D2 and left-D3 ($r = 0.551$, $p = 0.001$), right-D2 and left-D1 ($r = 0.379$, $p = 0.025$) and also between left-D3 and left-D1 ($r = 0.48$, $p = 0.003$). When we corrected these values using the Bonferroni multiple comparisons correction ($*P_{\text{Bonf}} < 0.016$), the correlations between right-D2/left-D3 and left-D3/left-D1 were still significant, while the correlation between right-D2/left-D1 was not. Figure 3 shows the very consistent relationship between threshold changes at the right-D2 and left-D3 (panel A) and between left-D1 and left-D3 (panel B) for each participant.

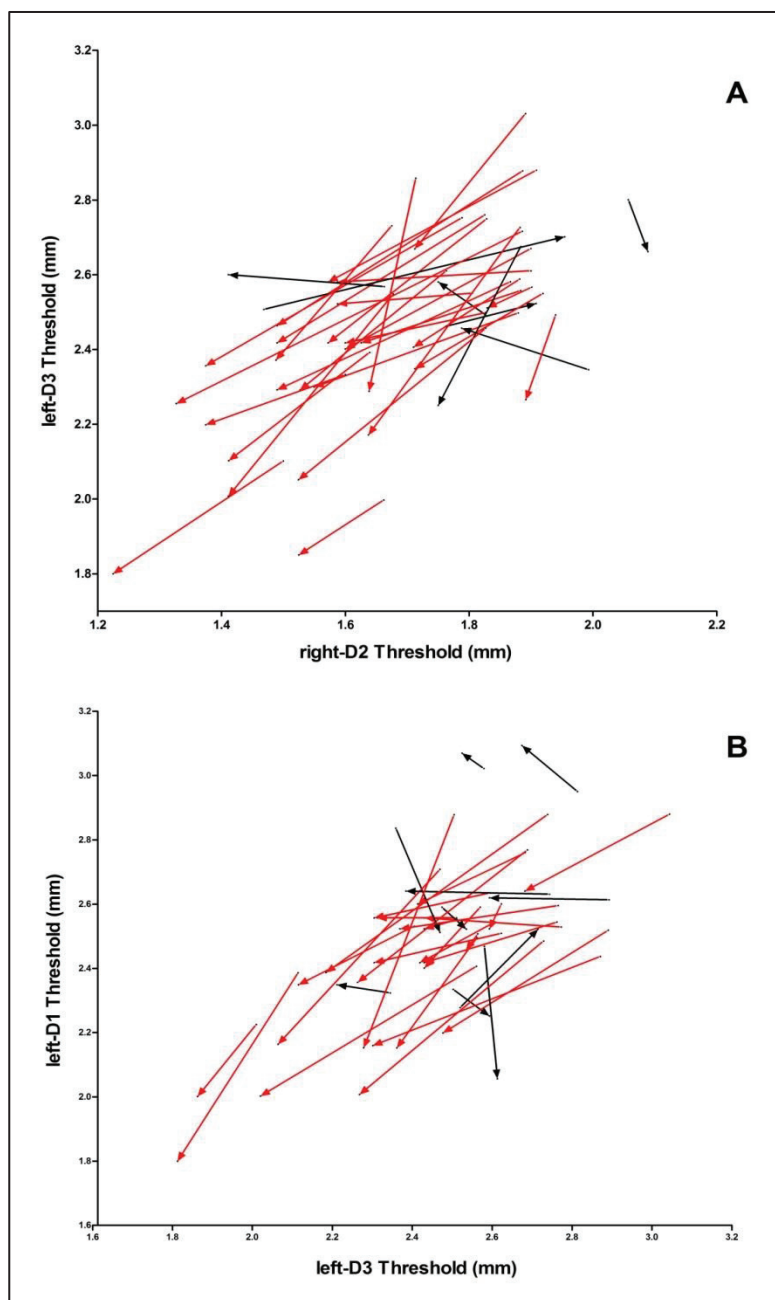


Figure 3: Relationship between threshold changes. Vector graphs show the relationship between threshold changes at the right-D2 and left-D3 (A) and between left-D1 and left-D3 (B) for each participant. The starting and ending points of vectors respectively represent Pre- and Post-RSS thresholds. Red vectors indicate parallel threshold decreases (i.e. tactile improvement) at both right-D2

and left-D3 (A) and left-D1 and left-D3 (B) whereas black vectors illustrate other combinations of threshold changes. Note that threshold decreases are very consistent across participants in both vector graphs, as confirmed by significant correlations ($*P_{\text{Bonf corrected}} < 0.016$).

Discussion

In this study we investigated the hypothesis that RSS on the right index fingertip improves tactile perception not only on the face [13][14], but also on non-stimulated fingers on both hands. To do this we examined changes in tactile acuity induced by RSS of the right-D2 both locally (on the right hand) and remotely (on the left hand). Despite the well-established local nature of the RSS-induced effect described for the stimulated right-D2 [7][8][9][10][11], and the relatively new finding showing that this effect transfers to the face [13][14], none of the previous studies investigating RSS-induced tactile improvement have ever reported effects on other fingers. In addition to replicating the remote effect on the face (see Supplementary section), the present series of experiments reveals that RSS also has remote effects on fingers on the non-stimulated hand, as it improved tactile acuity not only at the stimulated right-D2, but also at the left-D1 and left-D3.

1. No improvement transfer to adjacent fingers on the right hand. The fact that right-D3 did not benefit from changes induced by stimulation on its neighbour (right-D2) is not totally new, as a similar finding was reported by Godde and colleagues [8], albeit in a small sample ($n=7$). Here, we confirm this finding in a much larger sample (Exp1 and Exp2-RSS; $n=35$). RSS-induced effects on tactile acuity are thought to take place in SI [9][10][13][15]. Given this, and the fact that right-D1 is represented between the stimulated right-D2 and the face regions that improve (lips and right-cheek [14]), we expected right-D1 to benefit from RSS-induced changes in the same way as the more distant face. Contrary to our hypothesis, however, we found no change in tactile acuity at right-D1. At first glance this finding is surprising, but two studies support the absence of any change at right-D1. One showing that right-D1 somatosensory-evoked potentials (SSEPs) do not change after right-D2 RSS [9] and a second showing that 45 minutes of high-frequency RSS on right-D2 does not alter the

temporal discrimination thresholds of right-D1 [21]. The results reported here are the first to show that right-D1 tactile perception is unchanged after right-D2 RSS. Together with the lack of improvement at right-D3, these findings confirm the notion that RSS-induced effects within the stimulated hand are highly local and do not transfer to fingers adjacent to the stimulated finger.

The proximity of the SI representations of D1, D2 and D3 and the dense cortico-cortical connections that exist between them [22] together would constitute a suitable neuronal ground for possible inter-finger transfer of improvement. Functionally, however, these connections are thought to underlie lateral inhibition between fingers [23][24][25][26]. Therefore, activity in these inhibitory circuits could account for the lack of transfer and high specificity of the RSS-induced improvement within the stimulated hand. The increased activity in right-D2's cortical area due to improved synaptic transmission and expansion of the cortical area activated by inputs to right-D2 [10] might increase activity within lateral inhibitory connections thereby suppressing any potential improvement transfer to the adjacent right-D1 and right-D3. In particular, the enlarged representation of the right-D2 [10] might prevent improvement transfer to right-D1 and right-D3 by increasing activity in inhibitory cortico-cortical connections. An example of inhibitory interactions between fingers in presence of increased cortical activity was shown by a study investigating the cortical processing from fingertips in touchscreen users. Compared to nonusers, when thumb and index fingers of touchscreen users were stimulated simultaneously, enhanced intra-cortical inhibition was found [27]. The potential involvement of lateral inhibitory connections in explaining our results is consistent with the physiological significance of lateral inhibition, which is thought to have an important role in focusing neural activity and helping to sharpen perception, as first described in the visual [28] and later in the somatosensory [29] systems. Simulation studies of cortical networks suggest that under normal circumstances the cortex is under tonic inhibitory modulation, the so called inhibition dominant scheme, in which lateral connections maintain the dynamic balance between excitation and inhibition [30].

2. Improvement transfer to fingers of the left hand. Remarkably, we report here for the first time the existence of a remote transfer of perceptual improvement from the stimulated right-D2 to the two fingers on the left hand. This novel finding demonstrates that in addition

to the remote finger-to-face transfer [13][14], RSS also leads to a remote between-hand transfer. The topography of this between-hand transfer is highly specific as rD2-RSS did not improve all three tested fingers, but only the left-D1 and left-D3. As shown in several previous studies and confirmed here, no change in tactile acuity was observed at the left-D2 [8][9][10][11][12]. This means that the remote changes produced by RSS transfer selectively across hemispheres, following a specific topography which appears to be the opposite of that observed for the stimulated hand.

This pattern of results is in keeping with interhemispheric inhibition processes mediated by trans-callosal reciprocal connections between homotopic cortical areas [31][32][33]. Similar effects of release from interhemispheric inhibition were found by Björkman and colleagues [34] who showed that anesthetizing the right hand improved both discrimination and touch perception on the left hand. In their study, temporary *loss* of sensory inputs from one hand led to better tactile perception in the other. Here, temporary *increase* of sensory inputs from one finger leads to an improvement in its perception, but prevents adjacent fingers and the homologous finger on the opposite hand from improving. Changes in interhemispheric inhibition between the two index fingers might also account for the changes found in left-D1 and left-D3. The potential mechanism would involve a balance of increased/decreased inhibition within and between the hands. According to this account, increasing interhemispheric inhibition acting on left-D2 could reduce the intra-hemispheric lateral inhibition exerted by this finger over its neighbours. This release from inhibition of left-D1 and left-D3 could then result in improved perception (Figure 4A). Another, possibly co-existing, mechanism could be inhibition of right-D1 and right-D3 and subsequent disinhibition of their homologs on the left hand via changes in interhemispheric inhibition (Figure 4B). While further studies are clearly needed in order to disentangle these possibly non-mutually exclusive mechanisms, the current results clearly demonstrate that RSS-induced perceptual improvements are far less local (i.e., are not limited to the stimulated finger) than previously believed. While testing for change in left-D2 has become the standard control in RSS literature [7][8][9][10][11][12], the present study makes clear that the left hand is not immune to increased stimulation of the right hand.

3. A novel pattern of tactile improvement. RSS protocol shows that improvement of tactile performance in humans can be achieved through a few hours of passive, unattended stimulation on a fingertip [5][6][7]. Because of its nature, we also refer to RSS as training-independent sensory learning [5]. It has long been known that tactile improvement can be achieved through perceptual learning, where the gain in performance is achieved by intensive practice [35]. Studies of this kind of training-dependent learning show that training a finger for several days or weeks results in improved tactile acuity and transfer of this improvement to non-trained fingers [18][19]. For example, training the right-D3 also improves the two adjacent fingers (right-D2 and right-D4), as well as the homologous left-D3, but not left-D2 nor left-D4 [20]. This pattern of transfer is the perfect mirror-image of the one we report here where we found that improvement from a stimulated finger transferred to adjacent fingers on the contralateral hand, but not to adjacent fingers on the stimulated hand, nor to the homologous finger. The discrepancy between these two patterns is most likely explained by the totally different approaches of the two methods and hence the involvement of different neurophysiological mechanisms. The first major element to be considered is the role played by attention, which is known to play a fundamental role in sensory processing, for example by sharpening the contrast between the representations of attended and unattended fingers [36][37]. In training-dependent learning, participants are asked to actively and intensively practice the task to be learned. In doing so, they have to pay attention to the stimuli to which they are exposed. In contrast, in RSS-induced training-independent learning participants are neither asked to perform a task nor to pay attention to the stimuli (see Methods section for more details). Thus, the different way attention is involved in RSS versus training could result in the two different patterns described above.

4. Neural substrates of RSS-induced improvement transfer. Here we demonstrate that a passive, attention-free procedure such as RSS can produce finger-to-finger improvement transfer, as is the case for training-dependent procedures, albeit with a completely different transfer pattern. Although we cannot *a priori* rule out contributions from various subcortical or thalamic regions [38], most evidence points towards changes at the cortical level of sensory processing. Neurophysiological and imaging studies assessing the mechanisms underlying RSS-induced behavioural changes have consistently demonstrated that RSS induces reorganisation of the SI representation of the stimulated region [9][10][15] and influences the

region's inhibition [39]. Although RSS also induces changes in SII [10], the specific pattern of improvement that we observed suggests that the underlying neural changes occur within an early representation that contains well-ordered topographic maps. Furthermore, unlike changes in SI [9][10][15], changes in SII are not correlated with tactile improvement [10].

In our previous work showing a remote (finger-to-face) transfer of RSS-induced tactile acuity improvements we reported a bilateral tactile improvement at the lip, but an effect ipsilateral to the stimulated finger at the right-cheek [14]. Since the lips are more bilaterally represented than the cheeks [40], we suggested that this pattern of transfer to the face could be consistent with RSS-induced tactile improvement being limited to the left hemisphere (contralateral to the stimulated finger). On the contrary, the results we report here suggest the additional involvement of the right hemisphere, since tactile acuity on two fingers on the left hand clearly improves after RSS of right-D2. The hypothesis that remote effects of RSS are due to changes occurring in both hemispheres is in agreement with recent neuroimaging evidence showing bilateral changes in SI after RSS [13]. At this stage it is impossible to assert whether the transfer to the ipsilateral hemisphere occurs via trans-callosal or thalamo-cortical connections, although inter-hemispheric communication between homotopic cortical areas would appear to be the more likely candidate [31][32][33].

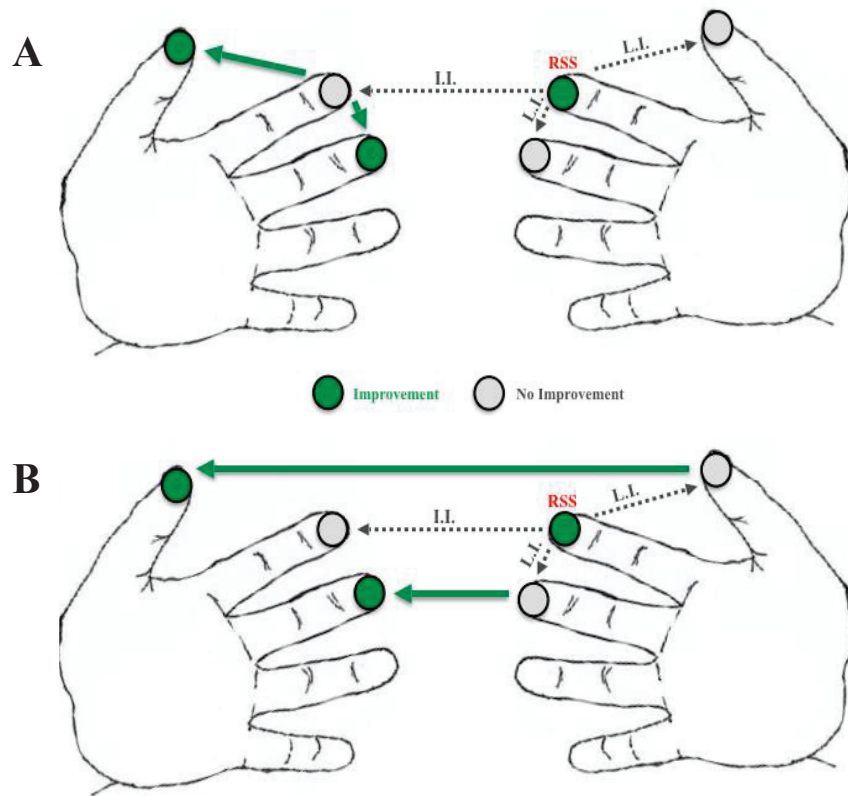


Figure 4. Schematic illustration of two hypothetical models explaining the observed pattern of tactile improvement. We suggest that excitatory/inhibitory processes are involved in the changes in tactile acuity we observe in this study. RSS on right-D2 would increase lateral inhibition (L.I.) between this finger and its neighbours (right-D1 and right-D3) and inter-hemispheric inhibition (I.I.) between this finger and left-D2. **Model A)** Increasing interhemispheric inhibition acting on left-D2 could reduce the intra-hemispheric lateral inhibition exerted by this finger over its neighbours. This release from inhibition of left-D1 and left-D3 (green arrows) could then result in improved perception. **Model B)** Another, possibly co-existing, mechanism could be inhibition of right-D1 and right-D3 and subsequent disinhibition of their homologs left-D1 and left-D3 (green arrows) on the left hand via changes in interhemispheric inhibition. Disinhibition of the homologs left-D1 and left-D3 could result in improved perception of these fingers.

Conclusions

The studies presented in this paper show for the first time that remote transfer of tactile acuity improvement after RSS of the right-D2 takes the form of a finger-to-face and an inter-manual (finger-to-finger) transfer, with the transfer to the fingers occurring only to fingers on the non-stimulated hand, in our case left-D1 and left-D3. In addition to making an important contribution to our understanding of the topography of RSS-induced perceptual changes at different body parts, these findings also open up new potential avenues for understanding plasticity mechanisms and studying spared-to-damaged hand therapeutic applications.

Methods

Participants. A total of 58 healthy volunteers participated in this study. They were enrolled in two separate experiments. Experiment 1: $n = 15$, mean age = 22.47; SD 2.47 years. In Experiment 2, we enrolled 43 participants but three of them (from EXP2-Sham) were excluded from the study because their percentage threshold change between the two baseline sessions was more than 2.5 SDs above the average threshold change in their group. Thus 40 participants were included in the final sample in Experiment 2 (mean age = 22.25; SD 2.75 years). All participants were right-handed according to the Edinburgh Handedness Inventory (Experiment 1, mean score = 84.67; SD 16.51; Experiment 2, mean score = 77.5; SD 18.08). The study conformed to the Helsinki Declaration, Good Clinical Practice Guidelines, French Law and was approved by the local ethical committee. All participants received detailed information about the study and provided written informed consent.

Experimental groups. Participants in Experiment 1 received RSS on right-D2. The 2PD task was performed on six body regions, the right and left D1, D2 and D3. The experiment was performed single blind. Experiment 2 was randomized, double-blind, and sham-controlled. Participants were randomly assigned to one of two different groups: EXP2-RSS ($n = 20$) or EXP2-Sham ($n = 20$). EXP2-RSS participants received the standard RSS procedure on the right-D2, while EXP2-Sham participants received a sham stimulation on Right-D2. Sham stimulation was designed so as to deliver stimuli without inducing any perceptual changes in

tactile perception. As in Experiment 1, the 2PDT was performed on six body regions, the right and left D1, D2 and D3.

Repetitive Somatosensory Stimulation (RSS). The RSS protocol we used here is a standard mechanical, attention-free and passive tactile stimulation method. It is based on the Hebbian postulate that the simultaneous activation of several cutaneous receptive fields produces temporally correlated inputs that induce plastic changes in somatosensory cortex and changes in tactile perception [7][8][9][15]. In all participants, an 8 mm diameter solenoid controlled by an MP3 player was taped to the volar surface of the right-D2 fingertip for three hours: this solenoid delivered brief (10ms duration) supra-threshold tactile stimuli. In order to prevent habituation, tactile stimuli were delivered with inter-stimulus intervals ranging from 100 to 3000ms randomly taken from a Poisson distribution, thus resulting in a mean stimulation frequency of 1 Hertz on average. Pulses were recorded digitally and were played back via a portable MP3 player, allowing unrestrained mobility of the participants during the stimulation period. Participants could freely move during stimulation and were explicitly instructed to ignore the stimulation and to continue with their daily activities (for example reading a book or watching a movie).

Sham Stimulation. The nature of the Sham stimulation (tactile and passive), the application method (mechanically, on the right-D2 fingertip, through the same diameter solenoid controlled by the same MP3 as the RSS stimulation) and the duration of the protocol (three hours) were exactly the same as the RSS procedure. The only difference was in the effective duration and distribution of the stimuli. In the RSS procedure, the stimuli were delivered continuously over the three hours. In contrast, for the Sham procedure, the stimuli were delivered during six blocks of 2.5 minutes spread over the three hours of the protocol, resulting in an effective total stimulation time of fifteen minutes. Between these blocks no stimulation was delivered. We decided to use as a control condition a stimulation which is as similar as possible to the RSS procedure in order to rule out any possible bias that might occur in participants were the stimulation simply switched off. As in RSS stimulation, participants were instructed to continue with their daily activities without paying any attention to the stimulation.

Experimental design. The experimental design was the same for both experiments. As in previous RSS studies from our laboratory [13][14], tactile acuity of the different body parts was tested in three different sessions (2 Pre-RSS sessions and 1 Post-RSS session) over two consecutive days. On Day 1, after an introductory period where participants became familiar with the 2PD task, we performed the first Pre-session (Session 1). On Day 2, we performed the second Pre-Session (Session 2), the RSS or sham stimulation on the right-D2 fingertip, and the Post-Session.

Tactile acuity assessment: two-point discrimination (2PD) task. The 2PD task is a well-known method for measuring tactile acuity in humans [8][9][14]. Spatial discrimination thresholds of different body regions were measured with the same paradigm in all subjects and experiments: the skin surface was touched with one or two probes separated by different distances and the subject had to report whether he/she felt “one” or “two” points. Subjects were instructed to be accurate and to answer “two” only when clearly perceiving two distinct points. No feedback was given during the task. Throughout the experiment the subject was blindfolded. 2PD thresholds were assessed using eight probes, one with a single tip and seven with two tips separated by various distances. Because of basic differences in the absolute sensitivity among the body parts tested, different sets of distances were used for D2 (0.7, 1.0, 1.3, 1.6, 1.9, 2.2, 2.5 mm), D1 and D3 (1, 1.4, 1.8, 2.2, 2.6, 3.2, 4 mm). For every site, each probe was tested 8 times in a pseudo-randomized order (no more than two consecutive repetitions of the same probe), resulting in 64 trials. Tips were always presented parallel to the longitudinal axis of the fingers. The eight probes were mounted on a rotatable disc which permitted rapid and unpredictable switching between distances. Participants were instructed to relax the hand and the forearm, and to remain still. At the beginning of each testing block the single probe and the two-tip probe with the largest tip separation (2.5 mm for D2; 4 mm for D1 and D3) were presented three times to the participant while the experimenter said “one” or “two”. Once participants declared that they clearly felt the difference between these two probes the testing began and lasted approximately 10 minutes for each body part.

Data analysis. Subject’s responses in 2PD task were plotted as a function of distance between the probes and the psychometric function was fitted with a binary logistic regression from which we then calculated the threshold, i.e. the distance at which participants responded

“two” 50% of the time. Participants were at first tested for their baseline performances, and excluded in case their percentage threshold change between the two baseline sessions was more than 2.5 SDs above the average threshold change in their group. Then, Session 1 and Session 2 were compared for baseline stability using paired sample t-tests (see Supplementary section for baseline stability analysis). Since no significant change was found, we defined as the Pre threshold as the average of Session1 and Session2 and the Post threshold as the threshold obtained in Session3. Pre- and Post-RSS thresholds were compared to evaluate acuity changes. In Experiment 1, the Pre/Post analysis was conducted using repeated measures ANOVAs, with Region (D1, D2, D3), Side (Right/Left) and Session (Pre/Post) as factors. In Experiment 2, a factor Group (RSS/Sham) was added. Threshold changes between Pre- and Post-Sessions were determined for each subject and region as a percentage of the Pre-Session threshold (average of Session1 and Session2) using the following formula: $[(\text{Threshold Post} - \text{Threshold Pre}) / \text{Threshold Pre}] * 100$. A further statistical analysis comparing Pre- and Post-Session threshold changes was performed using simple t-tests against zero. All statistical analyses were performed using Statistica® (v.13 StatSoft). Bonferroni post-hoc analyses were performed (* $P < 0.05$). All data are expressed as mean \pm standard error of the mean (SEM). All data were checked for normality using Kolmogorov-Smirnov tests.

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Supplementary Section

Topographical patterns of remote tactile improvement

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Additional Experiment S1. Right-D2 RSS: 2PD task on left and right D1, D2, upper-Lip. Here we report an additional experiment ($n=15$, mean age = $21.93 \pm \text{SD } 3.61$ years; Edinburgh Handedness Inventory mean score = $82.67 \pm \text{SD } 16.24$) investigating changes on tactile acuity of D1 and upper-Lip. The aim of this experiment was to investigate whether right-D2 RSS improves the tactile acuity of both upper-Lip and D1 at the same time. To this purpose, we assessed 2PD task Pre- and Post-RSS on six body sites: D1, D2 and the upper-Lip of each hemi-body. Data analysis is the same than that run in main manuscript. One omnibus three-way rmANOVA with factors Region (D1, D2, Lip), Side (right, left) and Session (Pre-RSS, Post-RSS) revealed significant main effects of Region [$F(2,28) = 2044.197$; $p < 0.001$] and Session [$F(1,14) = 135.972$; $p < 0.001$] but not Side [$F(1,14) = 0.764$; $p > 0.05$]. This analysis also revealed a significant Region x Side x Session interaction [$F(2,28) = 10.489$; $p < 0.001$]. Post-hoc Bonferroni analyses showed that rD2-RSS significantly decreased the 2PD threshold locally, on right-D2 ($p < 0.001$), and remotely, on both right-Lip ($p < 0.001$) and left-Lip ($p < 0.001$). No significant changes were found for left-D2 or either the left or right D1 (Figure S1A). The fact that post-hoc analysis for the interaction Region x Side x Session did not reveal any significant effect at D1 would suggest that this finger does not benefit from the tactile improvement induced by rD2-RSS. However, visual inspection of the left-D1 results in particular (see Figure S2) seems to hint at some changes, possibly escaping significance because of absolute threshold differences among regions. Indeed, lips and fingers display different sensitivity, with the first ones having higher 2PD thresholds compared to the fingers. To further explore changes at D1, one separate two-

way rmANOVA using as factors Side (right, left) and Session (Pre-RSS, Post-RSS) was run for this region. The separate rmANOVA showed significant main effect of Session ($F_{(1,14)} = 6.335$, $P = 0.0246$), but no significant main effect of Side ($F_{(1,14)} = 3.662$, $P = 0.0763$) nor Side x Session interaction ($F_{(1,14)} = 1.053$, $P = 0.3221$). Finally, when the difference of threshold between Pre- and Post-RSS was expressed in terms of percentage of the Pre-RSS threshold and compared to zero, threshold changes were significantly different only in left-D1 [$t(15) = -2.9669$, $p = 0.0102$], right-D2 [$t(15) = -12.9531$, $p < 0.0001$], right-lip [$t(15) = -13.6604$, $p < 0.0001$] and left-lip [$t(15) = -7.8795$, $p < 0.0001$] (see Figure S1B).

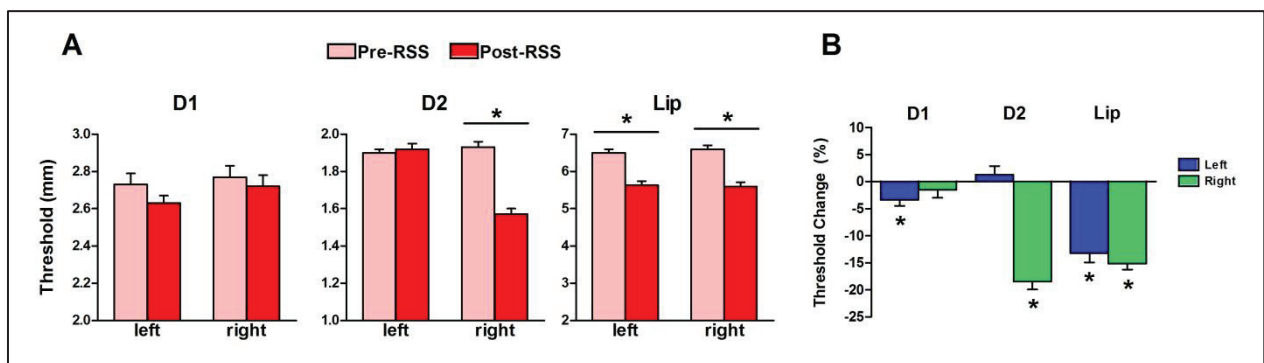


Figure S1: Effects of right-D2 RSS on tactile acuity in Additional Experiment S1 participants (n=15). (A) Mean two-point discrimination threshold pre (pink) and post (red) RSS applied to the right-D2, assessed at right/left D1, D2, and upper-Lip (mean \pm SEM). rmAnova and Bonferroni post-hoc tests revealed significant threshold decreases after RSS (* $P_{\text{Bonf}} < 0.05$) at right-D2 and right/left upper-Lip. (B) Threshold changes of the six tested regions. T-tests revealed that threshold changes were significantly different from zero ($p < 0.05$) at left-D1, right-D2 and right/left upper-Lip.

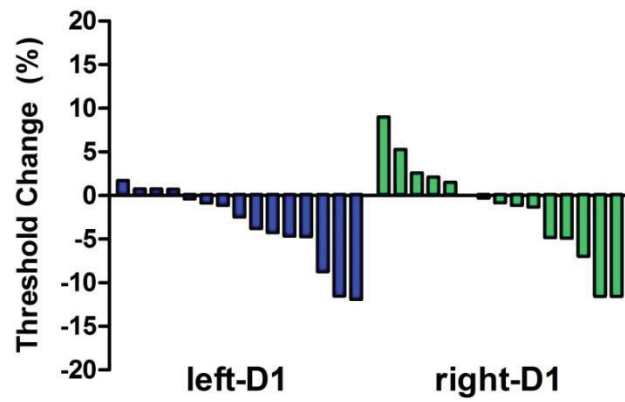


Figure S2: Individual threshold changes in 2PD task at D1 in Additional Experiment S1 participants (n=15). Each bar represents a single participant and values are rank-ordered. Note that changes at right-D1 (green) are equally distributed around zero, while changes at left-D1 (blue) are mostly distributed below zero, meaning that at left-D1 lower thresholds are most consistent across participants.

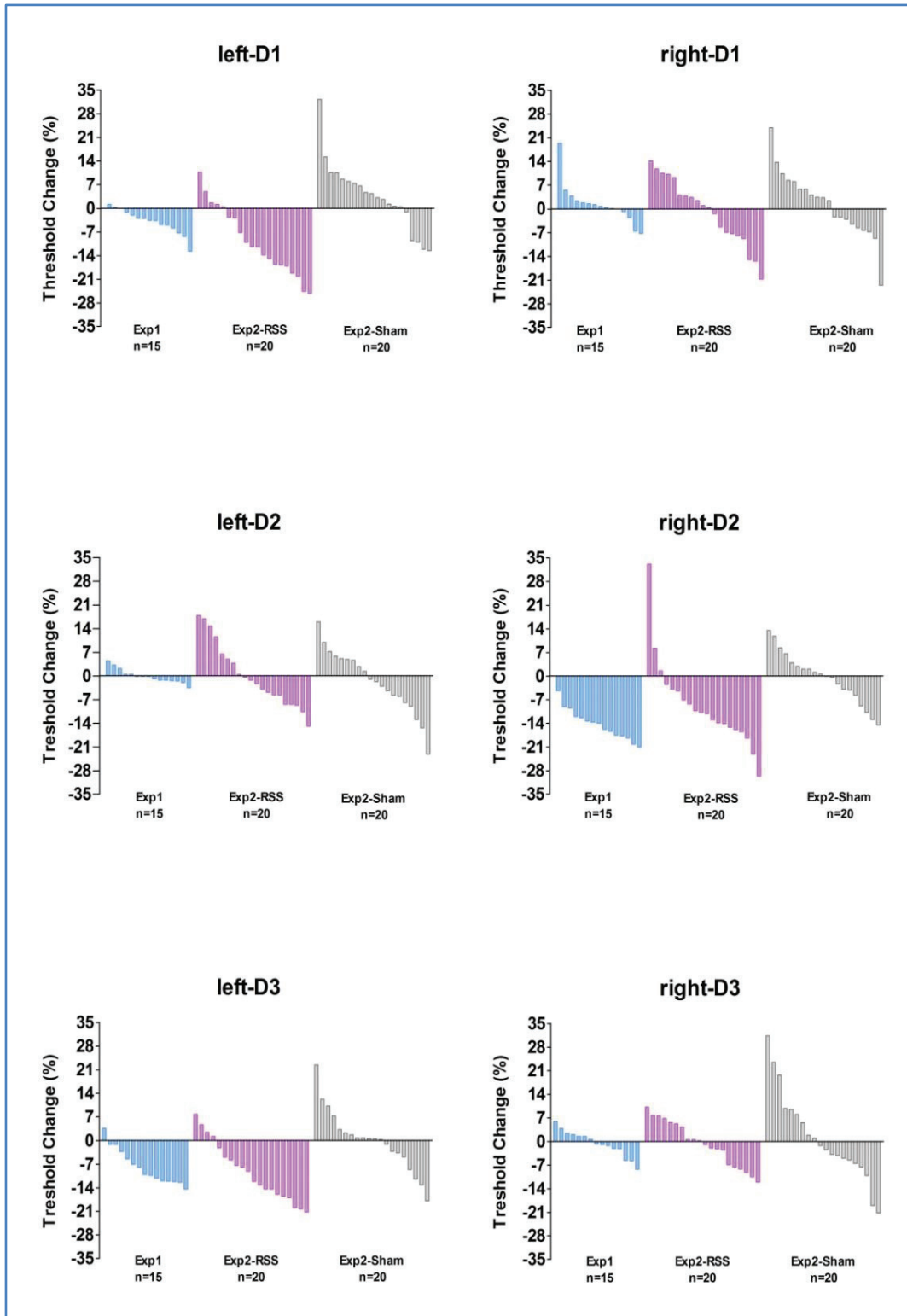


Figure S3: Individual threshold changes changes in 2PD task in Experiment 1 and Experiment 2 participants. This figure shows rank-ordered distributions

of individual participant threshold changes in 2PD task. The percentage change found at each left (on the left) and right (on the right) tested body part are shown in blue for EXP1, in purple for EXP2-RSS and in grey for EXP2-Sham. Each bar represents a single participant and values are rank-ordered so a given participant is not represented in the same position across graphs. Note that in the Sham group changes are equally distributed around zero. The same is true for right-D1, right-D3 and left-D2 in both EXP1 and EXP2-RSS. On the contrary, in both EXP1 and EXP2-RSS at the stimulated right-D2 and at left-D1 and left-D3 the changes are mostly distributed below zero, meaning that thresholds were consistently lower after RSS.

Multiple-Baseline stability of thresholds. For each participant, body region and Experiment, performance in two-point discrimination (2PD) task was tested in different sessions. In particular, after a preliminary familiarization period, the participant performance was tested at baseline in two separate sessions (Session 1 and Session 2). In this way, we wanted to make sure that any change in performance found after the application of RSS on the right-D2 was exclusively due to the stimulation and not to possible effects of training or re-testing. Thus, thresholds obtained at Pre-sessions S1 and S2 were analysed for baseline stability. In all experiments, analysis was conducted using paired t-tests. Analysis never showed significant comparison between Session 1 and Session 2 thresholds (all P values > 0.05). Thus, Session 1 and Session 2 thresholds were averaged (Pre-RSS) and compared to Post-RSS.

Study 2: RSS-induced perceptual improvement between hand and face is bidirectional

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Introduction

A case that has received great attention in the scientific community is the so called hand-face plasticity. Studies from the past two decades have report that following deprivation or temporary interruption of tactile inputs arising from the upper-limb there is a large spatial reorganization at level of the primary somatosensory cortex (SI), with the cortical area representing the deafferented limb which is “taken over” by the face area [1–3]. Reorganization across the hand-face border has long been considered as negative, since the competitive phenomena thought to exist between neighbouring regions have typically been associated with adverse psychophysical outcomes, such as painful phantom sensations [4,5]. Recently, however, we demonstrated that reorganization across the hand-face border caused by *increasing* rather than *decreasing* afferent inputs to the hand is associated with positive behavioural outcomes. Using a repetitive somatosensory stimulation (RSS) protocol whereby the fingertip is passively exposed to tactile stimuli [6–8] we demonstrated that another form of, non-competitive, plasticity exists across the hand-face border. We found that repetitive stimulation of the right index finger (right-D2) resulted in improved tactile acuity at that

fingertip and on the face [9,10] . This was the first time that stimulation at one site resulted in perceptual benefits at both the stimulated fingertip and the non-stimulated face. In addition, very new finding revealed that the same RSS on the right-D2 does not result in improved tactile acuity at the anatomically closer forearm, thus suggesting one privileged relationship between the face and the hand. These results attest to the importance of the face-hand relationship and raise the question of a possible bi-directional nature of the hand-face plastic changes. That is, can stimulation on the face improve perceptual acuity at the stimulation site but also at the non-stimulated hand? In order to test this question we investigated whether a local improvement in tactile acuity can be induced by stimulating the face, and whether this improvement transferred to the fingertips. To do this we applied RSS on the face and evaluated both local changes in tactile acuity and changes at the index and little finger fingertips. The aim of these experiments was to improve our knowledge of both the hand-face cross-border plasticity and RSS-induced plasticity.

Methods

Participants. Fifteen right-handed (according to the Edinburgh Handedness Inventory, mean score $95.33 \pm SD 7.43$) healthy adults participated in this study (8 female, mean age $24.40 \pm SD 2.67$). The study was performed in accordance with the 1964 declaration of Helsinki, Good Clinical Practice Guidelines, French Law and was approved by the local ethical committees. All volunteer participants received detailed information about the procedures and gave written informed consent before starting the experiment.

Experimental design. The experiment took place over two consecutive days. On the first day, participants underwent a practice session in order to become familiar with the two-point tactile discrimination task used to evaluate tactile acuity. After this practice session they then underwent their first experimental session (Session 1) in which their two-point discrimination (2PD) threshold was measured for the right and left upper-lip and index and little finger fingertips. On the second day, two further 2PD task session were performed, one before (Session 2) and one after (Session 3) three hours of repetitive sensory stimulation applied to the right upper-lip.

Repetitive Somatosensory Stimulation (RSS). The RSS protocol we used is a standard tactile, attention-free, passive stimulation method based on the Hebbian postulate that the simultaneous activation of several cutaneous receptive fields is able to produce temporally correlated inputs and to induce plastic changes in somatosensory cortex which then result in tactile perception changes [6-15]. Previous RSS studies have almost exclusively applied the stimulation to the volar surface of the right index finger (right-D2). Here, we investigated its effects when applied to the face. In all participants, a vibro-tactile device controlled by an MP3 player was taped to the right upper lip, over the region of skin between the upper lip and the nose (Figure 1). We created a plastic glasses-like support that could be easily worn by participants, and which served to ensure maximum comfort for the participant and to keep the device in contact with the same skin position during the three hours of stimulation. The vibro-tactile device consisted of a small, 8 mm diameter, membrane attached to a solenoid that moved the membrane to generate the tactile stimuli. This device was placed at an angle of 45° (with respect to the longitudinal body axis) between the upper lip and the nose. To prevent habituation during the three-hour stimulation period, the solenoid applied brief (10 ms) supra-threshold tactile stimuli with inter-stimulus intervals ranging from 100 to 3000 ms in a pseudo-randomized order. The mean stimulation frequency was 1 Hertz on average and the frequency distribution was Poisson. During the stimulation period participants could move freely and were explicitly instructed to pay no attention to the stimulation but instead to continue with their daily activities (for example reading a book or watching a movie).

Tactile acuity assessment: two-point discrimination (2PD) task. The 2PD task is a well-known method used for measuring tactile acuity in humans [9], [10], [13]. We used this method to measure spatial discrimination thresholds of different body regions. For each participant for each body region the skin was touched with one or two probes with different distances between them and the participant had to report whether they felt “one” or “two” probes. They were instructed to be accurate and answer “two” only when they clearly perceived two distinct probes. No feedback was given during the task. Throughout the experiment the participant was blindfolded. The 2PD task were assessed using eight probes, one with a single tip and seven with two tips separated by various distances. Because of basic differences in absolute sensitivity between body parts, different sets of distances were used for D2 (0.7, 1.0, 1.3, 1.6, 1.9, 2.2, 2.5 mm), D5 (1, 1.4, 1.8, 2.2, 2.6, 3.2, 4 mm) and the upper

lip (2, 3, 4, 5, 6, 7, 8 mm). For every site, each probe was tested 8 times in a pseudo-randomized order (no more than two consecutive repetitions of the same probe), resulting in 64 trials. Tips were always presented parallel to the longitudinal axis of the fingertips and face. When we tested the fingers, the eight probes were mounted on a rotatable disc which permitted rapid and unpredictable switching between distances. Participants were instructed to relax the hand and the forearm and to remain still. When we tested the upper lip, the probes were mounted on individual plexiglass sticks with ferromagnetic bases. To avoid face movements, the participant's head was stabilized using a head rest, their hands rested on the table, and they were instructed to keep their face and hands relaxed and immobile. Stimulation to the face was delivered manually by the experimenter perpendicular to the skin's surface to ensure that both tips (for the seven two-tip probes) touched the skin's surface at the same time. At the beginning of each testing block the single probe and the two-tip probe with the largest tip separation (2.5 mm for D2; 4 mm for D5; 8 mm for upper lip) were presented three times to the participant while the experimenter said "one" or "two". Once participants declared that they clearly felt the difference between these two probes the testing began and lasted approximately 10 minutes for each body part.

Data analysis. For each body part and 2PD task session the participant's responses were plotted as a function of distance between the probes and the psychometric function was fitted with a binary logistic regression. Threshold was then calculated from the fitted data, i.e. the distance at which they responded "two" 50% of the time. Pre- and Post-RSS thresholds were compared to evaluate possible changes in acuity due to the repetitive stimulation. We defined the Pre-RSS threshold as the average of the thresholds from Sessions 1 and 2 and the Post-RSS threshold as the threshold in Session 3. To make sure that any possible change in performance found after the application of the RSS was due exclusively to the stimulation and not to any effect of training or re-testing, we analyzed performance stability between the two baseline sessions (Session 1 and Session 2) by comparing thresholds measured in these sessions using paired t-tests. For each region, the effect of RSS on the face was evaluated by examining the Pre/Post difference using repeated measures ANOVAs with SIDE (Right/Left) and SESSION (Pre/Post) as factors. Bonferroni post-hoc analyses following rmANOVAs were performed (* $P < 0.05$). In addition, Pre- and Post-Sessions threshold changes were calculated and compared to zero using simple t-tests. Threshold changes between the Pre- and

Post-Sessions were calculated for each participant and each area as follows: [(Threshold Post - Threshold Pre) / Threshold Pre] *100. All statistical analyses were performed using Statistica® (v.12, StatSoft). Data were checked for normality using Kolmogorov-Smirnov tests. All data are expressed as mean ± standard error of the mean (SEM).

Results

We evaluated the tactile acuity of the right and left upper-Lip, index finger (D2) and little finger (D5) tips in three experimental sessions, two before and one after the application of RSS to the right upper-Lip. Thresholds were statistically stable across the two baseline sessions for all three regions (all p s > 0.05). For the upper-Lip, the two-way rmANOVA revealed a significant main effect of SESSION ($F_{(1,14)} = 16.65$, $p = 0.001$), meaning that tactile acuity improved on both sides of the upper lip following three hours of RSS on the right upper-Lip. For D2, the two-way rmANOVA revealed a significant main effect of SESSION ($F_{(1,14)} = 5.541$, $p = 0.034$) and a significant SIDE x SESSION ($F_{(1,14)} = 7.515$, $p = 0.016$) interaction. Bonferroni post-hoc analyses showed that 2PD thresholds decreased significantly at right-D2 only ($p = 0.008$), while no significant change was found at left-D2. Finally for D5, the two-way rmANOVA showed neither significant main effect nor an interaction. Thus, in addition to improving the acuity of the stimulated right upper lip, RSS on this site also improved the acuity of the unstimulated (but anatomically close) left upper lip as well as the anatomically distant right-D2 (Figure 1).

To better estimate the amount of RSS-induced changes and compare them across the different regions, we expressed the threshold changes between Pre- and Post-RSS sessions as the percentage of the Pre-RSS session. When we submitted these threshold changes to t-tests against zero we observed the same results as with the rmANOVA: the percentage of threshold change was significant only for the right upper-Lip [$t(15) = -3.256$, $p = 0.005$], left upper-Lip [$t(15) = -3.073$, $p = 0.008$] and right-D2 [$t(15) = -4.301$, $p < 0.001$] (Figure 2). Even if not statistically significant in any of the analysis we performed, Figure 2 clearly shows that the percentage of threshold change at right-D5 was in the direction of impairment in tactile acuity for this finger. Individual distribution of changes between Pre-RSS and Post-RSS which is displayed in Figure 3a shows that this tendency was present in 10 of the 15 participants, a tendency that is reflected in the positive percentage threshold change seen in Figure 2. To better investigate the threshold change at right-D5 and rule out the possibility that the lack of

significance for this finger was due to the average between the two Pre-RSS sessions (Session 1 and Session 2), we statistically compared the thresholds of each region between Session 2 and Session 3 (Post-RSS) using three separate repeated measures ANOVAs, with SIDE (right/left) and SESSION (Pre/Post) as factors. This analysis showed significant main effect of SESSION for both upper-Lip ($F_{(1,14)} = 15.173$, $p = 0.002$) and D2 ($F_{(1,14)} = 8.282$, $p = 0.012$), while once more no significant effect was found for D5. Regarding D2, the interaction SIDE x SESSION was not statistically significant and this might suggest that both left-D2 and right-D2 thresholds changed between Session 2 and Session 3. Contrariwise, the visual inspection of individual threshold changes between these two sessions (Figure 3b) clarified that changes were more consistent across participants for right-D2, while changes at left-D2 were equally balanced around zero.

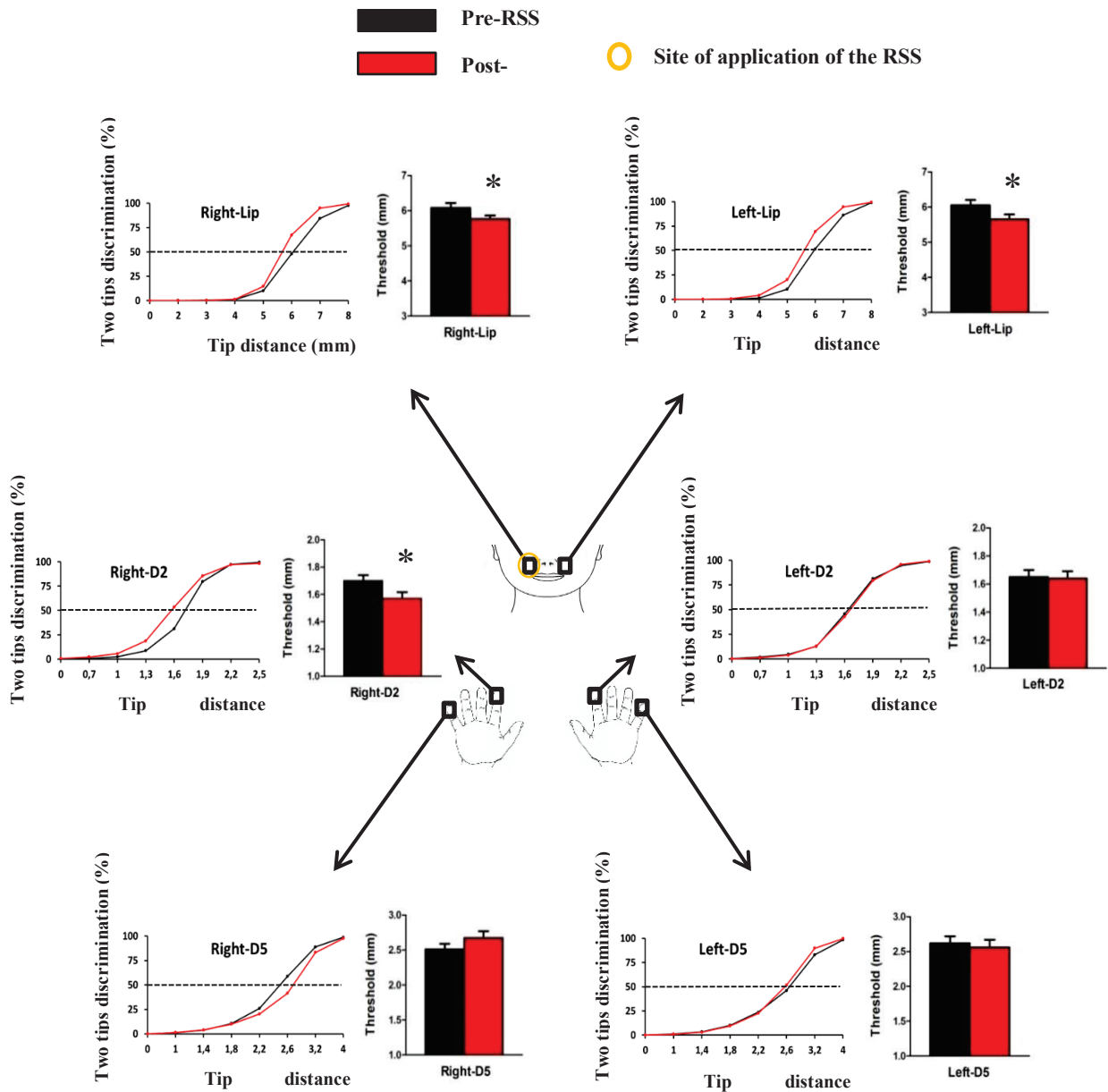


Figure 1. Changes in tactile acuity at the upper-Lip, index, and little fingers following RSS on the right upper-Lip. For each body part changes are displayed using average psychometric curves and bar plots. Psychometric curves: mean psychometric curves Pre- (black) and Post-RSS (red), which the horizontal line indicating the threshold value. Bar plots: mean two-point discrimination threshold Pre- (black) and Post-RSS (red) (mean \pm SEM). Threshold changes were statistically significant at the stimulated right upper-Lip and

unstimulated left upper-Lip and right-D2 (rmAnovas and Bonferroni post-hoc tests, $P_{\text{Bonf}} < 0.05$).

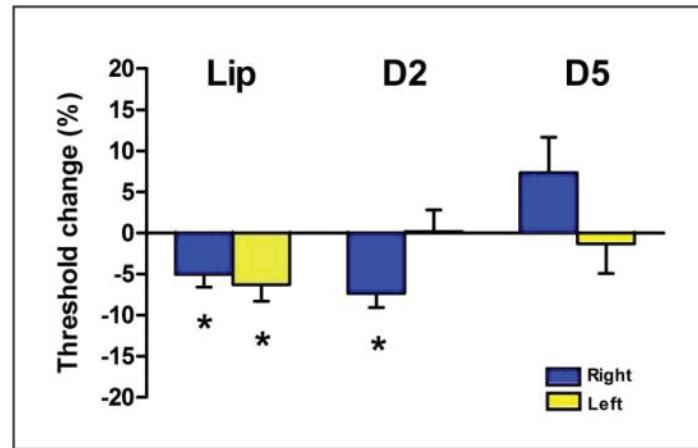
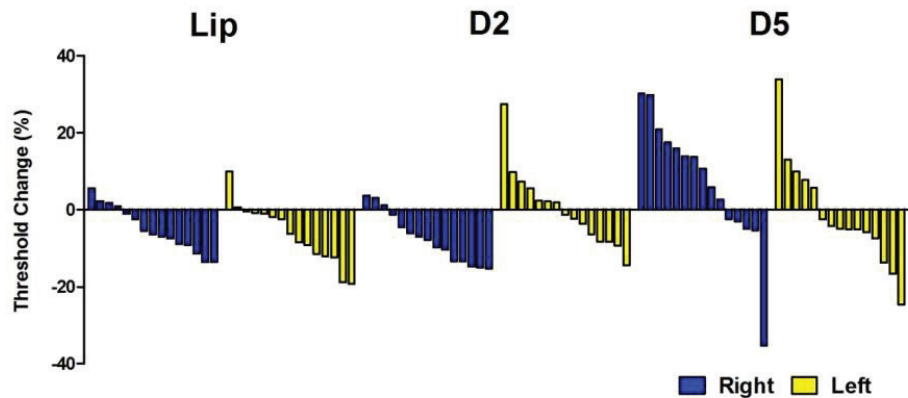


Figure 2. RSS-induced threshold changes expressed as a percentage of the threshold Pre-RSS. Mean two-point discrimination thresholds changes displayed for the six tested body parts (mean \pm SEM) following RSS on the right upper-Lip. Each threshold change was compared to zero. T-tests were significant ($p < 0.05$) at both sides of the upper-Lip and on the right-D2.

a) Post/Pre



b) Post/S2

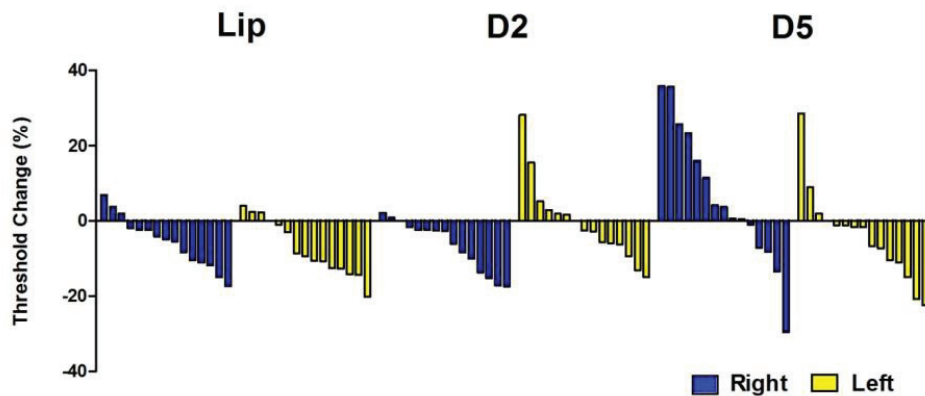


Figure 3. Percentage thresholds changes after RSS for each participant and each tested body part. a) Threshold changes after RSS were expressed as percentage of the Pre-RSS threshold (we defined as Pre the average of the thresholds from Sessions 1 and 2). **b)** Thresholds changes after RSS were expressed as percentage of the Session 2 thresholds (i.e. calculating the session immediately before the RSS only). In both graphs, participants are not represented in the same position across different body parts and graphs as the changes are rank ordered. Note that in both graphs changes in threshold are more consistent across participants at both sides of upper-Lip and right-D2 (on the left of both the graphs), while changes in threshold of left-D2, right-D5 and left-D5 (on the right of both the graphs) are reasonably balanced around zero.

Discussion

Today, it is widely accepted that RSS is a valid, training-independent method for improving tactile acuity at the stimulated fingertip (see [7, 8] for review). Data from our group suggested that not only is the stimulated finger improved after RSS, but that index finger stimulation simultaneously results in improvement at several (unstimulated) sites on the face [9, 10]. In light of these results, we asked whether this hand-face transfer was reciprocal, i.e. bidirectional. We found that three hours of RSS applied to the right upper-Lip improved spatial acuity at this site but also at the anatomically close left upper-Lip and the distant right-D2 fingertip. These findings demonstrate that the RSS protocol is not limited to use on the finger, but can also be successfully applied to the face and that face stimulation results in tactile improvement at the stimulated site as well as at other body sites.

Imaging studies investigating the neural substrates underlying tactile acuity changes after RSS suggest that SI is a key site for plastic changes thought to be responsible for acuity improvement [10-12],[15]. Although the exact mechanisms underlying RSS-induced plasticity remain unknown, it is thought to modulate the efficiency of synaptic transmission and has been shown to enlarge the SI representation of the stimulated region. This enlargement is thought to underlie the improved tactile acuity observed after RSS at it provides more resources for processing tactile information. The improvement transfer observed here, and in previous studies from the hand to the face [9, 10] could be due to changes in long-range cortico-cortical connections crossing the hand and face representations in SI [2, 16]. However, also the involvement of subcortical areas has to be considered [17, 18]. Thus, at this stage, the exact mechanisms underlying behavioural changes after RSS at either the index fingertip or the upper-Lip remain speculative. What is clear from the data is that proximity of body parts in cortical maps is not sufficient to ensure the transfer of behavioural changes from the stimulated region. Indeed, some study demonstrated that stimulation of the right index finger does not alter spatial acuity at the cortically close fingers (right-D3: [14]; right-D5: [10]). Thus, connections shared between the hand and face appear to react differently to RSS than those connecting the fingers (at least the index and middle fingers).

This difference could be explained from a functional viewpoint. Indeed, moving to a functional context, if we consider hand and face not as cortical representations but as functional units, hand and face are highly correlated and thus also likely to improve together in their perceptual abilities when an increase of stimuli arises from one them. Even if the fingers of one hand could appear more correlated across them compared to hand and face, it is important noting that the fingers need to be in some sort of “competition” with each other. This competition is particularly necessary to perform spatial or localization tasks with fingers. Several studies report how actually inhibitory interactions exist across fingers [19–23]. In contrast, the relationship between the hand and the face would not require this kind of (possibly) inhibitory relationship between the two body parts. Therefore, the fact to repetitively use and coordinate hand and face, in particular the mouth region, for eating for example, which perhaps is the most innate action we perform many and many times per day, might translate into a stronger connectivity at the level of SI. In this regard, evidences that this intrinsic hand-mouth association in behaviour is still present also into the cortices were found in different studies reporting that some ethological maps are encoded into the human motor cortex [24, 25]. Anyway, further investigations are needed to clarify which mechanism underlies the transfer we found from face to hand here, and from hand to face previously [9, 10].

Beyond the finding of a bidirectional transfer of improvement, another consideration must to be made about the pattern of improvements displayed by the tested body regions. RSS was applied on the right side of the upper-Lip, and improved tactile acuity was found at both sides of the upper-Lip and at the right-D2. On the contrary, no change was found at the left-D2 or at either D5. This improvement transfer seems to be specific for certain regions. This specificity would suggest that the underlying neural changes that bring about the perceptual improvement we observe occur within S1 representation, which contains well-ordered topographic maps and allows for this high spatial selectivity. Indeed, numerous studies have shown changes in SI after RSS. However, we cannot rule out *a priori* any other contribution from different subcortical or thalamic regions [17, 18].

If we first consider the changes at the upper-Lip, improvement transfers from one side to the other, i.e. from the right to the left hemi-body. This is in contrast with the consistently

demonstrated lack of improvement at the left-D2 after RSS on the right-D2 [9], [11], [12] and would suggest that the stimulation on finger and upper-Lip produces two different effects at the homologous region in the contralateral hemisphere. However, caution should be used before asserting this claim. First, based on the poor knowledge we have about RSS peripheral mechanic effect (i.e. RSS effects on the skin surface in contact with the stimulator), we are not able to rule out the possibility that improvement we saw at left upper-Lip is actually arising from mechanic transmission of the stimulation itself. We should consider that RSS on the right upper-Lip was applied very closely to the face midline, about 1 cm apart from the philtrum. Thus, it is possible that mechanic vibration produced by RSS on the right upper-Lip spread to the immediately close left upper-Lip. In this case, the improvement in spatial discrimination found at left upper-Lip would be not remote effect, but rather local effect as well as for the stimulated right upper-Lip. Further investigation is requested to disentangle this question. However, if we interpret as remote and not as local effect (i.e. mechanic transfer) the improvement at left upper-Lip, some reasoning could account for the different outputs shown at the homologous regions left-D2 (RSS on right-D2: no effect) left upper-Lip (RSS on right upper-Lip: improvement). For instance, we cannot do the analogy between these two regions. Indeed, the different body localization (at the body midline for upper-Lips and at the extreme periphery for fingers) makes these regions differently represented within SI. If the upper lips share a bilateral hemispheric representation [27–29], the representation of the fingers in SI is clearly unilateral and confined to the respective contralateral hemisphere [30, 31]. The bilateral representation of the upper lip could reasonably account for the changes found at both upper-lips, while the inhibitory interactions existing between homotopic areas into the two hemispheres [32, 33] could account for the lack of improvement at the homologous left-D2 after the RSS of the right-D2.

Then, if we also consider the change at right-D2, without any change at the left-D2, the transfer of improvement from the stimulated right upper-Lip to this ipsilateral finger is consistent with RSS acting at intra-hemispheric level. In this case, according to the bilateral representation of the upper-Lip and in line with previous finding [9], there would be no transfer from the left (hemisphere contralateral to the stimulation) to the right hemisphere. However, more recent neuroimaging evidence showed bi-hemispheric changes induced by

RSS [10], thus also in this case further investigations are needed to clarify whether RSS-induced effects are only intra- or also inter-hemispheric.

Finally, it is worth discussing the impaired performance at the right-D5. This impairment was never statistically significant in any of the analysis we did. Even if we cannot exclude the possibility that this finger actually had impairment in tactile acuity due to RSS-induced effects, we would rather suggest that this noticeable impairment could be due to fatigue and difficulty in performing the task. Indeed, performing 2PD task is particularly difficult at this region, as proven by its bigger variability compared to the other regions.

Taken all together, these results show that the pattern of changes induced by RSS is much more complex than previously thought. Indeed, we enriched the picture by observing changes in the tactile acuity of both sides of the upper lip and index finger after the RSS on the right upper lip, suggesting the existence of a bidirectional cross-border transfer of improvement from the face to the hand.

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Chapter 5: General Discussion

5.1 Main results

The main objective of the experimental work of this thesis was to investigate the topography of RSS-induced tactile improvement, within and between different body parts, in particular, the hand and face. Two different and complementary research lines were developed. The goal of the first line was to investigate the hypothesis that tactile improvement induced by repetitive somatosensory stimulation (RSS) at one finger (the right-D2) transfers to other non-stimulated fingers. Study 1 was conceived to address this question. The second line of research, investigated in Study 2 addressed two objectives. First, to ascertain whether applying RSS on the Lip improves tactile acuity of this body part. Second, to investigate whether tactile improvement induced by RSS on the Lip transfers to the (non-stimulated) hand.

Study 1 demonstrated that RSS on right-D2 improves tactile acuity *locally* (i.e. at the stimulated right-D2) and also *remotely* in the opposite hand, specifically at D1 and D3 in the left hand. In contrast, no change in tactile acuity was found at D1 and D3 in the right hand, nor at D2 in the left hand. The results of Study 2 revealed that RSS to the right-Lip induced *local* improvement in tactile acuity of this body part, comparable in magnitude to the local improvement found at the right-D2 after RSS on this finger. Moreover, Study 2 also revealed that RSS on the right-Lip produced *remote* improvement, specifically at the unstimulated, but close left-Lip, and at the unstimulated, but distant D2 in the right hand. In contrast, no tactile acuity changes were reported at D2 in the left hand, nor at D5 in either hand.

The results reported in Study 1 and 2 reveal a completely new topography of the perceptual changes in tactile acuity that occur *within* and *between* the hand and the face following the application of RSS. This new topography of RSS-induced changes is more complex than previously thought, and will be discussed in further detail in the next section. Figure 5.1 provides a visual overview of all the results reported in the Chapter 4.

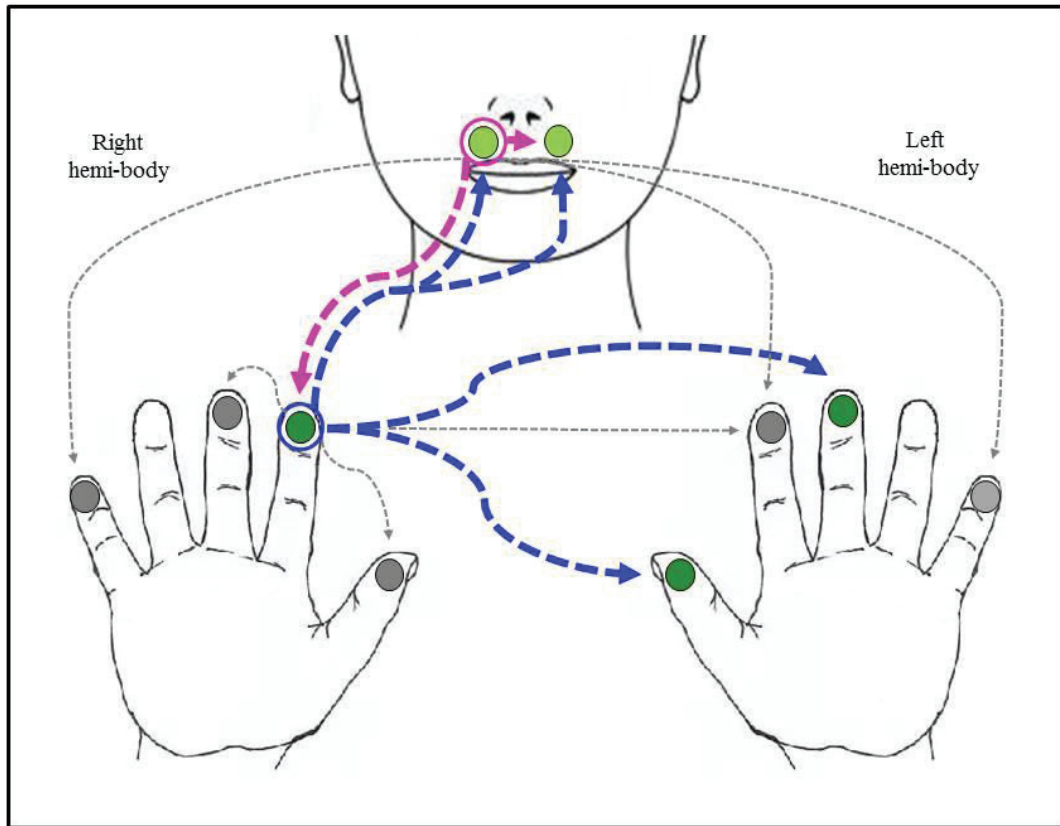


Figure 5.1: Topography of RSS-induced tactile improvement within and between different body parts. This figure summarises the main experimental findings reported in this thesis. Green spots indicate body regions that displayed improved tactile acuity following RSS, while grey spots indicate regions that did not display any improvement. The blue circle indicates the region (right-D2) where RSS was applied in Study 1, and blue arrows show those sites where the improvement transferred (right-Lip, left-Lip, left-D1 and left-D3); on the contrary, no improvement was found at left-D2, right-D1 and right-D3 (grey arrows). The pink circle indicates the region (right-Lip) where RSS was applied in Study 2, and pink arrows show those sites where the improvement transferred (left-Lip and right-D2); on the contrary, no improvement was found at left-D2, right-D5 and left-D5 (grey arrows).

5.2 New topography of RSS-induced tactile improvement

The first finding I would like to discuss is the transfer of tactile improvement from the stimulated finger (right-D2) to two unstimulated fingers (left-D1 and left-D3) in the contralateral hand (Study 1). This finding is particularly important in the RSS literature. Firstly, it demonstrates for the first time that an *inter-finger transfer* of tactile improvement following a training-independent RSS protocol can occur. Indeed, since the transfer was found to occur between the two hands, we should rather refer to it as an RSS-induced *inter-manual transfer* of tactile improvement. Together with (i) the remote tactile improvement at the face, previously reported in Muret's study (2014, see Annex 1) and confirmed here (see Supplementary Section of Study 1), the finding reported in this thesis demonstrates that RSS applied at one finger, besides having a local effect, has remote effects on the face and also on the contralateral hand. Importantly, the transfer to the contralateral hand seems to be highly specific. Indeed, changes in tactile acuity of three fingers of the contralateral hand (left-D1/D2/D3) were investigated, but significant changes were reported only at the left-D1 and left-D3. On the contrary, left-D2 did not display any noticeable change in its tactile acuity, as was largely expected from the results of numerous previous studies (Godde et al., 2000; Pleger et al., 2001, 2003; Hodzic et al., 2004; Dinse et al., 2003a,b; Bliem et al., 2008; Hoffken et al., 2007; Muret et al., 2014, 2016). Thus, the application of RSS on the right-D2 results in improved tactile acuity of the two adjacent D1 and D3 fingers, but in the left, contralateral hand. In contrast to this *inter-manual* transfer, no *intra-manual* transfer of tactile improvement was found in Study 1. The lack of improvement at both right-D1 and right-D3, together with the previously reported lack of improvement at the right-D5 (Muret et al., 2016), appear to suggest that RSS-induced effects do not occur in the ipsilateral (stimulated) hand, but only in the contralateral hand.

While further studies are clearly needed in order to disentangle the possible **mechanisms** accounting for this pattern of effects in the hands, I suggest that alterations of **excitatory-inhibitory interactions within and between fingers** might play a key role in changes found at left-D1 and left-D3, and also account for the lack of changes at right-D1 and right-D3. In order to further investigate this matter and to understand the possible neural mechanisms

underlying the results I observed, a more in-depth discussion of RSS-induced local changes (i.e. at the stimulated finger) is necessary.

5.2.1 Putative mechanisms for *in finger* RSS-induced effects

RSS of a finger induces transitory cortical activity changes in the SI representation of this finger (Pleger et al., 2001, 2003; Dinse et al., 2003; Godde et al., 2003; Hodzic et al., 2004; Höffken et al., 2007) and transitory behavioural changes in tactile spatial discrimination at this same finger (Godde et al., 2000, 2003; Pleger et al., 2001, 2003; Höffken et al., 2007; Dinse et al., 2003a,b; Bliem et al., 2008; Muret et al., 2014, 2016). Depending on the different imaging techniques used, the cortical changes are expressed in terms of an *enlargement* (Pleger et al., 2003; Hodzic et al., 2004) or a *shift* of the dipole source (Pleger et al., 2001; Dinse et al., 2003; Godde et al., 2003; Muret et al., 2016) of the stimulated finger's representation. This 'reorganization' of the stimulated finger's area could be interpreted as evidence that RSS leads to the recruitment of additional processing resources for information coming from the stimulated finger - a sort of additional cortical magnification - which would be responsible for the associated perceptual improvement (Pleger et al., 2001; 2003). According to this hypothesis, increasing the number of cells available to evaluate the stimulus will increase the precision in the judgment and this would explain how cortical recruitment, the increase in the size of the cortical area representing the stimulated sensory surface, might account for perceptual learning (Gilbert et al., 2001).

However, this hypothesis is partially inconsistent with evidence I reported in chapter 3 showing that RSS does not lower absolute touch threshold (Bliem et al., 2008; Dinse et al., 2003b; Kalisch et al., 2007) but only two-point discrimination threshold (for example Godde et al., 2000; Pleger et al., 2001, 2003; Muret et al., 2014, 2016). How is it possible that cortical recruitment can lead to lowered two-point discrimination thresholds but no change in absolute touch threshold? Apparently, other mechanisms have to take the field to produce the selective effects we saw after RSS (improvement in spatial discrimination but no change in absolute touch threshold). The fact that RSS seems to affect only tasks that involve spatial discrimination features, like two-point discrimination (for example Godde et al., 2000; Pleger et al., 2001, 2003; Muret et al., 2014, 2016) or grating orientation (Hodzic et al., 2004)

suggests that these effects, at least in the stimulated finger, are obvious only when more than one skin site is stimulated simultaneously. This means that RSS-induced effects are apparent only when neighbouring population activation peaks are evoked simultaneously. This clearly puts forward the involvement of lateral inhibition in explaining the specific alteration in discrimination of spatial features with not change in absolute touch threshold.

As reported in Chapter 1, lateral inhibition is a physiological mechanism that accounts for two-point spatial discrimination in fingers and other body regions. Lateral inhibition works exciting an interneuron which in turn suppresses the activity of principal cells, which are different than those that gave rise to the interneuron excitation (Isaacson and Scanziani, 2011; Roux and Buzsaki, 2015). Specifically, in spatial discrimination, when two close tactile stimuli evoke two activations peaks, lateral inhibition suppresses the cortical activity in between the two peaks, allowing for a clearer perception of two different stimuli (see Figure 1.4 in Chapter 1). Thus, under normal conditions, the presence – and likely even the *increase* – of lateral inhibition may allow for a finer spatial discrimination.

According (i) to its physiological role in spatial discrimination and (ii) to behavioural data in literature, an **increased lateral inhibition** would perfectly match with the improved spatial discrimination found systematically following RSS. Indeed, RSS would excite more cells but also more interneurons, as shown by the increased BOLD activation (Pleger et al., 2003; Hodzic et al., 2004); as a behavioural consequence, increased lateral inhibition would sharpen the tuning leading to improved two-point discrimination.

Contrariwise, a second hypothesis of **reduced lateral inhibition** following RSS would be consistent with a larger expansion of the stimulated finger representation. In this case, RSS of several receptive fields would produce a weakening in the strength of inhibitory interactions, possibly resulting in an enlarged cortical representation for all stimulated skin sites. Indeed, reducing the inhibitory interactions would allow the co-existing activation of an increased number of cells which would make more resources available for the sensory processing of tactile stimuli. Thus, the reduced *but still present* lateral inhibition in the cortical populations of the stimulated finger would allow for (i) the activation of an increased number of cells leading to (ii) a finer spatial discrimination and (iii) a larger representation of this finger (Pleger et al., 2016). Experimental evidence supporting RSS reduces inhibition within the

stimulated finger comes from Höffken's study (2007). They showed that RSS reduces paired pulse suppression in the SSEPs of the stimulated finger and interpreted the reduced paired-pulse suppression as a reduction of intra-cortical inhibition (Höffken et al., 2007). On the same line, other studies suggested that a reduced intra-cortical inhibition could be involved in RSS-induced effects (Wilimzig et al., 2012; Pleger et al., 2016).

Thus, despite the involvement of lateral inhibition in RSS plasticity would seem to be quite agreed, if it goes in the direction of increase or decrease is not yet well-defined and further investigation will be necessary to clarify the issue. Indeed, RSS plasticity has been investigated mostly in regard to the effects it can produce rather than in regard to the mechanisms can underlie it. Albeit there is still so much to be investigated at physiological level, several RSS-induced effects are well-known, both at neuroimaging and behaviour level, while the knowledge we have about the possible underlying mechanisms is scarce.

5.2.2 Putative mechanisms for *between fingers* RSS-induced effects

So far, changes in excitatory-inhibitory connections have been exclusively discussed in regard of the stimulated finger's representation, without considering changes at the representations of adjacent fingers. At this stage of the discussion, we have to address the question of what may happen to *inter-fingers intra-cortical inhibition*. To this regard, Höffken's study (2007) did not provide any information about a possible either reduction or increase of inter-fingers intra-cortical inhibition. Underlying the fact that any hypothesis is purely speculative in absence of adequate electrophysiological evidence, I would suggest that changes at the cortical representation of the stimulated finger would produce a large inhibition *between* the RSS stimulated finger and its adjacent ones. Indeed, the *enlarged* representation of the stimulated finger (Pleger et al., 2003; Hodzic et al., 2004) would put this finger in a 'favored' condition compared to the adjacent fingers (whose representations do not increase). This, in turn, would strengthen inhibitory interactions between the stimulated finger and the latter. In line with this possibility, I would suggest that this inter-fingers inhibition might also account for the lack of improvement at right-D1 and right-D3 (no intra-manual transfer) and a cascade of inhibitory interactions, for the transfer of improvement found at left-D1 and left-D3 (inter-manual transfer).

In order to avoid confusion between intra-finger and inter-fingers inhibition, from now on I will refer to “lateral inhibition” as the inhibitory connections existing among neurons representing skin regions within one finger and to “surround inhibition” as the inhibitory connections existing among neurons representing skin regions between adjacent fingers (Tanosaki et al., 2002).

The hypothesis of increased surround inhibition, irrespective of the directional (increase/decrease) change in lateral inhibition occurring within the cortical population of the stimulated finger, emerges from neuroimaging evidence of enlarged and stronger BOLD response after RSS evoked by tactile finger stimulation in that region (Pleger et al., 2003; Hodzic et al., 2004). Such an enlarged representation would perturb the reciprocal inhibitory relationships between the RSS stimulated finger and the adjacent fingers (Biermann et al., 1998; Tanosaki et al., 2002; Hoechstetter et al., 2001; Zhu et al., 2007). Indeed, several studies show that, because of the existence of between-fingers inhibitory connections, the strength of the somatosensory response to stimulation of a single finger is attenuated by simultaneous stimulation of an adjacent finger. Further, the magnitude of this suppression is bigger for closely adjacent fingers and decreases with increasing finger separation. Following RSS, these inhibitory connections might be increased. In particular, surround inhibition exerted by the stimulated finger toward close other fingers representations may increase. Thus, this putative **increase of surround inhibition** exerted on the right-D1 and right-D3 by the right-D2 would prevent these fingers from improving in spatial discrimination. In principle, this inhibition could even deteriorate spatial discrimination at these two fingers, but so far the data do not support this possibility, at least using the 2PD task. It would be interesting to investigate this possibility using different, possibly more sensitive tasks.

In turn, the increased surround inhibition exerted by right-D2 on right-D1 and right-D3 might also account for the improved spatial discrimination found at the left-D1 and left-D3. Proper dynamics in neuronal networks can only be maintained if the excitatory forces are counteracted by effective inhibitory forces and vice versa, otherwise the continuous activation of a stimulus would produce a cascade of events that led to functional breakdown. It follows from the principles of inhibition, which is nowadays thought to be important for cortical processing in the intact brain (Wood et al., 2017; Roux and Buzsaky, 2015; Carcea and

Froemke, 2013; Isaacson and Scanziani, 2011), that this increased inhibition, as well as any other form of external perturbation, needs to be *balanced* through excitatory-inhibitory interactions. In this frame of dynamic balance/re-balance of excitatory-inhibitory interactions, the stronger inhibition at right-D1 and right-D3 might be re-balanced by *releasing from inter-hemispheric inhibition* their two homologous fingers, i.e. left-D1 and left-D3. Similar to intra-cortical suppressive interactions between adjacent fingers (Biermann et al., 1998; Tanosaki et al., 2002; Hoechstetter et al., 2001; Zhu et al., 2007), suppressive inter-hemispheric interactions also exist between homotopic regions (Calford & Tweedale, 1990; Werhahn et al., 2002a,b, Bjorkman et al., 2004a). Thus, the inhibitory effect exerted transcallosally by right-D1 and right-D3 over the homologous left-D1 and left-D3 would be weakened. It follows that cortical populations of left-D1 and left-D3 would be *less inhibited* as compared to the cortical populations of their homologous fingers in the right hand, possibly leading to the improved spatial discrimination we observed at these fingers (inter-manual transfer). *Reduced inhibition* (arising from the re-balance of increased surround inhibition) within the cortical populations of left-D1 and left-D3 might thus be one likely explanation for their improved performance.

Yet, inter-hemispheric release from inhibition between homologous D1 and D3 in the two hands is not the only possible mechanism. A second, non-mutually-exclusive mechanism would involve again a release from inhibition, but intra-cortically, i.e. between the left-D2 and its adjacent left-D1 and left-D3. Indeed, changes in inhibitory interactions at the cortical population of the stimulated right-D2 would not only produce *increased surround inhibition* with the adjacent right-D1 and right-D3, but also *increased inter-hemispheric inhibition* towards the homologous left-D2. In this second case, the increased inhibition at the left-D2 (not displaying any perceptual worsening, similarly to the right-D1 and right-D3) might be re-balanced by *releasing from intra-hemispheric inhibition* its two adjacent fingers, i.e. left-D1 and left-D3. Similarly to the first mechanism, left-D1 and left-D2 would then be *less inhibited* as compared to the cortical populations of their adjacent left-D2, leading to the improved spatial discrimination we observed at these fingers (inter-manual transfer). It is worth noting that left-D2 would be *more inhibited* whatever is the involved pathway. In the first case (releasing from inter-hemispheric inhibition), the increased inhibition at the left-D2 might favour disinhibition of left-D1 and left-D3 under the influence of reduced interhemispheric

inhibition from right-D1 and right-D3. Alternatively (releasing from intra-hemispheric inhibition), the increased inhibition at the left-D2 might be the principal mechanisms for the inter-manual transfer so that left-D1 and left-D2 would be influenced by the disinhibition arising from this finger, and inhibitory interactions from right-D1 and right-D3 would favour this disinhibition without being its principal cause.

Given that at this stage I have only behavioural data, I am not able to neither endorse one or the other mechanism as the leading candidate for such behavioural effects. What is also possible is that the two mechanisms act concurrently to respond to the cascade of changes in inhibition brought by RSS. A possible model illustrating these potential mechanisms is included in chapter 4, in the Discussion section of Study 1. Irrespective of the precise (combination of) mechanisms the remote improvement may rely upon, there is improvement from a body region to a physically (not cortically) adjacent body region. In this regards, RSS-induced inter-manual transfer of improvement seems to be mediated via callosal interhemispheric connections through right-D1 and right-D3 and/or homologous left-D2 (Manzoni et al., 1980; Innocenti, 1986; Calford and Tweedale, 1990; Iwamura, 2000; Henry and Catania, 2006). Despite their hypothesised role in the transfer of RSS-induced plasticity, these regions themselves do not appear to be affected by RSS – at least behaviourally within the limits of the sensitivity of the test I used (2PD task). RSS-induced plasticity might thus transfer the behavioural improvement *beyond* the cortically closer (and inhibited) areas (in the specific case, right-D1 and right-D3). In this regard, it would be interesting to investigate whether any effect in tactile perception could be observed after right-D2 RSS on right-D4, so far not investigated in any study, but immediately adjacent to the inhibited right-D3.

5.2.3 Putative mechanisms for effects produced by RSS of *Lip*

This thesis contains the first findings showing that RSS applied not only on the finger, but also on the lip, produces changes in tactile acuity, both locally (on the stimulated finger/lip) and remotely (on cortically adjacent but also non adjacent body parts, see Study 2). The first element to be considered is the fact that RSS-induced *local effects are similar* in improving spatial discrimination of different body parts: fingertip (for example Godde et al., 2000;

Pleger et al., 2001, 2003; Muret et al., 2014, 2016), forearm (Muret and Dinse, 2018) and lip. This suggests that perceptual effects arising from the stimulation are similar and their emergency is not limited to a given body part.

Besides producing similar local effects, the effects that lip-RSS produces remotely might be different compared to the remote effects produced by finger-RSS. Indeed, while the latter does not improve the perception of adjacent fingers (though on the same hand), RSS of the right-Lip does improve the tactile perception of the adjacent left-Lip (though on the other hemi-face). In principle, the origin of the left-Lip improvement might be due to either a transfer of improvement from the stimulated right-Lip or a mechanical transmission of the stimulation over the skin. Studies investigating cutaneous vibration in hand report that mechanical vibration can propagate away from the origin of contact (Shao et al., 2016), sometimes beyond the hand itself (Delhaye et al., 2012). This demonstrates that when we mechanically stimulate a skin region, the vibration produced by the stimulation spreads far beyond the surface of contact between the stimulator and the skin. If we consider that RSS on the right upper-Lip was applied very close to the face midline (about 1 cm away from the philtrum), it is likely that mechanical vibration produced by RSS on the right upper-Lip spread to the immediately close left upper-Lip. In this case, the improvement in spatial discrimination found at left-Lip would not be a remote effect, but rather an extension of the local effect of the stimulation, similar to that observed for the stimulated right-Lip. Whatever the origin, following lip-RSS *spatial discrimination improvement* emerged across both hemi-lips. At a first look, this transfer of improvement would contrast with the lack of intra-manual transfer of improvement seen following finger-RSS. This would suggest that surround inhibition mechanisms accounting for the lack of intra-manual transfer might not be involved in lip-RSS changes. However, if it is true that right-Lip and left-Lip are adjacent, it is also true that the transfer of improvement from the first to the second crosses the body midline (similarly to the between-fingers interhemispheric transfer of improvement). To address the question whether lip-RSS involves mechanisms of surround inhibition, similarly to the mechanisms suggested for finger-RSS, future studies should test for changes in tactile perception at the adjacent right-Cheek.

The second body region where improvement transferred following RSS of the right-Lip was the right-D2. In my investigation, four fingers were considered (right/left D2 and D5) but significant tactile improvement was found at this finger only. As for the lack of improvement at the right-D5, as well as possible changes at other fingers in the right hand, further investigation are needed. Considering from the one side the close relationship between hand and face and from the other side the existence of inhibitory connections between fingers together with the lack of intra-manual transfer, it would be interesting to ascertain which of the two arguments (hand-face relationship or between-fingers interactions) would be mainly involved in lip-RSS plasticity. As a first attempt, lip-RSS might produce a graded improvement across fingers, perhaps following the fingers somatotopic representations, with a gradient of intra-manual improvement decreasing from D1 to D5. This hypothesis would explain the lack of improvement at the right-D5. Concerning the lack of improvement in the left hand (contralateral to the stimulated side of the lip), particularly at the left-D2, it might be consistent with an intra-cortical model of RSS-induced changes, as I will discuss below. However, as previously discussed for the transfer of improvement at the left-Lip, it should be noticed that the stimulation of the right-Lip could have propagated to the left-Lip. Thus, left-lip should be considered as stimulated through RSS as well. In this case, the lack of improvement at the left-D2 would be in contrast with the improvement at the right-D2, since the '*stimulation*' of the left-Lip should similarly improve the left-D2. On the contrary, in the case of improvement at the left-Lip due to an effective transfer of improvement and not to the mechanic transmission of the stimulation, the lack of improvement at the left-D2 would be according with intra-cortical RSS-induced changes.

As for the *face-to-finger transfer* of improvement, I would suggest a closely functional relationship to explain the coincident improvement of these body parts. Repeated use and coordination between the hand and face regions (in particular the mouth region) for instinctive actions like eating, for example, might translate into a stronger connectivity between these regions at the level of SI. In this regard, evidence that this intrinsic hand-mouth association in behaviour is still present also into the cortices were found in different studies reporting that some ethological maps are encoded into the human motor cortex (Desmurget et al., 2014; Graziano, 2016). Thus, in this sort of '*associative mechanism*' hand and face would be highly correlated and thus also likely to improve together in their perceptual abilities when an

increase of stimuli arises from one them. Experimental evidence corroborating the exclusive and strong relationship between hand and face were recently provided by Muret's study (2018). RSS of the right-D2 resulted in improved tactile perception of the lip but not in improved tactile perception of the right-forearm, demonstrating that RSS-induced effects transfer *specifically* between hand and face.

A possible **substrate** for hand-face changes could be represented by long-range cortico-cortical connections crossing the hand and face representations in SI (Manger et al., 1997; Florence et al., 1998; Fang et al., 2002). These long-range and cross-border connections might undergo plastic changes between the hand and the face regions, as described in chapter 2. Indeed, massive cortical reorganization described between the hand and the face representations following loss of inputs from the upper-limb (for example Pons et al., 1991, Flor et al., 1995) was at first thought to arise from widespread expansion of lateral connections in the sensory deprived area, likely driven by intra-cortical sprouting (Florence et al., 1998). However, new findings broke with this view that face-hand plasticity arises from cortical sprouting (Kambi et al., 2014; Chand et al., 2015, see Makin and Bensmaia, 2017 for review). These studies demonstrated that reorganization of SI is not accompanied with either an increase in intrinsic cortical connections between the hand and face representations, nor any change in thalamo-cortical inputs to these areas. On the contrary, changes occurring within the cuneate nucleus in the brainstem would be the only inputs necessary to drive the hand-face plasticity we saw at expressed at the cortical level. Indeed, selective inactivation of a cortical area does not block the emergence of the observed hand-face reorganization, while selective inactivation of the cuneate nucleus completely abolishes the plastic reorganization (Kambi et al, 2014). Thus, even if changes in map representations have been largely reported in cortex, the underlying mechanisms for these changes might be restricted (or predominantly present) in the brainstem.

5.2.4 Sites of action of RSS-induced changes

In this thesis I demonstrated that a passive, attention-free procedure such as RSS can produce finger-to-finger improvement transfer, as is also the case for training-dependent procedures,

albeit with a completely different transfer pattern. In parallel, this procedure can also produce face-to-finger improvement transfer, with a transfer pattern which was completely unexplored before doing this work. Since I have no imaging data but only behavioural data, I can only speculate about the neural site of this improvement transfer. In a previous study showing the first remote (finger-to-face) transfer of RSS-induced tactile acuity improvement (Muret et al., 2014, see Annexe 1) a bilateral tactile improvement at the lip, but an effect ipsilateral to the stimulated finger at the right-cheek were reported. Since the lips are more bilaterally represented than the cheeks (Nevalainen et al., 2006; Blatow et al., 2007; Disbrow et al., 2003), it was first suggested that this pattern of transfer to the face could be consistent with RSS-induced tactile improvement being limited to the left hemisphere (contralateral to the stimulated finger). However, a more recent MEG study (Muret et al., 2016) reported plastic changes following RSS in both hemispheres at the level of SI, thus suggesting that RSS does not only evoke *intra*-hemispheric plasticity. Instead these data suggest that the transfer of RSS-induced behavioural improvements to non-stimulated body parts should be considered within the context of a *bi-hemispheric model of RSS-induced plasticity*.

According to the behavioural data I presented in Study 1, RSS of the right-D2 appears to induce effects only in the contralateral hemisphere for this finger (no inter-manual transfer of improvement to the left-D2). Conversely, extrapolating from the behavioural changes of an inter-manual transfer to left-D1 and left-D3, effects seem to be induced in the ipsilateral hemisphere for these two fingers. Unless the behavioural changes observed in the left hand are due to alterations in the ipsilateral representations of these fingers (something that seems very unlikely given the predominant contralateral representation for the fingers in S1) then these data argue in favour of a bi-hemispheric model of RSS-induced plasticity. This hypothesis that remote RSS effects are accompanied by changes in both hemispheres is in agreement with recent neuroimaging evidence showing bilateral changes in SI after RSS (Muret et al., 2016). Inter-hemispheric communication between homotopic cortical areas would appear to be a likely candidate for these changes (Calford and Tweedale, 1990; Iwamura, 2000; Henry and Catania, 2006)

Concerning Study 2, beyond the finding of a *bidirectional hand-face transfer* of improvement, another point that deserves discussion is the pattern of improvement observed

in the tested body regions. In particular, the fact that face stimulation led to improvement in the right hand only. This observation is consistent with RSS on the lip acting at an *intra-hemispheric* level. If this were the case, then the previous finding of a transfer from right-D2 to both the left and right upper lips (Muret et al., 2014), would be explained by changes in the left hemisphere alone. However, the neuroimaging evidence recalled above showing bi-hemispheric changes induced by RSS of right-D2 (Muret et al., 2016), suggests that further imaging investigations are needed to clarify whether RSS-induced effects between the hand and face are explained by changes within the hemisphere contralateral to the stimulated site or whether there are also changes in the ipsilateral hemisphere. In particular, it will be important to understand why RSS of one finger induces bi-hemispheric changes in hands, while RSS on the right Lip (which itself has a bilateral S1 representation) appears to induce changes only in the right hand (and by inference only in the left hemisphere). As discussed above, in this frame it will be particularly important ascertain whether the improvement at the left-Lip is due to an effective transfer of improvement and not to the mechanic transmission of the stimulation.

In both studies, improvement transfer seems to be specific for certain regions. For example, in Study 1 neither the adjacent (right-D1 and right-D3) nor the homologous (left-D2) fingers were improved, whereas in Study 2 transfer of improvement was limited to the left-Lip (if we consider this improvement as transfer – see previous discussion about mechanical transfer) and the right-D2 (although not all fingers on both hands were tested). Together with imaging and electrophysiological data (Pleger et al., 2001, 2003; Dinse et al., 2003; Godde et al., 2003; Hodzic et al., 2004; Hoffken et al., 2007), this specificity would suggest that RSS-induced changes are expressed within S1, which contains well-ordered topographic maps and thus allows for this high spatial selectivity. But, are the sites of expression coincident with the sites of origin of the RSS-induced effects? In other words, are the mechanisms underlying RSS plasticity occurring in SI, i.e. where RSS plasticity has been thought to be expressed, or anywhere else? Obviously, behavioural data do not allow me to address this question. Several neurophysiological and imaging studies assessing the mechanisms underlying RSS-induced behavioural changes have consistently demonstrated that RSS-induced cortical plasticity is expressed in terms of an *enlargement* (Pleger et al., 2003; Hodzic et al., 2004) and a *shift* of the dipole source (Pleger et al., 2001; Dinse et al., 2003; Godde et al., 2003) of the stimulated

finger's SI representation (Pleger et al., 2001, 2003; Dinse et al., 2003; Hodzic et al., 2004) but also its SII representation (Pleger et al., 2003). In addition, paired-pulse suppression of the stimulated finger's SI representation is suppressed following RSS (Hoffken et al., 2007). However, despite the large body of studies proves that neural correlates of RSS-induced changes are *expressed* within the somatosensory cortex, the possibility that RSS plasticity *originates* elsewhere cannot be rules out *a priori*. In fact, as reported above, recent evidence (Kambi et al., 2014; Chand et al., 2015) completely changed the state-of-art on cortical plasticity, demonstrating that cortico-cortical or thalamo-cortical plastic changes are not necessarily driving the well-known face-hand reorganization described in chapter 2. On the contrary, the hand-face reorganization observed at the cortical level might be expressed at this level, but it appears to originate (at least in part) at the level of the brainstem nuclei. In light of this evidence, in-depth discussion about the neural sites underlying RSS-induced plasticity will be surely necessary to ascertain whether cortex only expresses or also generates all the neural and behavioral effects described in the last two decades following RSS.

5.3 Limitations

Studies reported in this thesis make an important contribution to the current understanding of RSS-induced perceptual changes in tactile acuity. Specifically, the studies I presented demonstrated strikingly how the topography of changes is considerably different from what was previously thought, involving several body parts and directions. However, these studies do not yet provide the complete picture of RSS-induced changes. One first limitation concerns the possible intra-manual transfer of tactile improvement. Data from different experiments (Study 1) did not allow me to definitively state whether RSS is able (or not) to induce *intra-manual transfer* of tactile improvement. Indeed, in our investigations we did not consider D4 or other more proximal, palmar regions of the hand. The reason is purely methodological. The test we used to evaluate tactile acuity and its changes was the two-point discrimination (2PD) task. This task is relatively long, since testing one body region takes about 10 minutes. Considering that in all experiments I performed, six body regions were tested, one single session on 2PD task lasts 1 hour. Again, considering that for each participant I performed 3 different sessions (plus one familiarization session before starting Session 1), the 2PD task

demanded more than 3 hours. Adding another body region into the experiment would have made it excessively difficult for the participants. Indeed, the 2PD task is not an easy task, and intense concentration is demanded to perform it. For all these reasons, I decided to limit to $n=6$ the number of tested body regions for each experiments.

A second limitation of this work concerns the *transfer or no transfer* to the left-Lip (Study 2). Indeed, based on the poor knowledge we have about RSS-induced peripheral mechanical effects (i.e. the effect produced by RSS on the skin surface which is in contact and close to the stimulator), I am not able to rule out the possibility that the improvement I saw at the left upper-Lip is actually arising from mechanical transmission of the stimulation itself. If we consider that RSS on the right upper-Lip was applied very close to the face midline, about 1 cm from the philtrum, it is likely that mechanical vibration produced by RSS on the right upper-Lip spread to the immediately close left upper-Lip. In this case, the improvement in spatial discrimination found at left upper-Lip would not be a remote effect, but rather a local effect. Further investigation is requested to disentangle this question.

5.4 Conclusions and Perspectives

The data I present in this thesis shed new light on the topography of RSS-induced tactile improvement. The demonstration that the improvement transfers from one hand to the other in a completely training-independent procedure, has definitely broken with the past view that only local effects arise from RSS of a single finger. I demonstrated that this is not true, since stimulating one finger with RSS improves tactile acuity of other unstimulated fingers. The demonstration that improvement of finger tactile acuity is also possible after stimulating the face clearly opens a whole new unexplored research field.

These findings have led to several hypotheses regarding the mechanisms underlying the improvement transfer, and future investigations should attempt to disentangle the various hypotheses proposed here. Concerning the inter-finger transfer observed in Study 1, a future perspective will be to investigate the hypothesis that RSS on a finger increases lateral inhibition with adjacent fingers, and thus that RSS increases intra-cortical inhibition. In this context, an electrophysiology study investigating cortical suppression of several adjacent

fingers could ascertain whether RSS actually affects lateral inhibition between fingers. Concerning the face-to-finger transfer observed in Study 2, this pattern needs to be investigated in further experiments. On the one hand, it will be important to test whether perceptual improvement transfers to other face regions (notably the cheek and the chin); on the other hand, further investigation of the improvement transfer to the hand will be necessary to understand the underlying sites of expression of RSS.

It is also important to highlight how these findings can be translated to a clinical application. Indeed, showing that tactile improvement of several stimulated and non-stimulated fingers can be achieved through the simple exposure to RSS for a few hours opens up to the possibility of leveraging this phenomenon for clinical applications, something that has already been positively explored, albeit in small scale. For example, RSS has been shown to improve sensorimotor performance in populations with sensory impairment (olders: Kalisch et al., 2008, 2010; stroke patients: Smith et al., 2009). Furthermore, RSS has been shown to improve not only tactile perception but also general sensorimotor performance, demonstrating how the recovery of sensory acuity plays a key role for the parallel recovery of motor ability. Indeed, even if it is difficult to distinguish and directly correlate sensory and motor impairment, motor impairment is accompanied, often enhanced, by sensory impairment, since sensory feedback is crucial for action.

In the particular case of the face-to-hand transfer of improvement I demonstrated in Study 2, the possibility of translating this finding to a clinical application is not only a perspective but a real project. Indeed, my collaborators and I have conceived a clinical study based on the results found in Study 2. This project has been funded and will begin at the beginning of 2019. The aim of the project will be to investigate sensory improvement in the hands after a protocol of RSS applied on the face of a population of stroke patients.

To conclude, there is still so much to be discovered about RSS-induced plasticity. Some elements have been added with the results of this thesis, many other elements will be added in future investigations.

Annexe 1

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Touch improvement at the hand transfers to the face

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The hand-face border is one of the most prominent features of the primate somatosensory cortex. A reduction of somatosensory input, following amputation or anesthesia, induces perceptual changes across this border that are explained by plastic competitive mechanisms [1–4]. Whether cross-border plasticity can be induced by learning processes relying on increased somatosensory input has been unclear. Here we report that training-independent learning [5] improves tactile perception, not only at the stimulated index finger, but also at the unstimulated face. These findings demonstrate that learning-induced tactile improvement can cross the hand-face border, suggesting that facilitation-based plasticity may operate in the healthy human brain.

Perceptual improvement can be induced by protracted training but also by brief training-independent learning through repetitive somatosensory stimulation (RSS) [5–7]. Applied to the index finger, RSS reliably improves tactile acuity at this finger [6,7], presumably via functional reorganization within somatosensory cortices [6]. Prior investigations concluded that RSS-induced changes were local, as no changes were found either at the adjacent or homologous fingers [7]. To investigate the possible spread of learning-induced changes across the hand-face border we applied RSS to the right index fingertip of healthy participants and tested tactile acuity at the unstimulated face. In experiment 1, two-point discrimination thresholds were assessed using force-controlled devices at the right (stimulated) and left (control) index fingertips (right/left-D2) and above the right and left upper-lip (right/left-Lip) in two groups of 15 participants before and after a three-hour period during which the

RSS device was either ON (RSS_{Exp1}) or OFF (Control_{Exp1}) (Figure S1).

To ensure our RSS protocol replicated the well-established finger-specific improvement of tactile acuity, fingertip thresholds were submitted to a rmANOVA. The triple interaction ($F_{(1,28)} = 5.90, P = 0.022$) revealed a significant decrease in right-D2 threshold after RSS in the RSS_{Exp1} group (Bonferroni-corrected: $P_{\text{Bonf}} = 0.002$), but no changes at left-D2 in this group or at either finger in the Control_{Exp1} group (P -values > 0.9) (Figure 1A). This acuity gain (−15.26% ± 3.85) is consistent with previous work (−15.6% on average; Supplemental Results in the Supplemental Information).

A double interaction from the same analysis on the lip data ($F_{(1,28)} = 7.37, P = 0.011$) revealed significantly lowered thresholds only in the RSS_{Exp1} group ($P_{\text{Bonf}} = 0.002$; $P > 0.9$ in Control_{Exp1} group) (Figure 1A). This indicates a transfer of the RSS-induced behavioural effect across the hand-face border,

likely arising from a spread of plastic changes from the right-D2 somatosensory representation [6] into the face region through horizontal intracortical connections. Although limited in number, these cross-border connections undergo Hebbian-based plastic changes [8] and are the most likely substrate for the interactions observed between the hand and face [2,3].

Notably, tactile improvement was side-specific at the fingers, but not at the lips, making transcallosal transfer unlikely. Instead, given the bilateral representation of the lips within the primary somatosensory cortex [9], the bilateral improvement observed at the lips may arise from transfer of right-D2's representational changes [6] to the neighbouring lips region within the left somatosensory cortices. To test this model of side-specificity, in experiment 2 (Supplemental Information) we measured two-point discrimination thresholds not only at the fingers and lips, but also at the cheeks (represented more

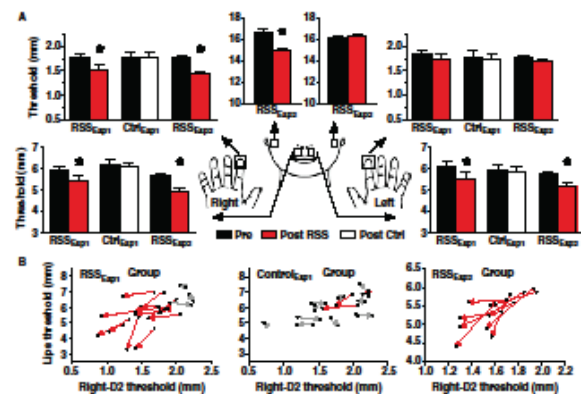


Figure 1. Improvement of touch acuity transfers from the finger to the face. (A) Mean two-point discrimination threshold pre (black) and post the procedure applied to the right-D2 (RSS: red; Control: white), assessed at right/left-D2, right/left-Lip and right/left-Cheek (mean ± SEM; see also Figures S1 & S2). Repeated measures ANOVAs on data from the fingers, lips, and cheeks followed by Bonferroni-corrected post-hoc tests revealed significant threshold decreases ($P_{\text{Bonf}} < 0.05$) at right-D2, both sides of the upper-lip, and right-Cheek in the RSS groups only (Supplemental Results). (B) Vectors showing the consistent relationship between threshold changes at the lips and right-D2 for each participant in the RSS_{Exp1} (left panel), Control_{Exp1} (central panel) and RSS_{Exp2} (right panel) groups. The starting and ending points of vectors respectively represent pre- and post-session thresholds. Red vectors indicate parallel threshold decreases at both right-D2 and lips, whereas gray vectors illustrate other combinations of threshold changes (see also Figure S1).

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contralaterally [9]), before and after RSS (RSS_{Exp2} group). In addition to replicating the significant threshold decreases at both upper-lips ($F_{(1,7)} = 18.25, P = 0.004$) and at the right- ($F_{(1,7)} = 36.56, P_{Bonf} < 0.001$) but not left-D2 ($P > 0.9$; Figure 1A), a side-specific effect was also found for the cheek ($F_{(1,7)} = 21.32, P < 0.001$), with a significant improvement at the right-Cheek only ($P_{Bonf} = 0.005$; Figure 1A), thus supporting our model.

D-prime analyses confirmed sensitivity gains for right-D2, right-Cheek and both upper-lips (RSS_{Exp1}: all P_{Bonf} -values ≤ 0.027 , RSS_{Exp2}: all P_{Bonf} -values ≤ 0.045), with no slackening of participants' response criterion in either experiment (Supplemental Table S1). Furthermore, the stable pattern observed in the equally-sized Control_{Exp1} group, whose baseline thresholds were similar to those of the RSS_{Exp1} group (P -values ≥ 0.8), rules out unspecific contributions of training or attention.

Threshold decreases at the left- and right-Lip were correlated with each other ($r = 0.57, P = 0.026$), but not with right-D2 threshold decrease (P -values ≥ 0.4 ; Supplemental Results). However, 12/15 RSS_{Exp1} participants and all RSS_{Exp2} participants had decreased thresholds at both the right-D2 and lips, whereas this was true for only 3/15 Control_{Exp1} participants (Figure 1B). Interestingly, all RSS_{Exp2} participants also exhibited acuity gains at both the right-D2 and right-Cheek, which tended to correlate ($r = 0.70, P = 0.051$). Averaging across experiments, the mean threshold at the lips and right-Cheek decreased respectively by 10.8% (± 2.8) and 9.8% (± 3.6), which represent 62.4% and 56.6% of the improvement observed at right-D2 (Figure S1C).

The distribution of threshold changes combined with the high proportion of transfer strengthens the hypothesis of a large and robust spread of plastic changes across the hand-face border. Consistent with the intra-hemispheric shift of right-D2's representation following RSS [6], the correlation between gains at both upper-lips and the side-specificity at other body parts support the intra-hemispheric hypothesis. Since there is currently

no evidence that RSS effects transfer to other fingers [7], our findings further imply that training-independent perceptual improvement transfers across the hand-face border, without necessarily transferring within the hand. This may be surprising given the position of the thumb's representation (between that of the index and face [10]), but is consistent with results showing that the thumb's cortical representation is unchanged after RSS of the right-D2 [6]. This might be due to differences in remote and local circuit properties [8], with long-range facilitatory connections allowing hand-face transfer and shorter-range lateral inhibition preventing inter-finger transfer.

The cross-border perceptual improvements reported here provide evidence that passively increasing input to a body part can positively affect touch perception at cortically close, but physically distant body-parts, and thus reveal a novel perceptual learning phenomenon whereby improvement transfers across the hand-face border. To date, the theoretical framework within which hand-face border crossings have been interpreted has been one of 'competition' [1-4], whereby the face cortical area invades the deprived territory after permanent or transient removal of hand afferent inputs [3,4]. Although the present findings might rely on the same connections, the functional context (increased input) and subsequent consequences (acuity gain at non-contiguous body parts) indicate the need to extend the framework of cross-border plasticity beyond 'competition', which might apply to specific conditions of dramatically reduced afferent inputs, to generate new models of cortical plasticity that also account for 'facilitation' based forms of cross-border plasticity.

Supplemental Information

Supplemental Information includes supplemental results, experimental procedures, two figures and one table, and can be found with this article online at <http://dx.doi.org/10.1016/j.cub.2014.07.021>.

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