Somatosensory and multisensory processing of the body in the human brain

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Abstract

Throughout our everyday lives we are exposed to incessant sensory inputs from external sensory stimuli, both proximal and distant, that impact our bodies. Nevertheless the brain constructs a unified representation of the world primarily through continuous integration processing of the simultaneous signals. Two fundamental principles of brain organization were classically associated with the processing and binding of sensory signals. First, according to the sensory division-of-labor principle, multiple sensory inputs are processed independently in different sensory cortices, and then transferred to associative areas where multiple inputs converge and are integrated. The second fundamental principle relates to the topographical organization of the sensory areas, in which nearby points in the stimulated space are represented by the responses of nearby cortical neurons, yielding retinotopic, cochleotopic, and somatosensory or motor somatotopic maps. The prevalent view was that in higher order sensory areas, this topographic organization is gradually replaced by more abstract or complex representations that have much larger receptive fields covering the entire or considerable parts of the sensory world.

Converging evidence in the last ten years however has challenged these canonical organization principles to some extent and suggested that the brain might be organized into task-oriented and sensory modality input independent operators rather than sensory-specific areas. Recent studies have shown that topographic organization is a fundamental principle not only in early sensory cortices but also in higher-order processing regions. However these competing views are far from being fully understood or resolved.

This thesis focuses on the somatosensory system of humans as a model to study these new views of brain organization using functional MRI (fMRI). Since the somatosensory system is involved in cross-modal integration and exhibits a highly somatotopic organization (at least in the first stages of cortical processing), it has

emerged as an appealing model to test these new views and to further postulate a general theoretical framework for such organizational principles. Specifically, I addressed these topics by studying a field which has been less well explored, and tested the topographical biases of the positive and negative blood-oxygenation-level-dependent (BOLD) signals of the tactile evoked imaging responses within and beyond what is commonly assumed to be the somatosensory cortex.

Specifically, using continuous and periodic unilateral tactile stimulation of the entire body and applying phase-locked analysis methods, I verified the well-known contralateral topographical organization of the primary somatosensory homunculus (S1), and observed a gradual shift in the representation of different body parts. Furthermore, I showed that the Penfield homunculus should be modified at the medial wall, since the full-body topographic gradient did not reach close to the corpus callosum medially but rather ended at the highest point of the PCG. I further found that different body segments elicit pronounced negative BOLD responses in both the contralateral and ipsilateral hemispheres but show different patterns. In the contralateral hemisphere, S1 contained a sharpening contrast mechanism in which a combination of positive and negative BOLD was evoked for each of the tested body segments, constructing a negative BOLD homunculus. I further showed that negative BOLD also characterizes the ipsilateral cortex, but in contrast to previous studies and to the contralateral hemisphere, the deactivation was not located solely in the ipsilateral homolog of the stimulated body parts but instead was widespread across many parts of the ipsilateral Penfield homunculus. These results, some confirming and elaborating previous observations and some of which are completely novel, suggest a complex pattern of baseline and activity dependent responses in the contralateral and ipsilateral sides, in which negative BOLD responses characterize both primary sensory-motor areas, and suggest that they are an important component of that sharpens the tuning curves of populations of neurons, as was previously reported for topographic gradients in both the visual and the motor cortices. More generally, the results show that a natural tactile stimulus combined with phase-locked analysis provide a powerful and sensitive tool for the mapping of whole-body somatosensory gradients at the group and single-subject levels, and have some clear practical advantages in both clinical and basic research settings. Thus, these methods should be the current gold standard to map whole body gradients.

In the second part of the thesis I focused on responses in what is usually considered by most researchers even today as the visual cortex. Here as well I found that, passive touch responses were not confined to the somatosensory cortex, but rather revealed a complex pattern in the visual cortex. I showed that passive touch robustly activated the tool selective parts of the Lateral-Occipital (LO) cortex while almost all other occipital-retinotopic-areas were massively deactivated. These passive touch responses in the visual cortex were specific to the hand and upper trunk stimulation. Resting state functional connectivity analysis showed that although different object selective areas in the lateral and ventral occipital cortex were highly interconnected, only Tactile-LO showed extensive connectivity with parietal areas, and was the sole connecting link of this complex to the hand areas in the primary somatosensory cortex. The results suggest that the LO is a fundamental hub which serves as a node between visual-tool-selectivity and continuous passive (and active) touch information from the hand representation in the primary somatosensory cortex, even in the resting state, probably due to the critical evolutionary role of touch in tool recognition and manipulation. These results might also point to a more general principle that recruitment or deactivation of the visual cortex by other sensory input depends on the ecological relevance of the information conveyed by this input to the task or computation performed by each area or network, and that this task selective recruitment might occur even when the information is received passively without any specific cognitive goal. This is a novel observation that expands the theory to a wider set of conditions and will help formulate better predictions concerning other brain areas. The findings also suggest that this observation might rely on a unique and differential pattern of connectivity for each brain area with the rest of the brain.

Altogether the results presented in this thesis suggest that both positive and negative responses reflect topographical biases in which within a given sensory cortex (i.e. somatosensory or visual), each body part only activates functionally relevant subareas, while deactivating the surrounding non-relevant areas. I suggest that the balance between the positive and negative BOLD signal and the ecological relevance of the input at each point in time might be crucial to our understanding of a large variety of intrinsic and extrinsic tasks including low level sensory processing, high-level cognitive functions and multisensory integration.

A letter of contribution

In chapters 2 and 3, Zohar Tal designed the experiments, collected the data, analyzed the data and wrote the chapters. Dr. Ran Geva designed the experiments and collected the data.

Contents

1. Introduction

In the last 100 years, one of the fundamental goals of neuroscience has been to discover the basic principles governing the large-scale organization of the brain. There is a general consensus that the major functional specializations correspond to neuroanatomical structures within the brain, on both the large-scale level (Damasio and Damasio, 2004; Golland et al., 2007; Mesulam, 1998), as well as micro arrangements as neuronal columns (Diamond et al., 2003; Mountcastle, 1997). One such large scale organizational principle is the division of the human brain into separate and unimodal cortical areas according to the sensory modality that elicits them, and into higher-order multisensory areas integrating information from these unimodal cortices (the sensory division-of-labor principle; (Zeki, 1978). In other words, multiple sensory inputs are processed independently in sensory cortices, and then transferred to associative areas where multiple inputs converge and are integrated (Calvert, 2001; Felleman and Van Essen, 1991; Zeki, 1978). Another fundamental property of sensory areas regardless of whether they are visual, auditory or somatosensory, is their topographical organization, in which nearby points in the stimulated space are represented by the responses of nearby cortical neurons, yielding retinotopic, cochleotopic, and sensory somatotopic maps, respectively. In the visual system, the one that has been the most extensively studied so far in this context, the topographic organization is so specific that it serves as the basic way to define the first 8 stations in cortical visual processing (areas V1-V8, Hagler and Sereno, 2006; Wandell et al., 2007). The prevalent view is that in higher order sensory areas, the topographic organization is gradually supplanted by more complex or abstract representations.

However, in the last ten years, a growing body of evidence has challenged these canonical principles of organization. Recent studies have cast some doubt on the sensory-specific and strictly hierarchical nature of brain organization by showing that multisensory integrative processing can take place in traditional unisensory and even in primary areas (Ghazanfar and Schroeder, 2006; Kayser, 2010; Pascual-Leone et al., 2005). Second, the topographical organization principle has been refined, especially by studies in the visual system (Grill-Spector and Malach, 2004; Malach et al., 2002; Sereno and Huang, 2006), which show that higher-order processing regions have clear retinotopic preferences in addition to their selectivity for complex visual features. For example, the parahippocampal place area (PPA) exhibits selectivity to place stimuli (such as pictures of houses) and a peripheral retinotopic eccentricity preference, whereas the fusiform face area (FFA) has a combined preference for face stimuli and a foveal retinotopic eccentricity (Malach et al., 2002). Using phase-locked approaches, recent studies by several groups have identified at least 8 new topographic spatial fields that were found not only in areas in the visual (occipital) cortex which was previously considered to be non-retinotopic (Malach et al., 2002) but even in the parietal and prefrontal cortices (Saygin and Sereno, 2008; Sereno and Huang, 2006). Both in early and higher-order areas, spatial-retinotopic maps have proved to be extremely useful in defining the borders between visual areas (from V1 and V2 and up to V7/V8 and the new fields in the parietal and prefrontal cortex) and the hierarchy of the visual system in general (Wandell et al., 2007). However, much less work has been done (especially in humans) on the somatosensory system. Although the most famous example of topographic organization is probably the classic primary somatosensory homunculus (Penfield and Brodley, 1937; Penfield and Rasmussen, 1950), not even one paper has been devoted to reporting an entire mapping of the somatosensory system using phase-locking approaches which are considered to be the most efficient methods for topographical mapping. This is one of the goals of this dissertation.

In general, functional MRI (fMRI) studies which record blood-oxygenation-level-dependent (BOLD) signals typically report positive BOLD responses (elevation of the signal above baseline) and interpret these as being ''involved'' in carrying out a specific task. Negative BOLD responses which are also seen in fMRI studies received less attention in early studies, and thus were not often reported, or reported without an adequate functional interpretation (Nair, 2005). In recent years, negative BOLD has been studied more frequently, in attempts to associate its physiological source and functional relevance to different brain processes (for review see Goense et al., 2012; Nair, 2005). The current literature on negative BOLD responses in the somatosensory domain is mostly confined to studies of interhemispheric responses; thus it is still not clear to what extent the negative BOLD signal represents a basic component of passive somatosensory responses. This question is another focus of this thesis.

In this dissertation I deal with the somatosensory system of humans as a model to study these new conceptualizations of brain organization using fMRI. Using phase-locked approaches and other complementary methods I discuss the prevalence of topographical biases of tactile responses both within the somatosensory cortex (section 1.1) as well as in cross-modal integration processes in what is classically termed the visual cortex (see section 1.2). I also address these topographical biases by an assessment of the positive and negative BOLD signals (section 1.3) of the tactile evoked responses. The two main research goals of my thesis were to map full body gradients in S1, and identify negative BOLD responses in the contralateral and ipsilateral hemispheres and characterize their putative topographical biases. In addition, I explored the pattern of tactile evoked response in the visual cortex, and tested for task-related cross-modal effects of both positive and negative BOLD signals.

1.1. Topography and cortical gradients in the brain and the topographic representation of passive touch

Sensory modalities are characterized by a topographical mapping of the sensory world onto the primary sensory epithelia (Besle et al., 2013; Engel et al., 1994; Mancini et al., 2012; Orlov et al., 2010; Sánchez-Panchuelo et al., 2014; Sereno and Huang, 2006). Topographic maps provide a processing mechanism that reduces the restrictions of long, slow, and metabolically demanding connections (Kaas, 1997), and thus has computational as well as developmental and evolutionary advantages (Aflalo and Graziano, 2006; Chklovskii and Koulakov, 2004; Kohonen and K., 1989). Recent studies show that topographic organization characterizes not only the sensorimotor areas but also higher-order cortices, and processing functions such as memory, spatial attention and numerosity (Hagler and Sereno, 2006; Harvey et al., 2013; Kastner et al., 2007; Silver et al., 2005). In fact, natural signals perceived by the nervous system, either from the external world, the internal milieu or the intrinsic system are usually composed of a series of successive elements in time or space (Golland et al., 2007; Hasson et al., 2004). Gradient continuity may therefore be of importance not only to somatotopic organization but to topographic organization in general.

Perhaps the most famous example of topographic organization is the classic homunculus described by Penfield in his seminal work on electrostimulation of the post central gyrus (PoCG) in awake humans (Penfield and Brodley, 1937; Penfield and Rasmussen, 1950; also verified by animal studies: Kaas, 1983; Kaas et al., 1979; Nelson et al., 1980; Rothemund et al., 2002; Shoham and Grinvald, 2001). This homunculus has been researched extensively in humans both at the theoretical level and in clinical settings. For example, topographical plastic changes and reorganization of the somatosensory system have been reported in human amputees (Ramachandran, 2005) and were also shown to be modulated in a use-dependent fashion (Makin et al., 2013). In the last decade the topographic nature of the somatosensory system has also been investigated by advanced neuroimaging methods that probe different parts of the homunculus while providing other important insights (Blankenburg et al., 2003; Chen et al., 2006; Fox et al., 1987; Huang and Sereno, 2007; Kell et al., 2005; Kurth et al., 1998; McGlone et al., 2002; Miyamoto et al., 2006; Nelson and Chen, 2008; Overduin and Servos, 2008; Schweizer et al., 2008). However, the vast majority of these studies have dealt with specific areas of the body surface, especially the hands and fingers (Blankenburg et al., 2003; Chen et al., 2006; Kurth et al., 1998; McGlone et al., 2002; Nelson and Chen, 2008; Overduin and Servos, 2008; Schweizer et al., 2008) or the face (Miyamoto et al., 2006; Sereno and Huang, 2006). Thus, the whole body sensory representation has never been tested with the high-resolution neuroimaging techniques available today.

Because a major part of the data on human cortical processing of unisensory inputs (and specifically visual information) derives from the use of different fMRI phase-locking methods, they constitute a key approach to the study of topographic gradients. Early studies (Engel et al., 1994, 1997; Sereno et al., 1995) employed phase-locked analysis of fMRI data to characterize the retinotopic nature of the visual cortex. These studies generated multiple retinotopic maps, which are organized in a mirror symmetry topography. These maps were then used as the basis for delineating different visual areas in humans and primates, in which each functionally separate visual area contained a map of the sensory epithelia (the retina, Grill-Spector and Malach, 2004; Hasson et al., 2003; Levy et al., 2001; Sereno and Huang, 2006). These methods were fundamental to understanding the visual system in humans and were subsequently used in other modalities such as the auditory (Hertz and Amedi, 2010; Striem-Amit et al., 2011) and motor domains (Zeharia et al., 2012, 2015), where they revealed additional cochleotopic and somatotopic motor maps. Despite their well-documented advantages in studying full and detailed topographic gradients both in terms of the large-scale organization of the brain and in clinical settings (see below), spectral analysis methods were only of very limited use in the somatosensory system. Specifically, these approaches were used to map detailed local gradients of the arm (Servos et al., 1998), fingers (Besle et al., 2013; Mancini et al., 2012; Overduin and Servos, 2008; Sanchez-Panchuelo et al., 2010), or in higher somatosensory face selective areas in the ventral intraparietal (VIP) cortex (Sereno and Huang, 2006) but were not employed to study detailed full body somatotopy. Hence, my first aim was to map the whole body representation in the human brain and to verify Penfield's homunculus using a high-resolution paradigm and analytical tools including phase-locking approaches.

1.2 Do sensory cortices specialize in unisensory processing or serve as sensory independent task operators?

Until recently and according to the division of labor principle (Zeki, 1978) there was a general consensus that multisensory integration occurs in high order associative and multisensory cortical areas (Andersen et al., 1997; Beauchamp, 2005; Benevento et al., 1977; Felleman and Van Essen, 1991; Fuster et al., 2000; Schlack et al., 2005). However, growing anatomical and functional evidence has challenged this approach by showing cross-modal responses in different classical unisensory areas (Ghazanfar and Schroeder, 2006; Molholm et al., 2002; Tal and Amedi, 2009;

Watkins et al., 2007; for reviews see: Kayser and Logothetis, 2007; Maidenbaum et al., 2014; Reich et al., 2012).

A fundamental issue in contemporary theories of multisensory processing in unisensory cortices has to do with the relevance of the cross-modal inputs to the tasks and computations performed by different functional areas. It is well-known that the visual cortex in sighted humans has a hierarchical organization and is comprised of different functional areas, each processing different aspects of vision. For example, different functional areas within the ventral visual stream show preferential activation for different object categories: the fusiform face area (FFA) shows a preference for processing faces, the middle temporal gyrus (MT) for visual motion, and the visual word form area (VWFA) for script reading and visual representation of language. However, in recent years there has been growing evidence that even the early stations in the visual cortex hierarchy may be less dependent on specific visual features and that the occipital visual cortex is not purely visual, in that it may also be activated by non-visual stimuli (Amedi et al., 2001, 2007; Merabet and Pascual-Leone, 2010; Pascual-Leone and Hamilton, 2001; Pascual-Leone et al., 2005; Reich et al., 2011; Renier et al., 2014). Specifically, these studies demonstrate that in both sighted and blind individuals, the functional specialization of the occipital visual cortex is independent of visual input and that different areas can retain their functional role even without any visual experience. These converging findings lead to the hypothesis that the visual cortex may process nonvisual inputs and that the brain may be in fact composed of task-selective rather than visual, sensory-modality-selective operators (Amedi et al., 2001; Pascual-Leone and Hamilton, 2001; also referred to as metamodal operators). These operators are local neural networks defined by a given computation that is applied regardless of the sensory input received. In other words, the driving force for recruitment of a given functional area is the task-related information rather than the sensory modality of the incoming inputs.

One of the first and probably most thoroughly investigated examples of a task selective area is the lateral occipital complex (LOC), in the occipito-temporal cortex which is preferentially activated by visual objects compared to scrambled images or textures (Malach et al., 1995). Because a visual object's three-dimensional shape can also be perceived haptically, studies have investigated whether the LOC region could also encode object information derived from touch. Using fMRI it was shown that the LOC region contained a sub-region which was activated by haptic perception of objects more than by the haptic perception of textures (Amedi et al., 2001). Therefore, this area was termed the lateral occipital tactile visual (LOtv) area, implying its bimodal nature in object perception via touch and vision. Moreover, lesions to LOtv which are usually associated to visual agnosia, were also reported to be linked to haptic impairment in object recognition (James et al., 2007). Subsequent studies using a visual-to-auditory sensory-substitution device (SSD) which embeds visual shape into sounds, further extended the metamodal characteristic of LOtv. These studies have shown that in both early blind and sighted individuals this area can also be activated by sound but only if these individuals learn to extract exact geometrical shapes from these sounds (Amedi et al., 2002, 2007; Meijer, 1992). Similarly, LO area was also activated by auditory stimuli that were created from recordings of objects impacting a hard surface. Specifically, area LO was more strongly recruited when subjects discriminated impact sounds based on the shape of the object that made them, compared to when subjects discriminated those same sounds based on material (James et al., 2011). Thus, the LOtv seems to be activated by visual, tactile and auditory inputs. Hence the "tv" suffix was omitted and this area is referred to simply as "LO". Furthermore, using an fMRI adaptation paradigm it has been shown that the same neuronal population is engaged in processing both vision and haptics (in contrast to different unimodal sub-populations), implying that the neuronal population in the occipito-temporal cortex may constitute a multimodal object-related network (Tal and Amedi, 2009). Such convergence at the neuronal (rather than areal) level was also supported by studies exploring the effectiveness of visual and haptic multisensory integration under different levels of task difficulty (Kim and James, 2010; Kim et al., 2012).

Task selectivity has been reported for other tasks and areas, including for example, selectivity to nonvisual motion in the visual middle temporal area (MT, Matteau et al., 2010; Poirier et al., 2006), sound localization in the middle-occipital gyrus (MOG, Collignon et al., 2011; Renier et al., 2010), and sounds of body shapes delivered through SSD in the Extrastriate body area (EBA, Striem-Amit and Amedi, 2014).

However, despite these converging studies supporting the framework of the brain as task-oriented and sensory-modality independent, this theory is still controversial in mainstream neuroscience due to several open questions and some conflicting results. In some studies, other sensory modalities trigger negative BOLD (thought to reflect reduced average neuronal firing, see section 1.3) rather than recruited activation (Hairston et al., 2008; Laurienti et al., 2002; Lewis et al., 2000; Shulman et al., 1997). Thus another fundamental question addressed in this dissertation was to test when the visual cortex is recruited and activated by a given sensory modality (here, by touch inputs) and when it is deactivated (or show negligible activation).

Another putative reason for skepticism is that most of the studies and evidence demonstrating task-selectivity activation of visual areas by non-visual stimuli have emerged from studies with blind participants. This raises the possibility that the results relate to plastic changes and compensatory mechanisms during the development of the visually deprived brain. For example, several studies have shown that the primary visual cortex plays a role that is highly distinct from its standard role in simple visual processing, and engages in the processing of language and memory (Amedi et al., 2003; Bedny and Caramazza, 2011; Bedny et al., 2011; Burton et al., 2002; Raz et al., 2005). Furthermore, the activation level of the primary visual cortex correlated to the memory performance in individual subjects (Amedi et al., 2003; Raz et al., 2005). TMS interference to the occipital pole of congenitally blind people was shown to cause interruptions to a verb-generation task (Amedi et al., 2004), suggesting a causal link between early visual cortex activity and successful performance on such tasks. This “task switching” of the primary visual cortex poses an important question concerning the consistency of task-retention in extreme cases of abnormal brain development. Thus, the cortical organization and functional processing of the blind might differ considerably from that of normally sighted individuals. Therefore, it is not clear whether a lack (or reduction) of visual experience leads to the creation of new functional and anatomical connections or if the observed task-selectivity represents a more general pattern that is present also in the sighted.

However, task-selective and sensory-independent recruitment of visual areas was also found in sighted (Amedi et al., 2001, 2007; Beauchamp et al., 2007; Costantini et al., 2011; Mahon et al., 2009). While reinforcing the metamodal task-selectivity model, these findings also suggest some alternative explanations. For example, most of our experiences are a combination of multisensory sensations, which can readily be linked and even translated from one sensory-modality to another. For example, we may perceive the shape of an object by touching it and identify it and even imagine it, visually, in a seemingly effortless process. Thus, tactile exploration of objects might evoke automated imagery processes which build up a visual representation of the stimuli (reviewed in Sathian, 2005). These visual imagery processes might in turn recruit visual cortical areas (such as the LO) through a top-down mechanism, and provide an alternative explanation for the meta-modal engagement and nature of these areas during non-visual tasks (in fact this might be the reason why most of the evidence for the brain as sensory independent metamodal task operators comes from studying congenitally blind who cannot have visual memories because they have no visual experience). Furthermore, in all the studies reporting on tactile object selectivity in the LO, the tactile activations emerged from active tool manipulation, which in all cases was also confounded to a certain extent with motor movements, naming, semantic input and object recognition. In this dissertation I address these questions from a different perspective, by studying the interaction between passive and task free tactile stimulation and the visual system. This made it possible to test tactile cross-modal responses in the visual system of normally sighted individuals directly, while minimizing confounding factors such as mental imagery and semantic processes. Using this approach combined with a detailed mapping of the visual system (including retinotopic mapping and higher order visual areas localizers), I addressed the following questions and was able to untangle a number of competing potential outcomes. First, are all the brain areas in fact multisensory areas? For instance, Kayser and Logothetis (2007) suggested that cross-modal interactions can take place even at the earliest stages of sensory cortical processing. Thus, the most extreme scenario would be that V1 and other retinotopic areas (and not only high order visual areas) are activated by passive somatosensory inputs. The other alternative is that all previous effects found in the sighted were driven by visual imagery and other confounding factors. In this case, I would expect to observe negligible or perhaps robust deactivation to simple passive touch inputs from the body. The third scenario is based on the task-machine hypothesis, which predicts a mixed pattern of positive and negative responses. Under this hypothesis, whenever input from another sensory modality is relevant to a task related to a given area, it will be recruited; when the information is not relevant to the task it will deactivate this area so as to maximize the signal to noise ratio and direct attentional resources to the stimulated modality.

1.3 Negative BOLD signals for passive touch within and beyond the system

Until recently, most imaging studies focused solely on reporting an elevation in the fMRI BOLD signal; i.e., the positive BOLD. The fMRI positive BOLD signal is a physiological process associated with a corresponding change in blood flow, blood oxygenation metabolism, local field potentials, and neural activity (for a review see Logothetis and Wandell, 2004). In the last ten years, growing attention has been directed to studying deflections of the BOLD signal below the baseline; i.e., negative BOLD responses. Whereas the exact physiological origin of the NBR remains only partially understood (Devor et al., 2007; Goense et al., 2012; for a review see Nair, 2005) converging evidence suggests that similar to the positive BOLD, the negative BOLD signal is a physiological process that is correlated with a corresponding decrease in cerebral blood flow, oxygen consumption, and neuronal activity (Boorman et al., 2010; Mullinger et al., 2014; Shmuel et al., 2002, 2006; Stefanovic et al., 2004). Thus, the negative BOLD signal indicates less neural processing for a given task as compared to a given baseline (Laurienti, 2004; Shmuel et al., 2002, 2006; Wade and Rowland, 2010). Most studies on negative BOLD signal have dealt with a network of the posterior- medial, posterior-lateral, and ventro-medial prefrontal cortex originally referred to as the ‘’default brain’’ network (Greicius and Menon, 2004; Raichle et al., 2001). This network exhibits high activity when the mind is not engaged in specific behavioral tasks and is deactivated by a variety of goal-directed cognitive functions in various sensory modalities (Greicius and Menon, 2004; Gusnard and Raichle, 2001).

Beyond the hundreds of papers (Callard and Margulies, 2014) studying different aspects of the DMN, there are a few other examples of negative BOLD responses outside this cortical network, in what is considered the classical uni-sensory cortices:

(1) Negative BOLD responses within early sensory cortices. This was first found in the visual cortex, whereas stimulation of central visual field evoked negative BOLD responses in the surrounding peripheral areas and vice versa (Shmuel et al., 2002, 2006). In the somatosensory system, however, negative BOLD responses have only been studied in the context of cross-hemispheric interaction following hand stimulation (Gröschel et al., 2013; Hlushchuk and Hari, 2006; Kastrup et al., 2008; Klingner et al., 2010, 2014); thus, it is not clear whether such negative BOLD responses can also be detected within the contralateral hemisphere. Therefore, another main goal of this dissertation was to explore this question, and to test whether negative BOLD responses would show topographical organization patterns. Specifically, one of the axes of topographical organization in retinotopic visual areas is the spatial eccentricity of the stimuli within the visual field. As described above, negative BOLD responses in V1 are also organized along this axis, since foveal stimulation results in the deactivation of peripheral areas and vice versa. In the primary somatosensory cortex, the topography is organized according to the body dermatomes, and thus if negative BOLD responses within the primary somatosensory cortex follow a topographic rule, a similar pattern to the visual system might be predicted. For example, stimulation of the lips would result in a negative BOLD in the foot area and vice-versa. Nevertheless, studies in the visual system testing the BOLD patterns in response to stimuli which were located at the edge points along the retinotopic gradient (fovea and periphery, Shmuel et al.,

2006), and have not directly tested the intermediate areas. Another advantage of using whole body tactile stimulation is that it can test whether this topographic organization of the negative responses is a general feature of the primary areas, or only involves the edges of the gradient (lips and feet in the somatosensory cortex and fovea and periphery in the visual cortex). If the negative responses serve a general sharpening mechanism for all body parts, then hand stimulation should result in negative responses in the corresponding lip and foot areas. On the other hand, the existence of weak positive responses in the lip and foot areas might imply a more distributed representation along S1.

(2) Deactivation of the sensory-specific cortex by cross-modal stimuli. For example, auditory or tactile stimulation elicited deactivation of major parts of the visual cortex (Kawashima et al., 1995; Laurienti et al., 2002; Merabet and Swisher, 2007; Sadato et al., 1996; Weisser et al., 2005). These findings however, seem to run counter the notion of cross-modal activation of task-selective areas in the visual cortex as described above. Thus, what determines whether a given visual area or network will be recruited or deactivated by a different sense is still poorly understood. As noted above, studying this question in the context of passive stimulation may help reduce many high-level confounding factors such as naming, haptic movements and mental imagery.

(3) Negative BOLD responses in sensory-specific areas during high-order cognitive tasks. For example, auditory cortex deactivations were found during visual mental imagery (Amedi et al., 2005) and verbal memory (Azulay et al., 2009) tasks. These results imply that any use or reference to internal representations or stored information may require the inhibition of cortices that usually process extrinsic sensory stimuli. The negative BOLD responses under these circumstances may serve as a mechanism directing attentional resources away from the deactivated brain area.

(4) Negative BOLD in the ipsilateral hemisphere. As briefly stated above, negative BOLD responses in the somatosensory cortex have been studied in the context of interhemispheric deactivation following unilateral stimulation of the hand (Gröschel

et al., 2013; Hlushchuk and Hari, 2006; Kastrup et al., 2008; Klingner et al., 2010, 2014). These studies showed that stimulation of one hand caused negative BOLD in the homologous hand area in the ipsilateral hemisphere. One limitation to these studies is that the stimulus was limited to one body part (the hand) and the evoked positive and negative BOLD responses were evaluated solely in the ipsilateral homologues area. Thus, here I explored the pattern of ipsilateral BOLD signal following stimulation of many body parts. This approach served to assess whether putative deactivations in the ipsilateral hemisphere are confined to the area of the ipsilateral stimulated body part as suggested by the current literature, or whether this could also be detected in other areas in the ipsilateral homunculus, reflecting a general mechanism for all non-stimulated body parts.

More generally, while this growing field of negative BOLD research has provided some important evidence suggesting that these negative responses reflect a functionally relevant measure of neuronal deactivation (Bressler et al., 2007; Ferbert et al., 1992; Kastrup et al., 2008; Klingner et al., 2010; Liepert et al., 2001; Schäfer et al., 2012), the significance of negative BOLD responses in the context of general organization principles of the brain discussed above (topographical organization of cortical gradients –section 1.1 and multisensory processing in classic unisensory cortices – section 1.2) is still understudied. Nevertheless, the somatosensory system, because it is involved in cross-modal integration and exhibits a highly somatotopic organization (at least in the first stages of cortical processing) could serve as an appealing model to test these questions (as detailed below) and to further postulate a general theoretical framework for such organization principles that includes both positive and negative hemodynamic responses.

To summarize this introduction, in my thesis I aimed to explore topographical biases of passive somatosensory inputs from the whole body, as manifested in the positive and negative BOLD signals, at two different levels of processing:

1) Within the primary somatosensory homunculi. This included: 1. Mapping full body gradients in S1 using continuous natural tactile stimulation combined with spectral

analysis techniques. 2. Searching for negative BOLD responses in the contralateral hemisphere, and specifically whether such responses are topographically biased, similar to the reported results in the visual and motor cortices. 3. Exploring negative BOLD responses in the ipsilateral hemisphere for different body parts. The assessment involved whether the ipsilateral deactivations are specific to the area of the ipsilateral stimulated body part (as suggested by previous studies) or could also be detected in other parts of the homunculi, reflecting a general mechanism to all non-stimulated body parts.

2) Cross-modal responses in the visual cortex. This included: 1. A study of the pattern of passive tactile response in the visual cortex 2. Whether the LO area can be activated by passive touch 3. If so whether there is somatosensory selectivity to different body parts? Can other areas in the visual system be also activated (or perhaps deactivated)? 4. A test of functional connectivity patterns that could support the creation and maintenance of such a-modal effects.

1.4 References

Aflalo, T.N., and Graziano, M.S.A. (2006). Possible origins of the complex topographic organization of motor cortex: reduction of a multidimensional space onto a two-dimensional array. J. Neurosci. *26*, 6288–6297.

Amedi, A., Malach, R., Hendler, T., Peled, S., and Zohary, E. (2001). Visuo-haptic object-related activation in the ventral visual pathway. Nat. Neurosci. *4*, 324–330.

Amedi, A., Jacobson, G., Hendler, T., Malach, R., and Zohary, E. (2002). Convergence of visual and tactile shape processing in the human lateral occipital complex. Cereb. Cortex *12*, 1202–1212.

Amedi, A., Raz, N., Pianka, P., Malach, R., and Zohary, E. (2003). Early “visual” cortex activation correlates with superior verbal memory performance in the blind. Nat. Neurosci. *6*, 758–766.

Amedi, A., Floel, A., Knecht, S., Zohary, E., and Cohen, L.G. (2004). Transcranial magnetic stimulation of the occipital pole interferes with verbal processing in blind subjects. Nat. Neurosci. *7*, 1266–1270.

Amedi, A., Malach, R., and Pascual-Leone, A. (2005). Negative BOLD differentiates visual imagery and perception. Neuron *48*, 859–872.

Amedi, A., Stern, W.M., Camprodon, J.A., Bermpohl, F., Merabet, L., Rotman, S., Hemond, C., Meijer, P., and Pascual-Leone, A. (2007). Shape conveyed by visual-to-auditory sensory substitution activates the lateral occipital complex. Nat. Neurosci. *10*, 687–689.

Andersen, R.A., Snyder, L.H., Bradley, D.C., and Xing, J. (1997). Multimodal representation of space in the posterior parietal cortex and its use in planning movements. Annu Rev Neurosci *20*, 303–330.

Azulay, H., Striem, E., and Amedi, A. (2009). Negative BOLD in sensory cortices during verbal memory: a component in generating internal representations? Brain Topogr. *21*, 221–231.

Beauchamp, M.S. (2005). See me, hear me, touch me: multisensory integration in lateral occipital-temporal cortex. Curr. Opin. Neurobiol. *15*, 145–153.

Beauchamp, M.S., Yasar, N.E., Kishan, N., and Ro, T. (2007). Human MST but not MT responds to tactile stimulation. J. Neurosci. *27*, 8261–8267.

Bedny, M., and Caramazza, A. (2011). Perception, action, and word meanings in the human brain: the case from action verbs. Ann N Y Acad Sci *1224*, 81–95.

Bedny, M., Pascual-Leone, A., Dodell-Feder, D., Fedorenko, E., and Saxe, R. (2011). Language processing in the occipital cortex of congenitally blind adults. Proc. Natl. Acad. Sci. U. S. A. *108*, 4429–4434.

Benevento, L.A., Fallon, J., Davis, B.J., and Rezak, M. (1977). Auditory--visual interaction in single cells in the cortex of the superior temporal sulcus and the orbital frontal cortex of the macaque monkey. Exp. Neurol. *57*, 849–872.

Besle, J., Sánchez-Panchuelo, R.-M., Bowtell, R., Francis, S., and Schluppeck, D. (2013). Single-subject fMRI mapping at 7 T of the representation of fingertips in S1: a comparison of event-related and phase-encoding designs. J. Neurophysiol. *109*, 2293–2305.

Blankenburg, F., Ruben, J., Meyer, R., Schwiemann, J., and Villringer, A. (2003). Evidence for a rostral-to-caudal somatotopic organization in human primary somatosensory cortex with mirror-reversal in areas 3b and 1. Cereb Cortex *13*, 987–993.

Boorman, L., Kennerley, A.J., Johnston, D., Jones, M., Zheng, Y., Redgrave, P., and Berwick, J. (2010). Negative blood oxygen level dependence in the rat: a model for investigating the role of suppression in neurovascular coupling. J. Neurosci. *30*, 4285–4294.

Bressler, D., Spotswood, N., and Whitney, D. (2007). Negative BOLD fMRI response in the visual cortex carries precise stimulus-specific information. PLoS One *2*, e410.

Burton, H., Snyder, A.Z., Diamond, J.B., and Raichle, M.E. (2002). Adaptive changes in early and late blind: a FMRI study of verb generation to heard nouns. J. Neurophysiol. *88*, 3359–3371.

Callard, F., and Margulies, D.S. (2014). What we talk about when we talk about the default mode network. Front. Hum. Neurosci. *8*, 619.

Calvert, G.A. (2001). Crossmodal processing in the human brain: insights from functional neuroimaging studies. Cereb. Cortex *11*, 1110–1123.

Chen, C.J., Liu, H.L., Wei, F.C., and Chu, N.S. (2006). Functional MR imaging of the human sensorimotor cortex after toe-to-finger transplantation. AJNR Am J Neuroradiol *27*, 1617–1621.

Chklovskii, D.B., and Koulakov, A.A. (2004). Maps in the brain: what can we learn from them? Annu Rev Neurosci *27*, 369–392.

Collignon, O., Vandewalle, G., Voss, P., Albouy, G., Charbonneau, G., Lassonde, M., and Lepore, F. (2011). Functional specialization for auditory-spatial processing in the occipital cortex of congenitally blind humans. Proc. Natl. Acad. Sci. U. S. A. *108*, 4435–4440.

Costantini, M., Urgesi, C., Galati, G., Romani, G.L., and Aglioti, S.M. (2011). Haptic perception and body representation in lateral and medial occipito-temporal cortices. Neuropsychologia *49*, 821–829.

Damasio, A.R., and Damasio, H. (2004). Cortical systems for retrieval of concrete knowledge: The convergence zone framework. In Large-Scale Neuronal Theories of the Brain, C. Koch, and L.D. Davis, eds. (Cambridge : The MIT Press), pp. 61–74.

Devor, A., Tian, P., Nishimura, N., Teng, I.C., Hillman, E.M.C., Narayanan, S.N., Ulbert, I., Boas, D.A., Kleinfeld, D., and Dale, A.M. (2007). Suppressed neuronal activity and concurrent arteriolar vasoconstriction may explain negative blood oxygenation level-dependent signal. J. Neurosci. *27*, 4452–4459.

Diamond, M.E., Petersen, R.S., Harris, J.A., and Panzeri, S. (2003). Investigations into the organization of information in sensory cortex. J Physiol Paris *97*, 529–536.

Engel, S.A., Rumelhart, D.E., Wandell, B.A., Lee, A.T., Glover, G.H., Chichilnisky, E.J., and Shadlen, M.N. (1994). fMRI of human visual cortex. Nature *369*, 525.

Engel, S.A., Glover, G.H., and Wandell, B.A. (1997). Retinotopic organization in human visual cortex and the spatial precision of functional MRI. Cereb Cortex *7*, 181–192.

Felleman, D.J., and Van Essen, D.C. (1991). Distributed hierarchical processing in the primate cerebral cortex. Cereb. Cortex *1*, 1–47.

Ferbert, A., Priori, A., Rothwell, J.C., Day, B.L., Colebatch, J.G., and Marsden, C.D. (1992). Interhemispheric inhibition of the human motor cortex. J. Physiol. *453*, 525–546.

Fox, P.T., Burton, H., and Raichle, M.E. (1987). Mapping human somatosensory cortex with positron emission tomography. J Neurosurg *67*, 34–43.

Fuster, J.M., Bodner, M., and Kroger, J.K. (2000). Cross-modal and cross-temporal association in neurons of frontal cortex. Nature *405*, 347–351.

Ghazanfar, A.A., and Schroeder, C.E. (2006). Is neocortex essentially multisensory? Trends Cogn. Sci. *10*, 278–285.

Goense, J., Merkle, H., and Logothetis, N.K. (2012). High-resolution fMRI reveals laminar differences in neurovascular coupling between positive and negative BOLD responses. Neuron *76*, 629–639.

Golland, Y., Bentin, S., Gelbard, H., Benjamini, Y., Heller, R., Nir, Y., Hasson, U., and Malach, R. (2007). Extrinsic and intrinsic systems in the posterior cortex of the human brain revealed during natural sensory stimulation. Cereb. Cortex *17*, 766–777.

Greicius, M.D., and Menon, V. (2004). Default-mode activity during a passive sensory task: uncoupled from deactivation but impacting activation. J. Cogn. Neurosci. *16*, 1484–1492.

Grill-Spector, K., and Malach, R. (2004). The human visual cortex. Annu Rev Neurosci *27*, 649–677.

Gröschel, S., Sohns, J.M., Schmidt-Samoa, C., Baudewig, J., Becker, L., Dechent, P., and Kastrup, A. (2013). Effects of age on negative BOLD signal changes in the primary somatosensory cortex. Neuroimage *71*, 10–18.

Gusnard, D.A., and Raichle, M.E. (2001). Searching for a baseline: functional imaging and the resting human brain. Nat. Rev. Neurosci. *2*, 685–694.

Hagler, D.J., and Sereno, M.I. (2006). Spatial maps in frontal and prefrontal cortex. Neuroimage *29*, 567–577.

Hairston, W.D., Hodges, D.A., Casanova, R., Hayasaka, S., Kraft, R., Maldjian, J.A., and Burdette, J.H. (2008). Closing the mind's eye: deactivation of visual cortex related to auditory task difficulty. Neuroreport *19*, 151–154.

Harvey, B.M., Klein, B.P., Petridou, N., and Dumoulin, S.O. (2013). Topographic representation of numerosity in the human parietal cortex. Science *341*, 1123–1126.

Hasson, U., Harel, M., Levy, I., and Malach, R. (2003). Large-scale mirror-symmetry organization of human occipito-temporal object areas. Neuron *37*, 1027–1041.

Hasson, U., Nir, Y., Levy, I., Fuhrmann, G., and Malach, R. (2004). Intersubject synchronization of cortical activity during natural vision. Science *303*, 1634–1640.

Hertz, U., and Amedi, A. (2010). Disentangling unisensory and multisensory components in audiovisual integration using a novel multifrequency fMRI spectral analysis. Neuroimage *52*, 617–632.

Hlushchuk, Y., and Hari, R. (2006). Transient suppression of ipsilateral primary somatosensory cortex during tactile finger stimulation. J. Neurosci. *26*, 5819–5824.

Huang, R.S., and Sereno, M.I. (2007). Dodecapus: An MR-compatible system for somatosensory stimulation. Neuroimage *34*, 1060–1073.

James, T.W., Kim, S., and Fisher, J.S. (2007). The neural basis of haptic object processing. Can. J. Exp. Psychol. *61*, 219–229.

James, T.W., Stevenson, R.A., Kim, S., Vanderklok, R.M., and James, K.H. (2011). Shape from sound: evidence for a shape operator in the lateral occipital cortex. Neuropsychologia *49*, 1807–1815.

Kaas, J.H. (1983). What, if anything, is SI? Organization of first somatosensory area of cortex. Physiol Rev *63*, 206–231.

Kaas, J.H. (1997). Topographic maps are fundamental to sensory processing. Brain Res Bull *44*, 107–112.

Kaas, J.H., Nelson, R.J., Sur, M., Lin, C.S., and Merzenich, M.M. (1979). Multiple representations of the body within the primary somatosensory cortex of primates. Science (80-.). *204*, 521–523.

Kastner, S., DeSimone, K., Konen, C.S., Szczepanski, S.M., Weiner, K.S., and Schneider, K.A. (2007). Topographic maps in human frontal cortex revealed in memory-guided saccade and spatial working-memory tasks. J. Neurophysiol. *97*, 3494–3507.

Kastrup, A., Baudewig, J., Schnaudigel, S., Huonker, R., Becker, L., Sohns, J.M., Dechent, P., Klingner, C., and Witte, O.W. (2008). Behavioral correlates of negative BOLD signal changes in the primary somatosensory cortex. Neuroimage *41*, 1364–1371.

Kawashima, R., O'Sullivan, B.T., and Roland, P.E. (1995). Positron-emission tomography studies of cross-modality inhibition in selective attentional tasks: closing the “mind's eye”. Proc. Natl. Acad. Sci. U. S. A. *92*, 5969–5972.

Kayser, C. (2010). The multisensory nature of unisensory cortices: a puzzle continued. Neuron *67*, 178–180.

Kayser, C., and Logothetis, N.K. (2007). Do early sensory cortices integrate cross-modal information? Brain Struct. Funct. *212*, 121–132.

Kell, C.A., von Kriegstein, K., Rosler, A., Kleinschmidt, A., and Laufs, H. (2005). The sensory cortical representation of the human penis: revisiting somatotopy in the male homunculus. J Neurosci *25*, 5984–5987.

Kim, S., and James, T.W. (2010). Enhanced effectiveness in visuo-haptic object-selective brain regions with increasing stimulus salience. Hum. Brain Mapp. *31*, 678–693.

Kim, S., Stevenson, R.A., and James, T.W. (2012). Visuo-haptic neuronal convergence demonstrated with an inversely effective pattern of BOLD activation. J. Cogn. Neurosci. *24*, 830–842.

Klingner, C.M., Hasler, C., Brodoehl, S., and Witte, O.W. (2010). Dependence of the negative BOLD response on somatosensory stimulus intensity. Neuroimage *53*, 189–195.

Klingner, C.M., Hasler, C., Brodoehl, S., and Witte, O.W. (2014). Excitatory and inhibitory mechanisms underlying somatosensory habituation. Hum. Brain Mapp. *35*, 152–160.

Kohonen, T., and K., M. (1989). The self organizing feature maps. Phys. Scr. *39*, 168–172.

Kurth, R., Villringer, K., Mackert, B.M., Schwiemann, J., Braun, J., Curio, G., Villringer, A., and Wolf, K.J. (1998). fMRI assessment of somatotopy in human Brodmann area 3b by electrical finger stimulation. Neuroreport *9*, 207–212.

Laurienti, P.J. (2004). Deactivations, global signal, and the default mode of brain function. J. Cogn. Neurosci. *16*, 1481–1483.

Laurienti, P.J., Burdette, J.H., Wallace, M.T., Yen, Y.-F., Field, A.S., and Stein, B.E. (2002). Deactivation of sensory-specific cortex by cross-modal stimuli. J. Cogn. Neurosci. *14*, 420–429.

Levy, I., Hasson, U., Avidan, G., Hendler, T., and Malach, R. (2001). Center-periphery organization of human object areas. Nat Neurosci *4*, 533–539.

Lewis, J.W., Beauchamp, M.S., and DeYoe, E.A. (2000). A comparison of visual and auditory motion processing in human cerebral cortex. Cereb. Cortex *10*, 873–888.

Liepert, J., Dettmers, C., Terborg, C., and Weiller, C. (2001). Inhibition of ipsilateral motor cortex during phasic generation of low force. Clin. Neurophysiol. *112*, 114–121.

Logothetis, N.K., and Wandell, B.A. (2004). Interpreting the BOLD signal. Annu Rev Physiol *66*, 735–769.

Mahon, B.Z., Anzellotti, S., Schwarzbach, J., Zampini, M., and Caramazza, A. (2009). Category-specific organization in the human brain does not require visual experience. Neuron *63*, 397–405.

Maidenbaum, S., Abboud, S., and Amedi, A. (2014). Sensory substitution: closing the gap between basic research and widespread practical visual rehabilitation. Neurosci. Biobehav. Rev. *41*, 3–15.

Makin, T.R., Cramer, A.O., Scholz, J., Hahamy, A., Henderson Slater, D., Tracey, I., and Johansen-Berg, H. (2013). Deprivation-related and use-dependent plasticity go hand in hand. Elife *2*, e01273.

Malach, R., Reppas, J.B., Benson, R.R., Kwong, K.K., Jiang, H., Kennedy, W.A., Ledden, P.J., Brady, T.J., Rosen, B.R., and Tootell, R.B. (1995). Object-related activity revealed by functional magnetic resonance imaging in human occipital cortex. Proc. Natl. Acad. Sci. U. S. A. *92*, 8135–8139.

Malach, R., Levy, I., and Hasson, U. (2002). The topography of high-order human object areas. Trends Cogn. Sci. *6*, 176–184.

Mancini, F., Haggard, P., Iannetti, G.D., Longo, M.R., and Sereno, M.I. (2012). Fine-grained nociceptive maps in primary somatosensory cortex. J. Neurosci. *32*, 17155–17162.

Matteau, I., Kupers, R., Ricciardi, E., Pietrini, P., and Ptito, M. (2010). Beyond visual, aural and haptic movement perception: hMT+ is activated by electrotactile motion stimulation of the tongue in sighted and in congenitally blind individuals. Brain Res. Bull. *82*, 264–270.

McGlone, F., Kelly, E.F., Trulsson, M., Francis, S.T., Westling, G., and Bowtell, R. (2002). Functional neuroimaging studies of human somatosensory cortex. Behav Brain Res *135*, 147–158.

Meijer, P.B. (1992). An experimental system for auditory image representations. IEEE Trans. Biomed. Eng. *39*, 112–121.

Merabet, L., and Swisher, J. (2007). Combined activation and deactivation of visual cortex during tactile sensory processing. J. … 1633–1641.

Merabet, L.B., and Pascual-Leone, A. (2010). Neural reorganization following sensory loss: the opportunity of change. Nat. Rev. Neurosci. *11*, 44–52.

Mesulam, M.M. (1998). From sensation to cognition. Brain *121 (Pt 6*, 1013–1052.

Miyamoto, J.J., Honda, M., Saito, D.N., Okada, T., Ono, T., Ohyama, K., and Sadato, N. (2006). The representation of the human oral area in the somatosensory cortex: a functional MRI study. Cereb Cortex *16*, 669–675.

Molholm, S., Ritter, W., Murray, M.M., Javitt, D.C., Schroeder, C.E., and Foxe, J.J. (2002). Multisensory auditory-visual interactions during early sensory processing in humans: a high-density electrical mapping study. Brain Res Cogn Brain Res *14*, 115–128.

Mountcastle, V.B. (1997). The columnar organization of the neocortex. Brain *120 (Pt 4*, 701–722.

Mullinger, K.J., Mayhew, S.D., Bagshaw, A.P., Bowtell, R., and Francis, S.T. (2014). Evidence that the negative BOLD response is neuronal in origin: a simultaneous EEG-BOLD-CBF study in humans. Neuroimage *94*, 263–274.

Nair, D.G. (2005). About being BOLD. Brain Res. Brain Res. Rev. *50*, 229–243.

Nelson, A.J., and Chen, R. (2008). Digit somatotopy within cortical areas of the postcentral gyrus in humans. Cereb Cortex *18*, 2341–2351.

Nelson, R.J., Sur, M., Felleman, D.J., and Kaas, J.H. (1980). Representations of the body surface in postcentral parietal cortex of Macaca fascicularis. J Comp Neurol *192*, 611–643.

Orlov, T., Makin, T.R., and Zohary, E. (2010). Topographic representation of the human body in the occipitotemporal cortex. Neuron *68*, 586–600.

Overduin, S.A., and Servos, P. (2008). Symmetric sensorimotor somatotopy. PLoS One *3*, e1505.

Pascual-Leone, A., and Hamilton, R. (2001). The metamodal organization of the brain. Prog. Brain Res. *134*, 427–445.

Pascual-Leone, A., Amedi, A., Fregni, F., and Merabet, L.B. (2005). The plastic human brain cortex. Annu. Rev. Neurosci. *28*, 377–401.

Penfield, W., and Brodley, E. (1937). Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain *60*, 359–443.

Penfield, W., and Rasmussen, T. (1950). The Cerebral Cortex of Man (New York: MacmillanMacmillan).

Poirier, C., Collignon, O., Scheiber, C., Renier, L., Vanlierde, A., Tranduy, D., Veraart, C., and De Volder, A.G. (2006). Auditory motion perception activates visual motion areas in early blind subjects. Neuroimage *31*, 279–285.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., and Shulman, G.L. (2001). A default mode of brain function. Proc. Natl. Acad. Sci. U. S. A. *98*, 676–682.

Ramachandran, V.S. (2005). Plasticity and functional recovery in neurology. Clin. Med. *5*, 368–373.

Raz, N., Amedi, A., and Zohary, E. (2005). V1 activation in congenitally blind humans is associated with episodic retrieval. Cereb. Cortex *15*, 1459–1468.

Reich, L., Szwed, M., Cohen, L., and Amedi, A. (2011). A ventral visual stream reading center independent of visual experience. Curr. Biol. *21*, 363–368.

Reich, L., Maidenbaum, S., and Amedi, A. (2012). The brain as a flexible task machine: implications for visual rehabilitation using noninvasive vs. invasive approaches. Curr. Opin. Neurol. *25*, 86–95.

Renier, L., De Volder, A.G., and Rauschecker, J.P. (2014). Cortical plasticity and preserved function in early blindness. Neurosci. Biobehav. Rev. *41*, 53–63.

Renier, L.A., Anurova, I., De Volder, A.G., Carlson, S., VanMeter, J., and Rauschecker, J.P. (2010). Preserved functional specialization for spatial processing in the middle occipital gyrus of the early blind. Neuron *68*, 138–148.

Rothemund, Y., Qi, H.X., Collins, C.E., and Kaas, J.H. (2002). The genitals and gluteal skin are represented lateral to the foot in anterior parietal somatosensory cortex of macaques. Somat. Mot Res *19*, 302–315.

Sadato, N., Pascual-Leone, A., Grafman, J., Ibañez, V., Deiber, M.P., Dold, G., and Hallett, M. (1996). Activation of the primary visual cortex by Braille reading in blind subjects. Nature *380*, 526–528.

Sanchez-Panchuelo, R.M., Francis, S., Bowtell, R., and Schluppeck, D. (2010). Mapping human somatosensory cortex in individual subjects with 7T functional MRI. J. Neurophysiol. *103*, 2544–2556.

Sánchez-Panchuelo, R.-M., Besle, J., Mougin, O., Gowland, P., Bowtell, R., Schluppeck, D., and Francis, S. (2014). Regional structural differences across functionally parcellated Brodmann areas of human primary somatosensory cortex. Neuroimage *93 Pt 2*, 221–230.

Sathian, K. (2005). Visual cortical activity during tactile perception in the sighted and the visually deprived. Dev. Psychobiol. *46*, 279–286.

Saygin, A.P., and Sereno, M.I. (2008). Retinotopy and attention in human occipital, temporal, parietal, and frontal cortex. Cereb. Cortex *18*, 2158–2168.

Schäfer, K., Blankenburg, F., Kupers, R., Grüner, J.M., Law, I., Lauritzen, M., and Larsson, H.B.W. (2012). Negative BOLD signal changes in ipsilateral primary somatosensory cortex are associated with perfusion decreases and behavioral evidence for functional inhibition. Neuroimage *59*, 3119–3127.

Schlack, A., Sterbing-D’Angelo, S.J., Hartung, K., Hoffmann, K.P., and Bremmer, F. (2005). Multisensory space representations in the macaque ventral intraparietal area. J Neurosci *25*, 4616–4625.

Schweizer, R., Voit, D., and Frahm, J. (2008). Finger representations in human primary somatosensory cortex as revealed by high-resolution functional MRI of tactile stimulation. Neuroimage *42*, 28–35.

Sereno, M.I., and Huang, R.S. (2006). A human parietal face area contains aligned head-centered visual and tactile maps. Nat Neurosci *9*, 1337–1343.

Sereno, M.I., Dale, A.M., Reppas, J.B., Kwong, K.K., Belliveau, J.W., Brady, T.J., Rosen, B.R., and Tootell, R.B. (1995). Borders of multiple visual areas in humans revealed by functional magnetic resonance imaging. Science *268*, 889–893.

Servos, P., Zacks, J., Rumelhart, D.E., and Glover, G.H. (1998). Somatotopy of the human arm using fMRI. Neuroreport *9*, 605–609.

Shmuel, A., Yacoub, E., Pfeuffer, J., Van de Moortele, P.-F., Adriany, G., Hu, X., and Ugurbil, K. (2002). Sustained Negative BOLD, Blood Flow and Oxygen Consumption Response and Its Coupling to the Positive Response in the Human Brain. Neuron *36*, 1195–1210.

Shmuel, A., Augath, M., Oeltermann, A., and Logothetis, N.K. (2006). Negative functional MRI response correlates with decreases in neuronal activity in monkey visual area V1. Nat. Neurosci. *9*, 569–577.

Shoham, D., and Grinvald, A. (2001). The cortical representation of the hand in macaque and human area S-I: high resolution optical imaging. J Neurosci *21*, 6820–6835.

Shulman, G.L., Corbetta, M., Buckner, R.L., Raichle, M.E., Fiez, J.A., Miezin, F.M., and Petersen, S.E. (1997). Top-down modulation of early sensory cortex. Cereb. Cortex *7*, 193–206.

Silver, M.A., Ress, D., and Heeger, D.J. (2005). Topographic maps of visual spatial attention in human parietal cortex. J. Neurophysiol. *94*, 1358–1371.

Stefanovic, B., Warnking, J.M., and Pike, G.B. (2004). Hemodynamic and metabolic responses to neuronal inhibition. Neuroimage *22*, 771–778.

Striem-Amit, E., and Amedi, A. (2014). Visual cortex extrastriate body-selective area activation in congenitally blind people “seeing” by using sounds. Curr. Biol. *24*, 687–692.

Striem-Amit, E., Hertz, U., and Amedi, A. (2011). Extensive cochleotopic mapping of human auditory cortical fields obtained with phase-encoding FMRI. PLoS One *6*, e17832.

Tal, N., and Amedi, A. (2009). Multisensory visual-tactile object related network in humans: insights gained using a novel crossmodal adaptation approach. Exp. Brain Res. *198*, 165–182.

Wade, A.R., and Rowland, J. (2010). Early suppressive mechanisms and the negative blood oxygenation level-dependent response in human visual cortex. J. Neurosci. *30*, 5008–5019.

Wandell, B.A., Dumoulin, S.O., and Brewer, A.A. (2007). Visual field maps in human cortex. Neuron *56*, 366–383.

Watkins, S., Shams, L., Josephs, O., and Rees, G. (2007). Activity in human V1 follows multisensory perception. Neuroimage *37*, 572–578.

Weisser, V., Stilla, R., Peltier, S., Hu, X., and Sathian, K. (2005). Short-term visual deprivation alters neural processing of tactile form. Exp. Brain Res. *166*, 572–582.

Zeharia, N., Hertz, U., Flash, T., and Amedi, A. (2012). Negative blood oxygenation level dependent homunculus and somatotopic information in primary motor cortex and supplementary motor area. Proc. Natl. Acad. Sci. U. S. A. *109*, 18565–18570.

Zeharia, N., Hertz, U., Flash, T., and Amedi, A. (2015). New whole-body sensory-motor gradients revealed using phase-locked analysis and verified using multivoxel pattern analysis and functional connectivity. J. Neurosci. *35*, 2845–2859.

Zeki, S.M. (1978). Functional specialisation in the visual cortex of the rhesus monkey. Nature *274*, 423–428.

2. Positive and negative somatotopic BOLD responses in contralateral vs. ipsilateral Penfield homunculus

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Abstract

One of the basic properties of sensory cortices is their topographical organization, such as the somatotopic organization of the body in the primary somatosensory cortex (S1). Here we studied this organization in both contralateral and ipsilateral S1 using optimal phase-locking mapping methods. Recently, there has been growing interest in the functional relevance and the physiological basis of the negative blood oxygenation level-dependent (BOLD) signal. Thus we also studied the organization of such negative responses in both hemispheres following tactile inputs. We found that different body segments elicit pronounced negative BOLD responses in both contra- and ipsilateral hemispheres but with different spatial patterns. In the contralateral hemisphere, we found a sharpening mechanism in which stimulation of a given body segment triggered a gradient of activation in neighboring parts with a significant deactivation in more remote body segments. For instance, touching the hands elicited positive BOLD in the hand and shoulder areas but massive deactivation in more ventral and dorsal areas of S1. In the ipsilateral cortex the deactivation was not only located in the ipsilateral homolog of the stimulated parts but rather was widespread across many parts of ipsilateral Penfield homunculus. Finally, analysis of the resting state fMRI signal in a number of topographic locations along the postcentral gyrus showed that in the baseline resting state, each body segment showed a gradient of connectivity to the neighboring contralateral body parts as well as to the ipsilateral homologous area. This enabled us to reconstruct the mirrored ipsilateral homunculus by showing somatotopically organized functional connectivity patterns between the hemispheres. Taken together, our results indicate a complex pattern of baseline and activity-dependent responses in both the contralateral and ipsilateral sides. Both primary sensory areas were characterized by negative BOLD responses, suggesting that they are an important component in sharpening the tuning curves of populations of neurons, as was demonstrated for topographic gradients in both the visual and the motor cortices.

2.1 Introduction

One of the basic properties of sensory cortices is their topographical organization. Recent studies have found that topographic mapping might also be a crucial component of brain organization for higher processing functions such as memory, spatial attention and numerosity (Hagler and Sereno, 2006; Harvey et al., 2013; Kastner et al., 2007; Silver et al., 2005). One of the most famous manifestations of topographic organization is the somatotopic organization of the somatosensory-motor system described by Penfield and Boldery (Penfield and Brodley, 1937) in the primary somatosensory (S1) and primary motor (M1) cortices of humans. This organization has been confirmed using non-invasive imaging techniques (Blankenburg et al., 2003; Chen et al., 2006; Fox et al., 1987; Huang and Sereno, 2007; Kell et al., 2005; Kurth et al., 1998; McGlone et al., 2002; Miyamoto et al., 2006; Nelson and Chen, 2008; Overduin and Servos, 2008; Schweizer et al., 2008)by showing that tactile stimulation of neighboring parts of the body evokes an increase in the blood oxygenation level-dependent (BOLD) signal in adjacent areas in the contralateral S1. However, the vast majority of these studies have only used up to three distinct body parts or focused on distinct areas of the body surface (Blankenburg et al., 2003; Chen et al., 2006; Huang and Sereno, 2007; Kurth et al., 1998; McGlone et al., 2002; Nelson and Chen, 2008; Overduin and Servos, 2008; Schweizer et al., 2008). However, phase-locked approaches, which have been proven to be extremely useful for mapping full topographic gradients, are only of limited use in the somatosensory system. These approaches have been used to map several sensory modalities such as the visual system and more recently the auditory and motor system (Besle et al., 2013; Engel, 2012; Engel et al., 1994, 1997; Hertz and Amedi, 2010; Striem-Amit et al., 2011; Zeharia et al., 2012, 2015). They were also used to study integration of visual and tactile responses in the human homolog of the face area VIP (Sereno and Huang, 2006) using an automated air-puff system. Surprisingly, the whole body sensory representation has never been tested with the high-resolution neuroimaging techniques available today. Thus, the first goal of the current study was to map full body gradients in S1 using continuous natural tactile stimulation combined with phase locking techniques.

The second recently observed and still controversial phenomenon which might characterize topographical mapping is the drop in the signal below baseline observed in the non-stimulated parts of the topographic gradient. This was reported in a study using simultaneous electrophysiological recording and fMRI imaging in the visual cortex of macaque monkeys on visual eccentricity maps (Shmuel et al., 2006). The findings indicated that both the multiunit electrode activity and the BOLD signals exhibited a peripheral drop in the signal below the baseline condition when the fovea was stimulated and vice versa. Such negative BOLD responses, or deactivations, have been found in the visual cortex of humans as well (Bressler et al., 2007; Pasley et al., 2007; Shmuel et al., 2002) and were suggested to reflect functional decreased neural activity and/or increased inhibition (Boorman et al., 2010; Bressler et al., 2007; Devor et al., 2007; Kastrup et al., 2008; Klingner et al., 2010; Schäfer et al., 2012; Shmuel et al., 2002, 2006; Stefanovic et al., 2004). Recently, our group extended these findings to the motor domain by showing the same phenomenon in the primary motor area (M1) for synchronous bilateral body movements but not in the supplementary motor area (SMA, (Zeharia et al., 2012)) or anywhere else in the other 8 homunculi outside M1 (Zeharia et al., 2015). However, it is not clear whether this mechanism is also present in the somatosensory system. Therefore, our second goal was to explore negative BOLD responses in the contralateral hemisphere, and specifically to test whether such negative responses would show a topographically biased organization similar to the results reported for the visual and motor cortices. Since such topographic negative BOLD responses mostly seem to characterize primary sensory and motor areas, we focused here on the primary somatosensory area. Our prediction was that stimulation of the feet would result in negative BOLD responses in the lip area and vice versa and that stimulation of the hands would result in deactivation in both the upper and lower parts of the body gradient.

Interestingly, negative BOLD responses in the somatosensory system have primarily been studied in the context of cross-hemispheric interactions. Specifically, negative BOLD was found in the ipsilateral primary somatosensory and motor cortices after unilateral hand or finger stimulation (Gröschel et al., 2013; Hlushchuk and Hari, 2006; Kastrup et al., 2008; Klingner et al., 2010, 2014) and hand movement (Allison et al., 2000; Ferbert et al., 1992; Hamzei et al., 2002; Newton et al., 2005; Perez and Cohen, 2008; Stefanovic et al., 2004). These ipsilateral somatosensory evoked deactivations were associated with an elevated sensory threshold (Kastrup et al., 2008) and their amplitude was found to increase with stimulus duration and intensity (Klingner et al., 2010), suggesting an underlying inhibition or dys-facilitation of the non-stimulated hand. However, one limitation of previous studies is that they stimulated one body part (the hands) and tested the positive and negative BOLD responses only in the contralateral and ipsilateral hand representation. Here, by taking a more holistic approach and looking at the pattern of ipsilateral BOLD signals following stimulation of many body parts, we can examine whether this deactivation in the ipsilateral hemisphere is specific to the area of the ipsilateral stimulated body part as suggested by previous studies (Gröschel et al., 2013; Hlushchuk and Hari, 2006; Kastrup et al., 2008; Klingner et al., 2010, 2014) or can be detected for all other ipsilateral body parts, thus reflecting a general mechanism for all non-stimulated body parts whether contralateral or ipsilateral.

2.2 Material and Methods

Subjects: A total of 21 healthy right-handed subjects (8 females) aged 24–37 (mean age 29) with no neurological deficits were scanned in the current study. All participants were scanned in the continuance-periodic somatosensory experiment, with different subsets of subjects participating in the block design experiment and resting-state scan (specified below). The Tel Aviv Sourasky Medical Center Ethics Committee approved the experimental procedure and written informed consent was obtained from each subject before the scanning procedure.

Experiments and stimuli:

1. Periodic experiment (n=21): This experiment included two scanning sessions of somatosensory stimulation. In each stimulation block, the body surface was stimulated sequentially by brushing the right side of the subjects' skin surface from the lips, and then continuously from the fingers and palm through the shoulder, waist, knee, and down to the toes. This stimulation order was reversed in the second scanning session, so each body segments was brushed backwards (i.e. toes to knee, knee to waist). The stimulus was passive and subjects were asked to concentrate on the tactile sensation. We chose this continuance stimulus paradigm as it has been shown to be an optimal method for topographical mapping (Engel, 2012; Engel et al., 1997; Sereno et al., 1995) that requires relatively short scanning sessions. The natural tactile stimuli were delivered using a four-centimeter-width paint brush by the same experimenter, who was well-trained prior to the scans to maintain a constant pace and pressure during the sessions. Precise timing of stimuli was achieved by auditory cues delivered to the experimenter through fMRI-compatible electrodynamic headphones (MR-Confon, Germany). The length of each stimulation cycle was 15 s (from lips to toes or vice- versa), which was followed by a 12 s rest baseline (**Figure 2.1A**). Each scanning session included 8 blocks of tactile stimulation. 30 seconds of silence were added before and after the 8 cycles of tactile stimulation for baseline.

2. Block-design experiment: In order to further test the pattern of somatotopically organized negative BOLD responses, we conducted a block-design experiment. In each block, the subject's right body was brushed in one of the following locations: lips, fingers and palm, shoulder, waist, knee and foot (in two perpendicular directions). A stimulation block lasted 9 seconds, followed by a 9 seconds rest baseline. Each body part stimulation was repeated 4 times, in a pseudo randomized order. A subset of 8 subjects participated in this experiment.

In both experiments, the tactile stimulation was delivered by manual brushing of the body. We chose this stimulus method for several reasons. First, since brushing the skin surface imposes a robust tactile stimulus, it is likely to activate both cutaneous and deep tissue receptors in the primary somatosensory area. This stimulation paradigm has been shown to result in a wider activation pattern and to be more effective in recruiting all the subareas of the primary somatosensory cortex, compared to air puff stimulation (Huang et al., 2012). Second, a broad stimulus has been found to be effective in activating higher somatosensory areas that are characterized by neurons with large receptive fields (Disbrow et al., 2000; Robinson and Burton, 1980). Although this stimulation method is somewhat less controlled than an automatic stimulus, and may lead to small variations in stimulus strength and timing, it provides an easy and fairly natural way to stimulate the whole body. Moreover, the relatively slow temporal sampling rate of the magnet entails a temporal resolution threshold in which small deviations from precise timing (on the order of tens to hundreds of milliseconds) will not affect the large scale somatotopic organization.

Functional and Anatomical MRI Acquisition: The BOLD fMRI measurements were obtained in a whole-body, 3–T Magnetom Trio scanner (Siemens, Germany). The scanning session included anatomical and functional imaging. The functional protocols were based on multi-slice gradient echoplanar imaging (EPI) and a standard head coil. The functional data were collected under the following timing parameters: TR (time repetition) = 1.5 s, TE = 30 ms, FA = 70°, imaging matrix = 80 × 80, FOV = 24 × 24 cm (i.e., in-plane resolution of 3 mm). 27-35 slices with slice thickness = 4.1-4.3 mm and 0.4-0.5 mm gap were oriented in the axial position, for complete coverage of the whole cortex. The first ten images (during the first baseline rest condition) were excluded from the analysis because of non-steady state magnetization. High resolution three-dimensional anatomical volumes were collected using a 3D-turbo field echo (TFE) T1-weighted sequence (equivalent to MP-RAGE). Typical parameters were: Field of View (FOV) 23cm (RL) x 23cm (VD) x 17cm (AP); Foldover- axis: RL, data matrix: 160x160x144 zero-filled to 256 in all directions (approx. 1mm isovoxel native data), TR/TE=9ms/6ms, flip angle = 8°. Cortical reconstruction included the segmentation of the white matter using a grow-region function embedded in the Brain Voyager QX 2.0.8 (Brain Innovation, Maastricht, Netherlands) software package. The cortical surface was then inflated. Group results were superimposed on a 3D cortical reconstruction of a Talairach normalized brain (Talairach and Tournoux, 1988).

Preprocessing of fMRI Data: In order to reduce artifact and noise-related signal components, a series of operations is typically performed on raw functional data sets. The essential steps of these preprocessing operations were initially performed using the Brain Voyager QX 2.0.8 software package and included:

Slice scan timing correction- The problem of different slice scanning times stems from the fact that a functional volume is usually not covered at once but with a series of successively measured 2D slices. In order to correct for different slice scan timings, the time series of individual slices are "shifted" in time to match a reference time point. Correcting differences in slice timing using the data-shifting approach requires re-sampling the data at time points falling in-between measured data points. This study used the *Cubic spline interpolation* with ascending slice scanning order.

3-D motion correction- Estimation of subject's head movements based on one reference volume and realignment of the time series. The realignment is applied by rigid body transformations, combination of three translation (in mm) and three rotation parameters (pitch, roll, yaw; in degrees). Interpolation was used to correct the motion which is a combination of *trilinear* for detection and *sinc* for correction. No data included in the study showed translational motion exceeding 2 mm in any given axis, or had spike-like motion of >1 mm in any direction.

Temporal filtering - Voxel time courses of fMRI data often show low-frequency drifts. If not taken into account, these signal drifts reduce substantially the power of analysis. These drifts are removed by using a high-pass filter, such a filter allows high frequencies pass but removes low frequencies, i.e. the signal drifts. High-pass filtering is performed separately for the time course of each individual voxel since neighboring voxels can exhibit different drifts. The presence of low frequencies is estimated in frequency domain, but the filtering is performed in the time domain, i.e. the domain of the originally measured data. Two cycles per time course was set to be the cutoff for sine and cosine predictors. The time courses were de-trended to remove the mean value and linear drifts, and in the periodic experiment a temporal smoothing (4 s) in the frequency domain was also applied to remove drifts and to improve the signal-to-noise ratio. For group analyses the functional data also underwent spatial smoothing (spatial Gaussian smoothing, full width at half maximum = 6 mm) to overcome inter-subject anatomical variability within and across experiments. Functional and anatomical datasets for each subject were aligned and fit to the standardized Talairach space (Talairach and Tournoux, 1988).

Data analysis:

Spectral analysis: Spectral analyses were conducted with an in-house program using MATLAB (MathWorks, Natick, MA). Following standard retinotopy procedures (Engel et al., 1994, 1997), we applied Fourier analysis to the time course of each voxel, locked to the stimulus repetition frequency (Hertz and Amedi, 2010; Striem-Amit et al., 2011; Zeharia et al., 2012). The Fourier analysis delivered amplitude and phase values of the time course for the repetition frequency in each voxel.

The complex Fourier coefficient at the repetition frequency f_{rep} is denoted by:

[1] $$F\left(f_{rep}\right) \equiv a\left(f_{rep}\right) \cdot e^{i \cdot \varphi\left(f_{rep}\right)}$$

where $a\left(f_{rep}\right)$ represents the amplitude and $\varphi\left(f_{rep}\right)$ the phase. It is calculated by the discrete Fourier transform at the repetition frequency:

[2] $$F\left(f_{rep}\right) = \sum_{k=1}^{N} TC[k] \cdot e^{-i2\pi \cdot (k \cdot f_{rep})}$$

where *TC* represents the sample time course, *N* is the number of sampled time points (144) and *K* is the time variable.

Figure 2.1B shows the Fourier amplitudes in various frequencies in a typical voxel at the postcentral gyrus. In this voxel, the amplitude was the highest at the repetition frequency (0.037Hz). For each voxel, both the amplitude and phase parameters were used to construct a pure cosine which served as a model of the activation:

[3] $$Model_{f_{rep}} \equiv a\left(f_{rep}\right) \cdot \cos\left(2\pi f_{rep} \cdot t + \varphi\left(f_{rep}\right)\right)$$

A Pearson correlation coefficient was then calculated between the model and the original time course, yielding a correlation coefficient for each voxel.

Figure 2.1C shows the BOLD signal in the same voxel, along with a pure cosine function made up of the amplitude and the phase values at the repetition frequency.

This cosine profile served as a model of the activation for further statistical evaluation of the results. A Pearson correlation coefficient was calculated between this model cosine and the time course in each voxel and this was used as a direct measure of the voxel’s response to the tactile stimulation (regardless of the specific body segment represented in this voxel).

The correlation coefficient R was transformed ($\frac{R \cdot \sqrt{N-2}}{1-R^2}$) and used as a *t* statistic with N−2 degrees of freedom (in our case N=144) to calculate, independently for each voxel, the significance of the cortical response to the somatosensory stimulus.

In regions showing high correlation to the stimulus repetition frequency, the phase value was inspected. Phase values were distributed between –π and π, and were linearly transformed to range between 0 and 27, representing time points in each stimulus cycle. Since the tactile stimulation of a given body segment was always made at a fixed time point in the stimulus cycle, the phase value served as a measure of the body segment being touched. Due to the time delay of the hemodynamic response, the phase code does not temporally overlap with the stimulus presentation time. The onset of the first response detected in the postcentral gyrus (PoCG) was considered to represent the response to the first body part that was stimulated (lips or foot, according to the stimulus session). Similarly, the latest response observed in PoCG was assumed to correspond to the last stimulus that was presented. These values formed the phase code corresponding to the specific preferred body area of each voxel, and resulted in individual phase code maps which corresponded to the individual tactile maps. The resulting known somatotopic gradients in S1 and M1 are shown in **Figure 2.1D**, in which the color code is a measure of the phase value (and the body segment being stimulated) and ranges from red to blue to depict the first to last phase responses, respectively. Phase-locked analysis methods require the body parts to be organized in a highly ordered fashion, which might introduce biases in the BOLD signal. To overcome this problem, we averaged the maps of both scan directions—lips-to-toe and toe-to-lips. The average direction is shown as lips to toe, where the first phase response was attributed to lip stimulation and the last phase response was attributed to the toe stimulation.

On the group level, to run the random effect analysis, we used general linear model (GLM) parameter estimators derived from a complementary analysis, as follows. First, a GLM analysis was carried out at the single-subject level using the pure cosine model described above as a predictor. The pure cosine model predictor is positively biased, because it is derived from the Fourier analysis. To account for this bias, we applied the same approach to 20 other non- stimulus related frequencies for each subject. The average GLM parameter estimator value from these analyses was used as the bias estimator and subtracted from the GLM parameter estimator values in the stimulus representation frequency. The resulting GLM parameter estimator values were then used in a second-level analysis for the group random effect. Finally, the random effect results were corrected for multiple comparisons using the Monte Carlo method (1,000 iterations, $\alpha < 0.05$) with an a-priori threshold of $P < 0.05$. The phase maps of the individual subjects were averaged to create a mean phase map. The phase maps were thresholded by both the averaged correlation coefficient and the random effect corrected for multiple comparison maps.

Cross-Correlation Analysis. A boxcar function 2 Time of Repetition (TRs) long (the duration of stimulation of one body segment) was convolved with a two gamma hemodynamic response function (HRF) to derive predictors for the analysis. These predictors and the time course of each voxel were cross-correlated, allowing for 12 lags with one TR interval time to account for the stimulation duration of each cycle (10 TRs) and two additional TRs to account for the hemodynamic delay. For each voxel, we obtained the lag value with the highest correlation coefficient between the time course and 1 of the 12 predictors and the value of this correlation coefficient. The cross-correlation maps of the individual subjects were averaged across the two scan directions to create a mean cross-correlation map. The random effect group results were obtained using the same method described above for the spectral analysis maps.

GLM analysis: In order to assess the negative BOLD responses elicited by specific body segments, we applied a general linear model (GLM) analysis on the periodic and block design experiments using predictors convolved with a typical two gamma hemodynamic response function (HRF). Since we were interested in the somatosensory and motor cortices, the GLM analysis was restricted to these areas by applying a cortical mask to the model. Cross- subject statistical parametric maps were calculated using hierarchical random-effects model analysis (Friston et al., 1999). A statistical threshold criterion of $P < 0.05$ was set for all results. This threshold was corrected for multiple comparisons using a cluster-size threshold adjustment for multiple comparisons, based on a Monte Carlo simulation approach extended to 3D datasets, using the threshold size plug-in BrainVoyager QX (Forman et al., 1995).

In the periodic experiment, the raw time course of each cycle of responses to the continuous full body tactile stimuli was divided into five brushing segments corresponding to the stimulation of cortically adjacent body parts according to Penfield's classic homunculus (lip, hand, shoulder and upper trunk, waist to knee and knee to toe). This division of the continual stimulus into five segments roughly reflected the dermatomal arrangement of the skin surface: lips (trigeminal cranial nerve), arm and trunk (cervical dermatomes) and waist and leg (thoracic and lumbar dermatomes). The responses to brushing the five segments were averaged from the two sessions with lips-to-toe and toe-to-lips strokes to avoid order and attention effects. Error bars display the standard error across subjects and sessions.

Regions of interest analysis: To investigate the phase shifts in the hemodynamic responses as a continuance and to test for negative BOLD responses, we sampled the raw BOLD signal from LH (contralateral to the stimulated body side) S1 and M1 homunculi at sequential points across the group mapping sequence (Engel et al., 1997). The time course of activation from these ROI was sampled and GLM analysis was conducted in each ROI for the two scanning sessions, across all subjects, yielding the GLM parameter estimators of stimulation for each of the body segments versus the rest baseline. In order to apply a similar analysis to the ipsilateral hemisphere, we defined homologous set of S1 ROIs in the right hemisphere (by vertical axis inversion), based on the bilateral symmetries of these homunculi.

Functional connectivity MRI acquisition and data analysis (n=13): In contrast to classic task-response studies which view spontaneous modulation of the BOLD signal that cannot be attributed to the experimental paradigm or any other explicit parameter as noise, resting-state studies focus specifically on such slow (<0.1 Hz) fluctuations in the BOLD signal as the signal of interest. This was first observed by Biswal et al. (1995) study of the motor cortex, which found that time courses of low frequency fluctuations in resting brain have a high degree of temporal correlation within motor-related regions. Since then it has been shown that spontaneous BOLD activity is not just random noise, but rather it creates specific spatial patterns in the brain, that are temporally coherent and reproducible across known functional networks, and this coherence is termed ‘functional connectivity’ (Nir et al., 2006; Smith et al., 2009; Yeo et al., 2011). Furthermore, these spontaneous resting-state activity fluctuations appear to span the entire cortical surface and are of similar amplitude to those produced during task performance (Nir et al., 2006).

Among the different methods aimed to identify and study spatial patterns of the resting-BOLD (For review see (Fox and Raichle, 2007)), a seed-region based approach is of a wide use owing to its simplicity, sensitivity and ease of interpretation. In this analysis, the time course of a-priori defined region of interest (ROI) is sampled, and the correlation between this time course and the rest of the brain is calculated. Therefore, this approach could identify which areas in the brain share the same spontaneous fluctuation in the BOLD signal, suggesting they are part of the same anatomical or functional network. For example, seed-based method was used to study functional connectivity patterns in the motor system and revealed highly symmetrical and topographic networks of newly identified homunculi (Zeharia et al., 2015). Striem-Amit et al. (2015) studied topographical mapping of the visual scene in congenitally blind adults and found that the blind demonstrated an intact functional connectivity network structural organization of the three main retinotopic mapping axes: eccentricity, laterality, and elevation throughout the retinotopic cortex.

Here, a dataset of spontaneous blood oxygen level-dependent (BOLD) fluctuations for the investigation of intrinsic functional connectivity was collected while the subjects lay supine in the scanner without any external stimulation or task. To obtain full coverage of the subjects' brains, 35 slices of 4 mm thickness were used (data in-plane matrix size, 64 X 64; FOV, 24 X24 cm; TR = 2000 ms; flip angle, 90°; TE= 30 ms). 160 whole-brain images were collected in one functional scan and the first two images of each scan were excluded from the analysis because of non-steady state magnetization. Ventricles and white matter signals were sampled using a grow-region function embedded in the Brain Voyager from a seed in each individual brain. Using MATLAB (MathWorks, Natick, MA), ventricle and white matter time courses were regressed out of the data and the resulting time course was filtered to the frequency band-width of 0.1-0.01 Hz (in which typical spontaneous BOLD fluctuations occur). The resulting data were then imported back into BrainVoyager for group analyses. Single subject data were spatially smoothed with a three-dimensional 6 mm half-width Gaussian to reduce inter-subject anatomical variability. Seed ROIs were defined as group peak activations of the 5 stimulated body segments from the periodic experiments. Individual time courses from these seed ROIs were sampled from each of the subjects who participated in the rest scans, *z*-normalized, and used as individual predictors in the whole-brain group connectivity analysis using a general linear model (GLM) with a hierarchical random effects. The minimum significance level of the results was set to $p<0.05$ (corrected for multiple comparisons) to inspect the whole brain connectivity pattern or to $p<0.01$ to view the peak connectivity in the ipsilateral hemisphere.

2.3 Results

Using a set of functional MRI experiments, including a unilateral tactile passive stimulation of the whole body, we tested for gradients and topographic biases of both positive and negative BOLD responses in the contralateral and ipsilateral S1. We hypothesized that in addition to the positive responses in the contralateral hemisphere, tactile stimulation of different body parts would result in topographically organized deactivations in areas corresponding to the non-stimulated body parts in both the ipsilateral and contralateral hemispheres. The data were analyzed on several levels and approaches, both at the group and single subject level: First, to characterize the large-scale somatotopic organization of the tactile responses we implemented two complementary phase-locked analysis methods: spectral analysis and cross-correlation. Next, we searched for negative BOLD responses in the contralateral and ipsilateral hemispheres through whole brain and regions-of-interest (ROI) GLM analysis of the periodic and block design experiments. Finally, we investigated the connectivity patterns between the somatosensory homunculi, using functional connectivity analysis of resting-state fMRI.

Our first goal was to map the primary somatosensory homunculus following a continuous and periodic tactile stimulation of the right side of the body (**Figure 2.1A**). This periodic design enabled us to apply phase-locked analysis methods which have been shown to be optimal for detecting areas that contain gradual representations or topographic gradients (Besle et al., 2013; Engel, 2012; Engel et al., 1994, 1997; Hertz and Amedi, 2010; Sereno and Huang, 2006; Striem-Amit et al., 2011; Zeharia et al., 2012, see **Materials and Methods**).Two phase-locked analysis methods were used. First, we applied spectral analysis, in which for each voxel, the correlation between the BOLD signal and a Fourier based model, locked to the stimulus repetition frequency was calculated (**Figure 2.1B&C**). Phase values were inspected in regions showing a high correlation with the stimulus repetition frequency, and served as a measure of the body segment being stimulated. Second, we applied cross-correlation analysis. A hemodynamic response function (HRF) predictor corresponding to the stimulation time of one body segment was cross-correlated with the BOLD signal, yielding a set of correlation values for the different lags of the shifted predictors. For each voxel, the predictor with the highest correlation value was chosen as a measure of the body segment being stimulated. The resulting group maps extracted by these methods are presented in a coronal view (**Figure 2.1D**), and on the inflated cortical surface (**Figure 2.1E&F**). Both methods revealed the detailed somatotopic organization of the primary somatosensory cortex contralateral to the stimulated body side. The whole-body detailed somatotopic maps were also evident at the single subject level using both phase-locked methods on spatially smooth and non-smooth datasets (**Figure S2.1**). A complementary GLM analysis presenting the peak response for each of the body segments along the postcentral gyrus (PoCG) verified the topographic ventral-to-dorsal lip-to-toe organization (**Figure 2.1F, right**).

Interestingly, while providing detailed verification of the topographic gradient in S1, the results revealed one difference from Penfield's original maps. In its original illustration (**Figure 2.1D, left**), the representation of the foot and toes extended into the medial wall, close to the cingulate cortex. Our results show that the foot and toe representations are confined to the uppermost part of the medial wall. This suggests a modification of the full-body gradient version of Penfield's sensory homunculus aligned to our maps in S1 (**Figure 2.1D**, adapted from Kell et al., 2005, see **Discussion**).

A completely different pattern was revealed in the ipsilateral hemisphere. Although most of the tactile-evoked responses were localized in the posterior parietal lobe, posterior to the postcentral sulcus, there was no phase-locked response in the ipsilateral S1. These findings are consistent with previous studies showing that ipsilateral activations are localized posterior to the contralateral ones (Iwamura, 2000; Nihashi et al., 2005). The only exception was the response to lip stimulation, which was visible in the ventral ipsilateral cortex. This result was expected, given that this was the only body area in which the stimulus was bilateral.

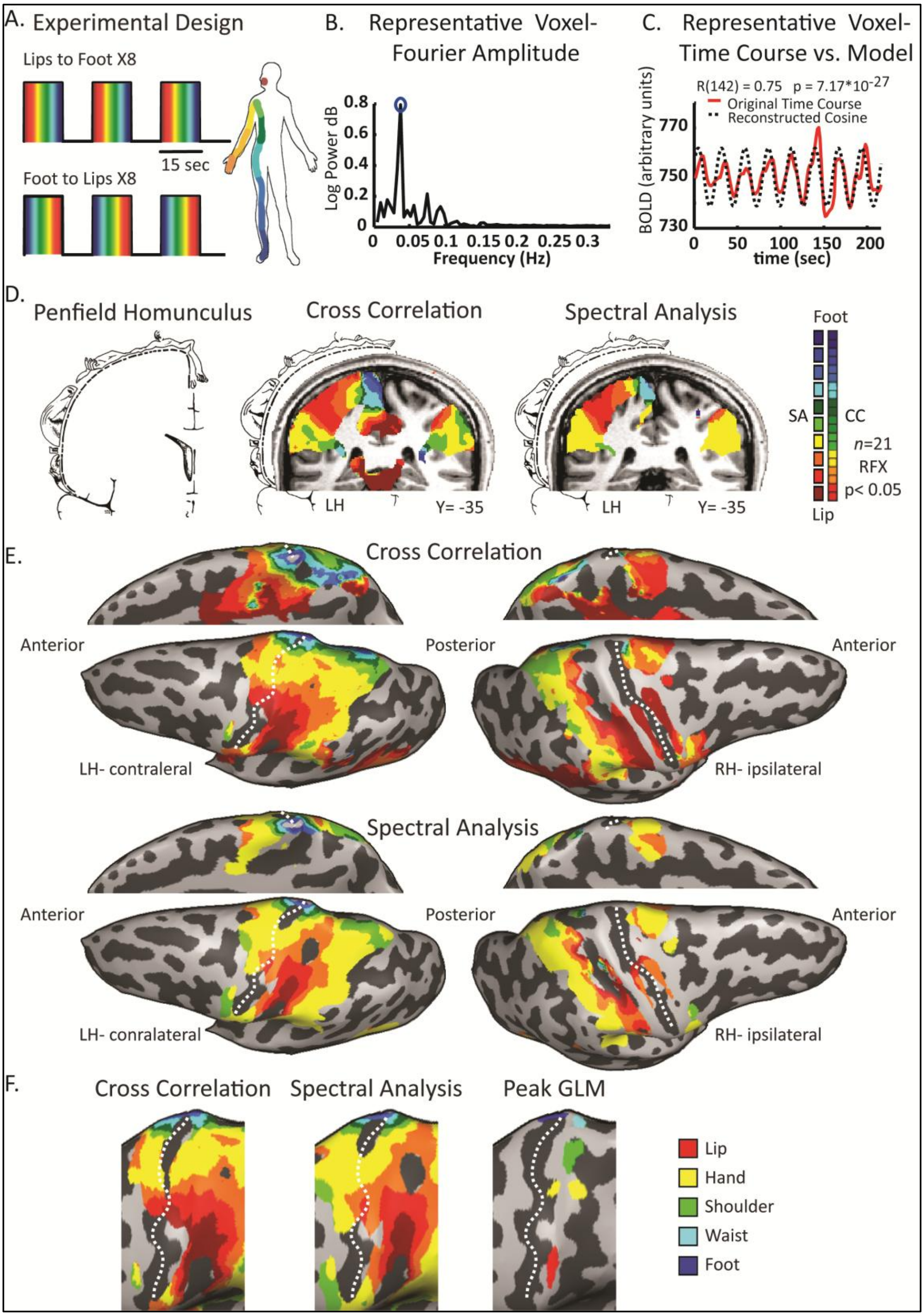


Figure 2.1: Experimental design and phase-locked mapping of the primary somatosensory homunculus. A. The experimental design of the periodic experiment, comprising eight cycles of whole body passive tactile stimulation from lips to toe and eight reversed cycles from toe to lips. **B.** The Fourier amplitude in various frequencies of a typical voxel from the postcentral gyrus. High amplitude at the repetition frequency of the experiment (marked by

a blue circle) indicates that this voxel was responsive to touch. **C.** The amplitude at the repetition frequency and the phase value were derived from the Fourier analysis of the time course in a given voxel, and were used to build a cosine, which served as a model of activation for this voxel. **D.** Full-body group maps of the homunculus in S1 obtained by cross-correlation and spectral analysis are shown on a coronal slice which also shows the modified illustration of Penfield's somatosensory homunculus (adapted from Kell et al., 2005). The original Illustration of Penfield's homunculus is presented in the left panel (adapted from Penfield and Rasmussen, 1950).**E**. The same maps as is in D are presented on an inflated brain reconstruction in lateral and medial views. Note that in the medial view images, the hemispheres were flipped for illustrative purposes and alignment with the maps on the lateral view. **F**. Magnification of the primary somatosensory cortex showing the similarity between the maps obtained by cross-correlation and spectral analysis as well as the peak activation of each body segment obtained by GLM analysis. Dashed line marks the central sulcus.

Next we tested for negative BOLD responses in the contralateral hemisphere. Since both phase-locked analysis methods use the highest correlation value between the model and the voxel's time course as a measure of the body segment that was stimulated, they are not appropriate for detecting simultaneous negative evoked responses. Thus, to do so, we defined 7 consecutive region-of-interests (ROIs), from the most ventral lip representation to the most dorsal toe representation in the contralateral S1 (**Figure 2.2A**). The BOLD signal from each ROI was sampled and a group GLM analysis was calculated for the body segments. **Figure 2.2B&C** present the extracted GLM parameter estimator and the average time course for the separate body segments in S1 ROIs. The results also serve as a complementary method to test the gradual shift in the representation of different body parts along S1, as depicted by the peak parameter estimator and time course. Importantly, this analysis can also test for significant deactivations in the primary somatosensory homunculus (Zeharia et al., 2012). Specifically, in most of the ROIs along the PoCG we found a combined pattern of significant positive and negative BOLD responses to different body parts. For example, whereas in the most ventral ROI within the PoCG the lips and hand evoked positive BOLD responses, the waist and foot evoked negative BOLD. This pattern was reversed in the most dorsal ROI of the PoCG, where the foot stimulation resulted in positive BOLD and the lips and hand evoked deactivation.

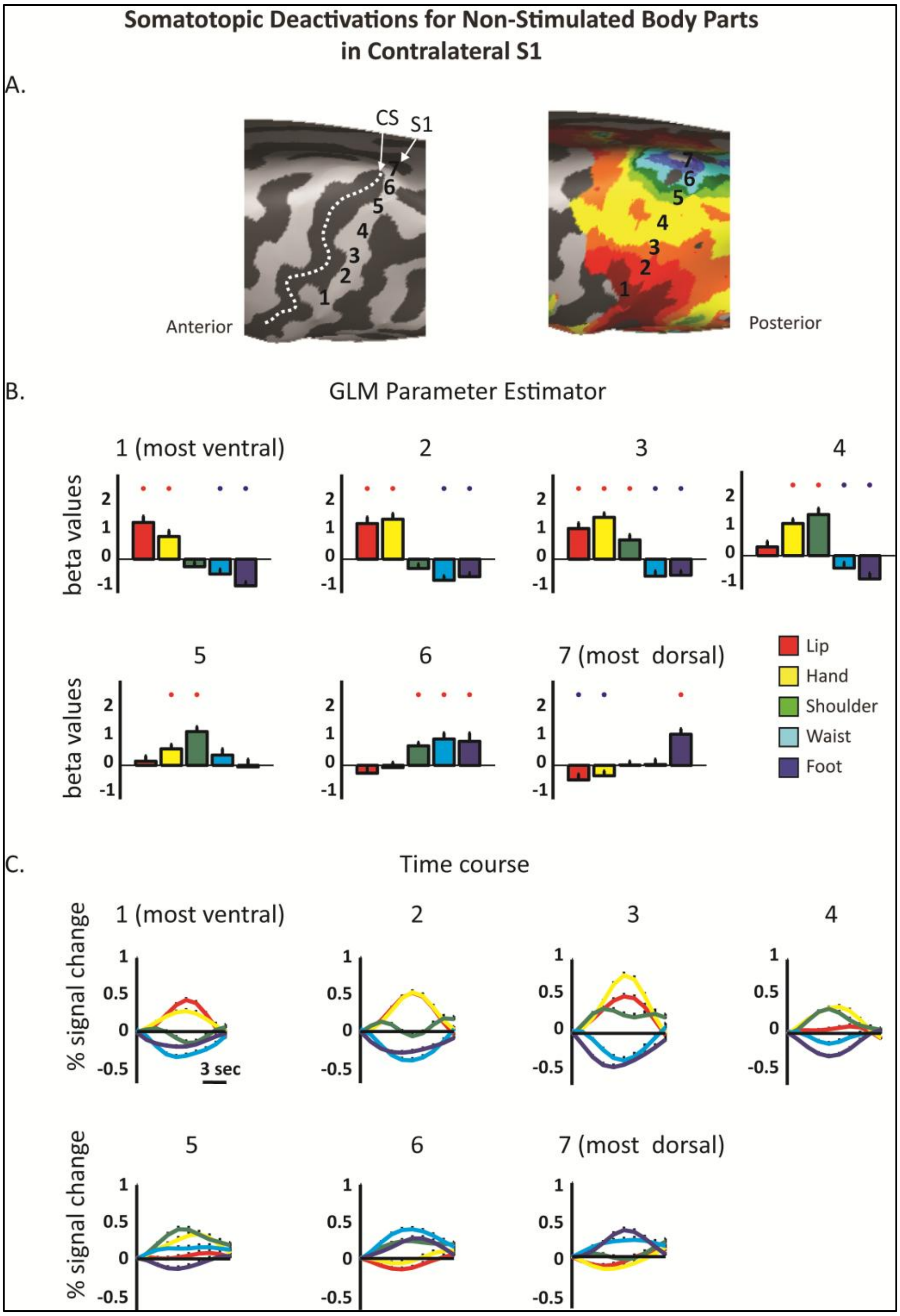


Figure 2.2: ROI GLM analysis of positive and negative BOLD responses in the contralateral S1. A. Consecutive region-of-interests (ROI) were defined along the contralateral hemisphere from the ventral to the dorsal PoCG. **B.** GLM parameter estimators extracted from the contrast of each body segment vs. baseline rest. Red and blue asterisks denote significant activation and deactivations respectively ($p<0.05$). **C.** Average time courses in the same ROIs demonstrate the mix pattern of positive and negative BOLD along the contralateral primary somatosensory homunculus.

A similar trend was also observed in the contralateral M1 (**Figure S2.2**, see **Discussion**). Therefore, this analysis clearly shows that unilateral tactile stimulation of the body results not only in positive BOLD in the corresponding somatotopic area within S1, but that it also deactivates other parts of the homunculus corresponding to the non-stimulated body part. This deactivation in the somatosensory cortex, although weaker than the positive BOLD responses (resembling the lower amplitudes of negative BOLD in the motor and the visual system), is still quite robust, and attains average up to 70 % of the positive responses (maximum negative response -0.28 ± 0.11 % signal change, maximum positive response 0.4 ± 0.13 % signal change) and is evident in most of the ROIs.

In the next step, we explored the tactile evoked negative responses in the ipsilateral hemisphere. We showed above that the ipsilateral S1 was not activated using the phase-locked analysis methods (**Figure 2.1**). In order to apply a similar ROI GLM analysis approach, we defined homologous ROIs in the ipsilateral hemisphere using the same 7 ROIs (see **Materials and Methods**). These ROIs served as the GLM parameter estimation analysis. **Figure 2.3** presents these results for the separate body segments vs. the baseline as well as the contrast of all body segments versus baseline. Both types of analysis revealed several interesting and novel findings. First, when contrasting all body segments with the baseline, a general deactivation was observed in most of the ROIs of the ipsilateral PoCG. Second, inspection of the separate responses for the different body segments showed that the evoked negative BOLD responses in the ipsilateral hemisphere were not confined to the homologous area within S1 (as previously suggested), but rather extended to other parts of the homunculi. For example, stimulation of the hand evoked significant negative BOLD in medial ROIs (ROIs 4&5 in the PoCG), corresponding to hand representation, but also in dorsal ROIs (ROIs 6&7 in the PoCG), corresponding to waist and foot representations. Furthermore, foot evoked deactivations were evident almost in the entire ipsilateral S1, though they did not reach significance in the most dorsal ROIs. There were two exceptions to these results. One is trivial - the lips were the only area in which the stimulation was bilateral and therefore there was a significant activation for the lips in the most ventral ROI, whereas significant deactivations were observed in most of the other ROIs. Second, the only body segment that showed a trend for positive parameter estimator rather than negative (though not significant above baseline) in response to unilateral stimulation was the shoulder and upper trunk. This result is consistent with previous studies showing that midline structures in the axis of the body (such as the trunk) have symmetrical bilateral representations (Eickhoff et al., 2008; Fabri et al., 2005). To summarize, we showed that beside the axial bilateral structures, in all other ROI not only was the negative BOLD not limited to the ipsilateral stimulated segment, but usually it was not even the peak of the negative BOLD (in term of the beta GLM parameter estimator).

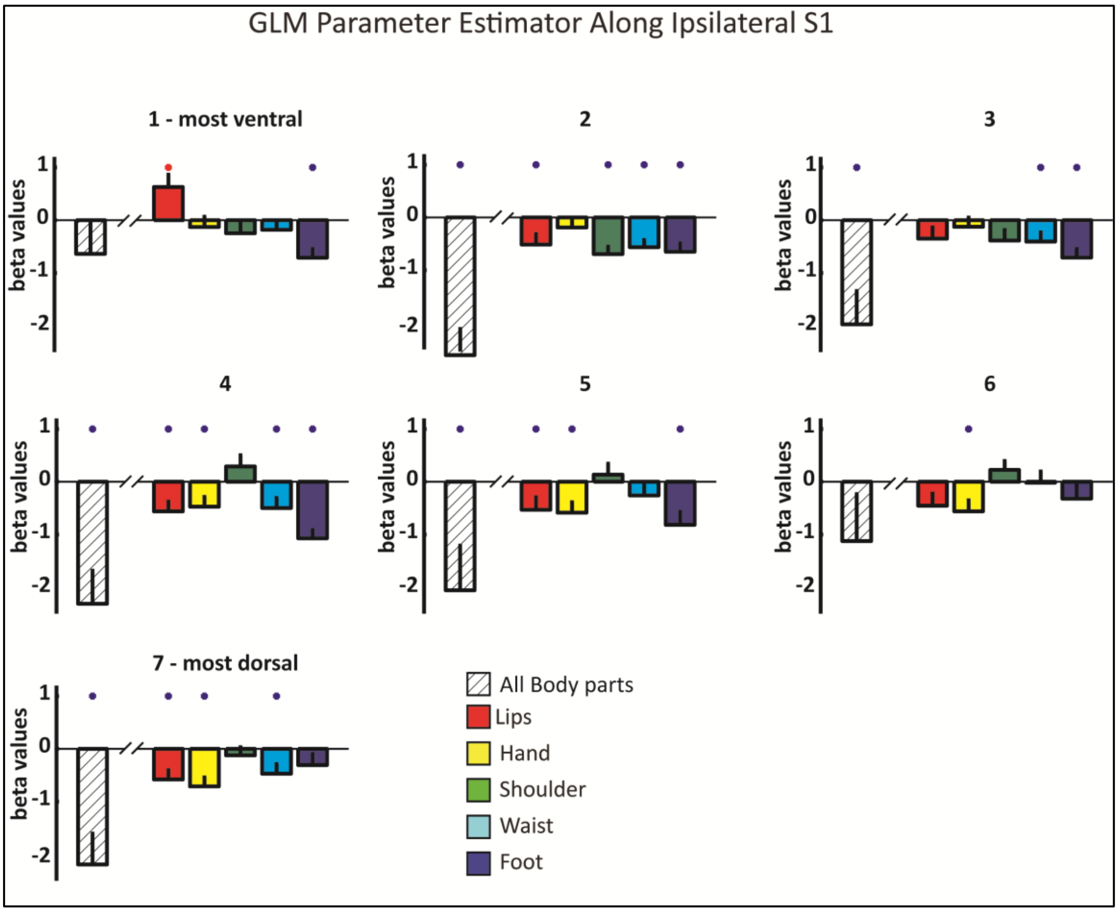


Figure 2.3: ROI GLM analysis in ipsilateral S1 reveals widespread negative BOLD responses. GLM parameter estimator depicted in the ipsilateral hemisphere using the homologous ROIs in Figure 2.2. Color bars represent the GLM parameter of the separate responses to the different body parts vs. baseline rest. Striped bars represent the GLM parameter of the contrast of all body segments vs. baseline rest. Red and blue asterisks denote significant activation and deactivations, respectively ($p<0.05$).

To further characterize the positive and negative BOLD across the two hemispheres and to verify the results using another complementary method, we conducted a GLM analysis of the BOLD signal across the entire contra- and ipsilateral sensory-motor cortices (this was done on a voxel by voxel basis unlike the ROI approach above; see **Material and Methods**). The general pattern of activation and deactivation in response to lips, hand and foot stimulation is presented in **Figure 2.4**. Because negative BOLD was defined as a decrease in the BOLD signal relative to the rest baseline, the negative responses were seen when contrasting stimulation periods with rest. The results revealed a somatotopic organization of the negative BOLD in S1 (**Figure 2.4A**, $t(20) = 2.2$, $p<0.05$, corrected for multiple comparisons). In the contralateral hemisphere, where lip stimulation elicited positive BOLD, hand and foot elicited negative BOLD; where hand stimulation evoked positive BOLD, foot evoked negative BOLD, and where foot stimulation elicited positive BOLD, the lips and hand elicited negative BOLD. In the ipsilateral hemisphere, positive BOLD responses were observed in the most posterior parts of S1 and the posterior parietal cortex whereas the negative BOLD responses were localized mostly to the anterior part S1, along the posterior bank of the central sulcus. The pattern of the negative BOLD in the ipsilateral hemisphere was more extensive compared to the contralateral side, and also included the homologous area of the unilateral stimulated body segment. Thus, the areas in the ipsilateral hemisphere corresponding to the hand and foot were deactivated by the ipsilateral body segments and not only by the hand or foot. The inverse relations of the positive and negative BOLD in S1 are clearly visible when the statistical parametric maps are plotted separately for positive or negative BOLD (**Figure 2.4B**). Inspection of the negative BOLD maps reveals a completely different pattern for contralateral vs. ipsilateral responses. In the contralateral side we found a negative BOLD homunculus which is so body- segment specific it could be portrait in terms of the responses in the non-stimulated body segments. By contrast, in the ipsilateral hemisphere the negative BOLD responses overlapped, reflecting the widespread characteristics of the ipsilateral BOLD.

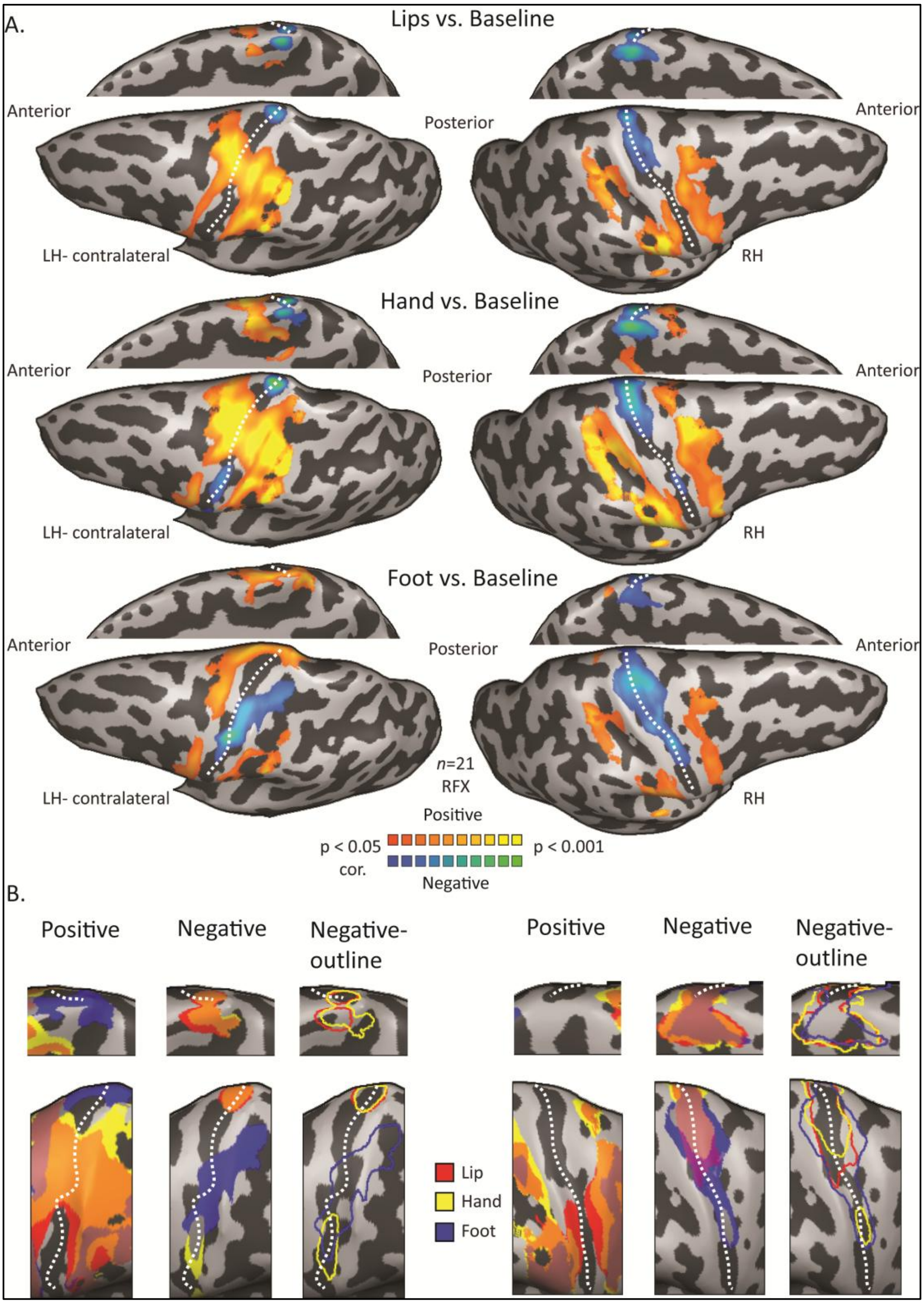


Figure 2.4: Somatotopic versus widespread negative BOLD in the contralateral and ipsilateral homunculi. A. Statistical parametric maps of the positive and negative BOLD responses to lips (upper), hand (middle) and foot (lower) tactile stimulation. An anatomical mask of the sensory-motor cortex was applied to the GLM analysis. Negative BOLD is somatotopically organized in the contralateral S1 and adjacent to the positive BOLD,

whereas a more extensive pattern of the negative BOLD can be seen in the ipsilateral hemisphere. Note that in the medial view representations, the hemispheres were flipped for illustrative purposes and alignment with the maps on the lateral view. **B.** The combined positive BOLD responses to lips, hand, and foot stimulation from A are plotted on a magnification of the PoCG (left panel for each hemisphere magnification) showing the somatotopic organization of the contralateral S1. The combined negative BOLD responses to these stimuli (middle and right panels in each hemisphere magnification, for full maps and outlines) showing a coarse negative homunculus in the contralateral S1 and an overall deactivation in the ipsilateral S1. Dashed line marks the central sulcus.

Finally, to further investigate the connectivity patterns of the bilateral somatosensory homunculi, and to assess the potential connections mediating the bilateral positive and negative responses, we conducted a functional connectivity analysis of resting state fMRI data. For this purpose, we identified 5 seed ROIs in the contralateral hemisphere which were defined as peak group activations of the five stimulated body segments derived from the periodic experiments. We then used the time courses from each of these seed ROIs separately as predictors in a group random-effect GLM analysis. The functional connectivity maps of the different body segments are shown in **Figure 2.5** ($t(12)=4.2$, $p<0.01$, corrected), and indicate that for each body segment seed, the peak connectivity in the ipsilateral hemisphere is localized in the homologous area to the body segment. In other words, these maps reveal that the ipsilateral homunculus can be reconstructed from the connectivity pattern of the contralateral homunculus.

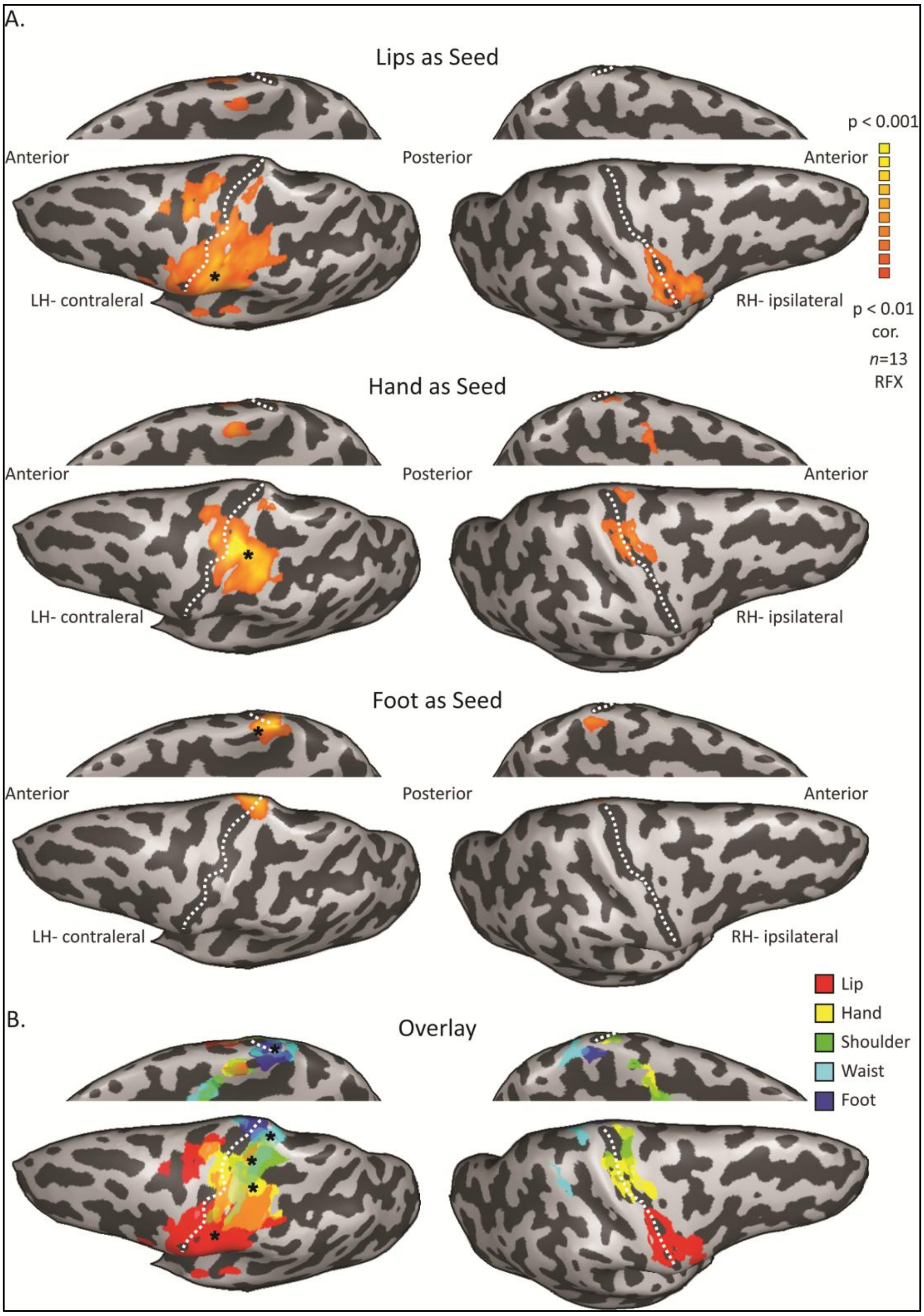


Figure 2.5: Functional connectivity analysis. A. Statistical parametric maps of the random effect whole brain functional connectivity analysis of the resting BOLD signal from the lips (upper), hand (middle) and foot (lower) seeds in the contralateral hemisphere (marked by asterisks) show that the peak connectivity in the ipsilateral hemisphere is localized in the homologous area of each contralateral seed. **B.** Overlay of the functional connectivity maps of all five body segment seeds shows the reconstruction of the ipsilateral homunculus.

2.4 Discussion

In this work we studied the somatotopic organization of the positive and negative BOLD responses in contra- and ipsilateral primary somatosensory homunculi and found several novel results along with several verifications and extensions of the previous literature. Using continuous and periodic unilateral tactile stimulation of the entire body and applying phase-locked analysis methods, we were able to verify the well-known contralateral topographical organization of S1, and to demonstrate the gradual shift in the representation of different body parts (**Figures 2.1**, **2.2**, **S2.1**). Beyond the demonstration of the Penfield homunculus we suggest that this homunculus should be modified at the medial wall, since the full-body topographic gradient did not reach medially to the corpus callosum.

We also showed that S1 contains a sharpening contrast mechanism in which a combination of positive and negative BOLD was evoked for each of the tested body segments (**Figures 2.2**, **2.4**, **S2.3**). Taken together with previous literature from the motor and visual systems, this seems to be a general mechanism in all topographic sensory and motor areas. We further showed that this negative BOLD also characterizes the ipsilateral cortex, but in contrast to previous studies and to the contralateral hemisphere we found that these negative responses are much widespread and overlap following stimulation of the body segments (**Figure 2.3**, **2.4**, **S2.3**). The same pattern of contralateral and ipsilateral responses was also found at the single-subject level (**Figure S2.1**) or when conducting an additional block design experiment on a subset of the subjects. (**Figure S2.3**). This shows that the results could not be attributed to the continuous periodic design paradigm, or to data pooling over the group, but rather reflect a basic property of the BOLD signal in primary sensory areas. Although its manifestation might be different in the contra- and ipsilateral hemispheres, we argue that the purpose of this negative BOLD might also be to act as a sharpening mechanism that enhances the tactile signal in the first stage of cortical processing.

2.4.1 Mapping the primary somatosensory homunculus

Since its discovery by Penfield and Boldrey (1937), the principal organization of the primary somatosensory cortex has been verified in large number of species, using variety of methods (Chen et al., 2005, 2007; Kaas, 1983; Kaas et al., 1979; Nelson et al., 1980; Rothemund et al., 2002; Shoham and Grinvald, 2001). The somatotopic organization of S1 in humans has been partially confirmed non-invasively by neuroimaging studies (Huang and Sereno, 2007; Kell et al., 2005; Kurth et al., 1998; McGlone et al., 2002; Miyamoto et al., 2006; Nelson and Chen, 2008; Overduin and Servos, 2008; Schweizer et al., 2008). However, the vast majority of these studies focused on distinct body part stimulation. Hence a detailed full-body somatotopic organization in humans has not been fully investigated using imaging techniques. Moreover, using only one or a few body parts makes it impossible to use a phase-locking approach to map whole body gradients; this was the first goal of this study. Here, using cross-correlation and spectral analysis we mapped Penfield's homunculus in great detail. These maps revealed the phase shifts of activation from the lip activated area in the lateral surface of the postcentral gyrus to the foot and toe activated area at the most dorsal part of the postcentral gyrus and hemispheral rim (**Figure 2.1** for group results; **Figure 2.2** for phase shift in the time course; **Figure S2.1** for single subjects and raw unsmooth data). One fundamental difference between these two somatotopic maps has to do with the somatotopic organization of the medial wall. In the classic homunculus illustration (Penfield and Rasmussen, 1950), the foot and toes are represented deeply in the medial wall, close to the border with the cingulate cortex, whereas the genitals are represented deeper in the medial wall, neighboring the corpus callosum. Our data show that the foot and toe representations do not extend beyond the most upper part of the medial wall. This result was consistent across both phase-locked analysis methods (**Figure 2.1**) and GLM (**Figure 2.4**) as well as for single subjects (**Figures S2.1 & S2.3**). These findings are congruent with recent neuroimaging and intracranial recording studies (Huang et al., 2012; Kell et al., 2005; Di Russo et al., 2006) assigning the foot representation to the upper-most parts of the medial wall. However, it could be argued that the difference between our results and Penfield's homunculus is related to the representation of the genitals, which were not stimulated in our study and thus are missing from the full-body gradient in the medial wall. However, a recent fMRI study by Kell and colleagues (2005) focused on the mediolateral sequence of somatosensory foot, penis, and lower abdominal wall representations found that the penile representation was localized lateral to the foot representation, and overlapped with the representation of lower abdominal wall. On the basis on these finding, they introduced a modified version of Penfield's somatosensory homunculus in which the genitals are represented in a topographical relationship to that of adjacent body parts. Hence the S1 homunculus terminates in the most dorsal part of the PoCG, excluding the medial wall (Kell et al., 2005). Potentially, the foot representation might be pushed more laterally and dorsally to the rim of the cortex might be due to upper body segment sensitivity in the medial wall towards the cingulate cortex (see the responses to the lip and hand stimulation in the medial view of **Figure 2.4**). Interestingly, this was also hinted at by Penfield in his final paper (Penfield and Jasper, 1954), which proposed a "supplementary somatosensory area" in the medial wall, which to date has not been studied or confirmed. We found phase-locking reversal of the gradient in the medial wall, but the time course and GLM parameter estimators were not conclusive enough to draw conclusions. Future studies focusing on the somatosensory gradients of the medial wall, using higher resolution with smaller voxel size might provide a better way to reach clearer conclusions on this issue by providing detailed maps of this area, similar to the recent findings in the motor system (Zeharia et al., 2015).

In this study, we used two phase-locking analytic approaches for somatotopic mapping: cross- correlation and spectral analysis. These approaches are considered the classical means of defining early visual areas (Engel et al., 1994, 1997; Sereno et al., 1995; Wandell and Winawer, 2011) and have also been used to map other topographically organized sensory (Hertz and Amedi, 2010; Orlov et al., 2010; Striem-Amit et al., 2011) and motor (Zeharia et al., 2012, 2015) gradients. They yield a highly robust topographic mapping and can pinpoint gradients undetected by standard GLM analysis (Engel, 2012; Zeharia et al., 2015). In the somatosensory system, these approaches have been used to map detailed local gradients of the arm

(Servos et al., 1998), fingers (Besle et al., 2013; Mancini et al., 2012; Overduin and Servos, 2008; Sanchez-Panchuelo et al., 2010), or in higher somatosensory face selective area in the ventral intraparietal (VIP) cortex (Sereno and Huang, 2006). Moreover, in contrast to most of the previous studies which used air puff stimulation, we applied a more natural tactile stimulation of passive brushing of the skin. This stimulation paradigm has been shown to result in a wider activation pattern and to be more effective in the recruitment of the primary somatosensory cortex than air puff stimulation (as also observed by Huang et al., 2012). However, it is important to note that despite the power of these phase-locked methods in non-invasive mapping of topographic gradients, they are not the optimal method to infer the exact locus of representation of each body part along the topographic gradient (although this kind of localization is possible, see Besle et al., 2013). Such a validation of the results could be achieved using other methods such as GLM analysis, which enables a direct contrast between the responses to different body parts.

Our results demonstrate that a natural tactile stimulus combined with phase-locked analysis provide a powerful and sensitive tool for the mapping of whole-body somatosensory gradients at the group and single-subject levels. These experimental paradigm and analytical approaches should in our view be the current golden standard to map whole body gradients in both basic research and in the clinic. Furthermore, beyond improved resolution and clearer gradients, this periodic experimental design has some clear practical benefits especially in the clinical setting as it requires a shorter scanning time and fewer repetitions compared to other experimental designs.

2.4.2 Negative BOLD responses in the contralateral homunculus

Negative BOLD responses have been studied most extensively in the visual system of both primates and humans (Bressler et al., 2007; Pasley et al., 2007; Shmuel et al., 2002; Smith et al., 2004; Tootell et al., 1998; Wade and Rowland, 2010). These studies have shown that the negative BOLD responses in the early visual cortex can be elicited in areas surrounding the positively activated areas. Specifically, stimulation of central visual field evoked negative BOLD responses which were coupled to decreased local field potentials and multiunit activity in the surrounding peripheral areas (Shmuel et al., 2006). Such a precise pattern of deactivation has been shown to contain stimulus-specific distributed information and was suggested to play an important role in the resulting visual percept (Bressler et al., 2007). Our results document a similar phenomenon following tactile stimulation of the body. For the first time we show topographically organized negative BOLD responses in the areas of the non-stimulated body parts along the primary somatosensory and motor homunculi. The current literature on negative BOLD responses in the somatosensory system has focused on unilateral stimulation of the hand, which was shown to result in deactivation of the homologous area in the ipsilateral hemisphere (Gröschel et al., 2013; Hlushchuk and Hari, 2006; Kastrup et al., 2008; Klingner et al., 2014; Schäfer et al., 2012). We extend these findings and show that negative BOLD responses are a defining characteristic of the contralateral Penfield homunculus (**Figures 2.2**, **2.4 & S2.3** for ROI analysis of the BOLD time course, whole brain group and single subject analysis, respectively). The logic behind this might be very similar to fovea vs. periphery in vision: when we focus on the periphery or the foot we deactivate the fovea or the lips respectively (and vice versa). Our results concur with recent studies of the motor system (Zeharia et al., 2012, 2015), in which negative BOLD responses following bilateral movements of different body parts were found in the primary motor homunculus, but not in any of the other recently discovered motor homunculi (Zeharia et al., 2015). A similar trend in M1 was also evident in our results, though both positive and negative BOLD signals were lower and less significant (**Figure S2.3**).

Taken together, the results from the visual and motor domains as well as the current somatosensory study indicate that negative BOLD responses are manifested in primary sensory-motor areas, and suggest that they are an important component of the BOLD signal by serving as a sharpening mechanism of the signal-to-noise ratio. These topographic negative responses seem to specifically characterize primary cortical areas, as higher order sensory and motor fields contain neurons with larger and overlapping receptive fields. It would be interesting to test whether additional topographic sensory areas such as the primary auditory cortex contain the same sharpening mechanism. In fact, though this was not tested directly, hints were found in a previous work by our group which identified multiple cochleotopic maps in the human auditory cortex (Striem-Amit et al., 2011). Specifically, closer inspection of the time courses from different points along the auditory gradients (see Figure 6 in Striem-Amit et al., 2011) suggest that such topographic negative BOLD responses are evident also in the auditory cortex.

2.4.3 Negative BOLD responses in the ipsilateral hemisphere

Here, by using unilateral body stimulation and inspecting the pattern of ipsilateral BOLD signal following stimulation of different body parts, we also extend the results in the literature on deactivation in the ipsilateral hemisphere. This allowed us to further compare the patterns of both hemispheres, since one limitation of previous works by our group in the motor domain (Zeharia et al., 2012) was that the movements were bilateral and could not address this issue. Surprisingly we found that the negative BOLD responses were not limited and did not peak in the ipsilateral homologous area of the stimulated body segment. Rather, the ipsilateral deactivations extended to areas of the non-stimulated body parts, resulting in an overlap of the negative BOLD in the ipsilateral hemisphere across large portions of the homunculus (**Figures 2.3**, **2.4 & S2.3** for ROI analysis of the BOLD time course, whole brain group and single subject analysis, respectively). Our results seem to run counter previous studies that assigned the ipsilateral negative BOLD to the homologous area of the stimulated hand or fingers (Gröschel et al., 2013; Hlushchuk and Hari, 2006; Kastrup et al., 2008; Klingner et al., 2010, 2014; Schäfer et al., 2012). However, a closer inspection of the published data shows that in many cases the pattern of ipsilateral deactivations appears to have been more extensive than the representation of the hand (see for example Figures 2&3 in Kastrup et al., 2008 and Gröschel et al., 2013), which is consistent with the present results. Since these studies did not include stimulation of other body parts, the precise pattern of the deactivation could not be tested directly. Another potential explanation for the some level of discrepancy of the results could be related to differences in the experimental setup. For example, previous works used median nerve stimulation with various intensities and time intervals (Kastrup et al., 2008; Klingner et al., 2010; Schäfer et al., 2012) which were associated with alteration in the strength of the negative BOLD response (Klingner et al., 2010). In contrast, we applied a more ecological stimulus of brushing the body surface, which was found to evoke robust positive BOLD responses in all the subareas of the somatosensory cortex (Huang et al., 2012) and therefore, could also result in more pronounced negative responses as described here. The fact that these widespread ipsilateral patterns were also observed in the block-design paradigm of single subjects (**Figure S2.3**) rules out the possibility that the results arose from the cyclic stimulation paradigm or group averaging.

2.4.4 The physiological source and functional role of the negative BOLD

Even though the precise physiological mechanism underlying negative BOLD responses is still not fully understood, increasing evidence suggests that these responses reflect a functional measure of neuronal deactivation (Bressler et al., 2007; Ferbert et al., 1992; Hamzei et al., 2002; Kastrup et al., 2008; Klingner et al., 2010; Mullinger et al., 2014; Schäfer et al., 2012). Some of this evidence comes from studies of the somatosensory system, which provides a good model to study the interaction between the BOLD signal and physiological parameters of blood flow, blood volume, metabolic rate and neuronal activity. First, the negative BOLD responses found in the ipsilateral hemisphere (**Figures 2.3, 2.4 & S2.3**) following unilateral hand stimulation rule out the "hemodynamic steal" of blood by an adjacent activated cortical region explanation (Devor et al., 2007; Harel et al., 2002; Shmuel et al., 2002) as both cerebral hemispheres belong to different vascular territories (Nair, 2005). Our results evidencing somatotopically distributed negative BOLD (together with the recent findings from the motor domain (Zeharia et al., 2012)) show that this hemodynamic blood-stealing phenomenon also cannot account for the negative responses within each hemisphere (the contralateral negative homunculus), since two different blood vessels supply the ventral-lateral and dorsal-medial parts of the homunculus (Kiernan and Barr, 2009). Second, direct intracortical recordings have demonstrated an inhibition of neuronal activity in S1 in response to ipsilateral stimulation (Boorman et al., 2010; Lipton et al., 2006). In humans, simultaneous BOLD, electroencephalography (EEG) and cerebral blood flow (CBF) recording further support a neuronal mechanism underling the negative BOLD responses (Mullinger et al., 2014).

The functional role and the precise pathway mediating the negative BOLD response to unilateral somatosensory stimulation are still largely unclear. While all subareas of the primary somatosensory cortex are bidirectionally connected to the thalamus, which could exert an excitatory or inhibitory influence on specific brain regions (Sherman, 2007), intra- and intercortical connections seem the most likely pathways. Although interhemispheric connections were considered to take place mainly between bilateral S2 (Picard et al., 1990; Sutherland, 2006), recent studies indicate that such inhibitory connections could arise as well between the primary somatosensory homunculi (Iwamura, 2000; Ragert et al., 2011). Specifically, there is evidence of interhemispheric transfer between homologous areas of S1, mainly BA2s (Hlushchuk and Hari, 2006; Iwamura et al., 2001; Klingner et al., 2011), which in turn, are densely connected to BA1/BA3b. Unilateral tactile stimulation of the hand activates the central and posterior regions of the corpus callosum (Fabri et al., 2014), and resection of the posterior corpus callosum in humans eliminates the ipsilateral responses (Fabri et al., 1999).

2.4.5 Resting- state functional connectivity patterns characterized by strong bilateral consistency

A growing body of evidence suggests that resting state functional connectivity patterns can be a powerful marker of the baseline state of a system (see Harmelech and Malach, 2013 for review). These patterns have been shown to correlate between areas that are parts of the same functional network (Smith et al., 2009, see Fox and Raichle, 2007 for review), closely mimicking anatomical (although not necessarily monosynaptic) connectivity. In the motor system for example, resting-state functional connectivity patterns characteristically show strong bilateral consistency, resulting in highly symmetrical and topographic networks (Biswal et al., 1995; Yeo et al., 2011; Zeharia et al., 2015). Here we show the same phenomenon in the somatosensory system, because the peak ipsilateral functional connectivity from different body segments in the contralateral hemisphere were somatotopically localized to the homological areas in S1 (**Figure 2.5**). Thus, the topographical gradient of ipsilateral S1 could be reconstructed by the connectivity patterns from seeds in the contralateral hemisphere. Although these findings do not necessarily point to direct interhemispheric connections, they support a common functional connectivity, which might imply interhemispheric integration.

Furthermore, comparing the group evoked negative BOLD responses in the ipsilateral hemisphere (**Figure 2.4**) with the resting state connectivity maps (**Figure 2.5**) reveals that both tend to peak around the central sulcus, probably corresponding to areas BA3/BA1 in S1. Though the spatial resolution of the data presented here were not sufficient to specifically draw the borders between S1 subareas, this putative overlap between the negative responses and the connectivity pattern stress the dynamic change in tactile processing across the two hemispheres, which ranges from symmetrical streams of inputs (i.e. during bimanual tactile exploration) and lateralized activation patterns evoked by unilateral sensation.

2.4.6 Concluding remarks

In this work we studied the somatotopic organization of the positive and negative BOLD responses in contralateral and ipsilateral S1. We verified the Penfield homunculus in detail and suggested a revised anatomical span limiting it to the dorsal part of the parietal medial wall. We also found that Penfield's homunculi are characterized by a combination of positive and negative BOLD patterns which differ in the contra- and ipsilateral hemispheres. Our results indicate a complex pattern of baseline and activity dependent responses in the contralateral and ipsilateral sides, in which negative BOLD responses characterize both primary sensory-motor areas, and suggest that they are an important component that contribute to sharpening the tuning curves of populations of neurons, as was previously demonstrated for topographic gradients in both the visual and motor cortices.

2.5 References

Allison, J.D., Meador, K.J., Loring, D.W., Figueroa, R.E., and Wright, J.C. (2000). Functional MRI cerebral activation and deactivation during finger movement. Neurology *54*, 135–142.

Besle, J., Sánchez-Panchuelo, R.-M., Bowtell, R., Francis, S., and Schluppeck, D. (2013). Single-subject fMRI mapping at 7 T of the representation of fingertips in S1: a comparison of event-related and phase-encoding designs. J. Neurophysiol. *109*, 2293–2305.

Biswal, B., Zerrin Yetkin, F., Haughton, V.M., and Hyde, J.S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar mri. Magn. Reson. Med. *34*, 537–541.

Blankenburg, F., Ruben, J., Meyer, R., Schwiemann, J., and Villringer, A. (2003). Evidence for a rostral-to-caudal somatotopic organization in human primary somatosensory cortex with mirror-reversal in areas 3b and 1. Cereb Cortex *13*, 987–993.

Boorman, L., Kennerley, A.J., Johnston, D., Jones, M., Zheng, Y., Redgrave, P., and Berwick, J. (2010). Negative blood oxygen level dependence in the rat: a model for investigating the role of suppression in neurovascular coupling. J. Neurosci. *30*, 4285–4294.

Bressler, D., Spotswood, N., and Whitney, D. (2007). Negative BOLD fMRI response in the visual cortex carries precise stimulus-specific information. PLoS One *2*, e410.

Chen, C.J., Liu, H.L., Wei, F.C., and Chu, N.S. (2006). Functional MR imaging of the human sensorimotor cortex after toe-to-finger transplantation. AJNR Am J Neuroradiol *27*, 1617–1621.

Chen, L.M., Friedman, R.M., and Roe, A.W. (2005). Optical imaging of SI topography in anesthetized and awake squirrel monkeys. J Neurosci *25*, 7648–7659.

Chen, L.M., Turner, G.H., Friedman, R.M., Zhang, N., Gore, J.C., Roe, A.W., and Avison, M.J. (2007). High-resolution maps of real and illusory tactile activation in primary somatosensory cortex in individual monkeys with functional magnetic resonance imaging and optical imaging. J Neurosci *27*, 9181–9191.

Devor, A., Tian, P., Nishimura, N., Teng, I.C., Hillman, E.M.C., Narayanan, S.N., Ulbert, I., Boas, D.A., Kleinfeld, D., and Dale, A.M. (2007). Suppressed neuronal activity and concurrent arteriolar vasoconstriction may explain negative blood oxygenation level-dependent signal. J. Neurosci. *27*, 4452–4459.

Disbrow, E., Roberts, T., and Krubitzer, L. (2000). Somatotopic organization of cortical fields in the lateral sulcus of Homo sapiens: evidence for SII and PV. J Comp Neurol *418*, 1–21.

Eickhoff, S.B., Grefkes, C., Fink, G.R., and Zilles, K. (2008). Functional lateralization of face, hand, and trunk representation in anatomically defined human somatosensory areas. Cereb. Cortex *18*, 2820–2830.

Engel, S.A. (2012). The development and use of phase-encoded functional MRI designs. Neuroimage *62*, 1195–1200.

Engel, S.A., Rumelhart, D.E., Wandell, B.A., Lee, A.T., Glover, G.H., Chichilnisky, E.J., and Shadlen, M.N. (1994). fMRI of human visual cortex. Nature *369*, 525.

Engel, S.A., Glover, G.H., and Wandell, B.A. (1997). Retinotopic organization in human visual cortex and the spatial precision of functional MRI. Cereb Cortex *7*, 181–192.

Fabri, M., Polonara, G., Quattrini, A., Salvolini, U., Del Pesce, M., and Manzoni, T. (1999). Role of the corpus callosum in the somatosensory activation of the ipsilateral cerebral cortex: an fMRI study of callosotomized patients. Eur. J. Neurosci. *11*, 3983–3994.

Fabri, M., Polonara, G., Salvolini, U., and Manzoni, T. (2005). Bilateral cortical representation of the trunk midline in human first somatic sensory area. Hum. Brain Mapp. *25*, 287–296.

Fabri, M., Pierpaoli, C., Barbaresi, P., and Polonara, G. (2014). Functional topography of the corpus callosum investigated by DTI and fMRI. World J. Radiol. *6*, 895–906.

Ferbert, A., Priori, A., Rothwell, J.C., Day, B.L., Colebatch, J.G., and Marsden, C.D. (1992). Interhemispheric inhibition of the human motor cortex. J. Physiol. *453*, 525–546.

Forman, S.D., Cohen, J.D., Fitzgerald, M., Eddy, W.F., Mintun, M.A., and Noll, D.C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. Magn. Reson. Med. *33*, 636–647.

Fox, M.D., and Raichle, M.E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat. Rev. Neurosci. *8*, 700–711.

Fox, P.T., Burton, H., and Raichle, M.E. (1987). Mapping human somatosensory cortex with positron emission tomography. J Neurosurg *67*, 34–43.

Friston, K.J., Holmes, A.P., and Worsley, K.J. (1999). How many subjects constitute a study? Neuroimage *10*, 1–5.

Gröschel, S., Sohns, J.M., Schmidt-Samoa, C., Baudewig, J., Becker, L., Dechent, P., and Kastrup, A. (2013). Effects of age on negative BOLD signal changes in the primary somatosensory cortex. Neuroimage *71*, 10–18.

Hagler, D.J., and Sereno, M.I. (2006). Spatial maps in frontal and prefrontal cortex. Neuroimage *29*, 567–577.

Hamzei, F., Dettmers, C., Rzanny, R., Liepert, J., Büchel, C., and Weiller, C. (2002). Reduction of excitability (“inhibition”) in the ipsilateral primary motor cortex is mirrored by fMRI signal decreases. Neuroimage *17*, 490–496.

Harel, N., Lee, S.-P., Nagaoka, T., Kim, D.-S., and Kim, S.-G. (2002). Origin of negative blood oxygenation level-dependent fMRI signals. J. Cereb. Blood Flow Metab. *22*, 908–917.

Harmelech, T., and Malach, R. (2013). Neurocognitive biases and the patterns of spontaneous correlations in the human cortex. Trends Cogn. Sci. *17*, 606–615.

Harvey, B.M., Klein, B.P., Petridou, N., and Dumoulin, S.O. (2013). Topographic representation of numerosity in the human parietal cortex. Science *341*, 1123–1126.

Hertz, U., and Amedi, A. (2010). Disentangling unisensory and multisensory components in audiovisual integration using a novel multifrequency fMRI spectral analysis. Neuroimage *52*, 617–632.

Hlushchuk, Y., and Hari, R. (2006). Transient suppression of ipsilateral primary somatosensory cortex during tactile finger stimulation. J. Neurosci. *26*, 5819–5824.

Huang, R.S., and Sereno, M.I. (2007). Dodecapus: An MR-compatible system for somatosensory stimulation. Neuroimage *34*, 1060–1073.

Huang, R.-S., Chen, C., Tran, A.T., Holstein, K.L., and Sereno, M.I. (2012). Mapping multisensory parietal face and body areas in humans. Proc. Natl. Acad. Sci. U. S. A. *109*, 18114–18119.

Iwamura, Y. (2000). Bilateral receptive field neurons and callosal connections in the somatosensory cortex. Philos. Trans. R. Soc. Lond. B. Biol. Sci. *355*, 267–273.

Iwamura, Y., Taoka, M., and Iriki, A. (2001). Bilateral activity and callosal connections in the somatosensory cortex. Neuroscientist *7*, 419–429.

Kaas, J.H. (1983). What, if anything, is SI? Organization of first somatosensory area of cortex. Physiol Rev *63*, 206–231.

Kaas, J.H., Nelson, R.J., Sur, M., Lin, C.S., and Merzenich, M.M. (1979). Multiple representations of the body within the primary somatosensory cortex of primates. Science (80-.). *204*, 521–523.

Kastner, S., DeSimone, K., Konen, C.S., Szczepanski, S.M., Weiner, K.S., and Schneider, K.A. (2007). Topographic maps in human frontal cortex revealed in memory-guided saccade and spatial working-memory tasks. J. Neurophysiol. *97*, 3494–3507.

Kastrup, A., Baudewig, J., Schnaudigel, S., Huonker, R., Becker, L., Sohns, J.M., Dechent, P., Klingner, C., and Witte, O.W. (2008). Behavioral correlates of negative BOLD signal changes in the primary somatosensory cortex. Neuroimage *41*, 1364–1371.

Kell, C.A., von Kriegstein, K., Rosler, A., Kleinschmidt, A., and Laufs, H. (2005). The sensory cortical representation of the human penis: revisiting somatotopy in the male homunculus. J Neurosci *25*, 5984–5987.

Kiernan, J.A., and Barr, M.L. (2009). Barr's the Human Nervous System: An Anatomical Viewpoint (Lippincott Williams & Wilkins).

Klingner, C.M., Hasler, C., Brodoehl, S., and Witte, O.W. (2010). Dependence of the negative BOLD response on somatosensory stimulus intensity. Neuroimage *53*, 189–195.

Klingner, C.M., Huonker, R., Flemming, S., Hasler, C., Brodoehl, S., Preul, C., Burmeister, H., Kastrup, A., and Witte, O.W. (2011). Functional deactivations: multiple ipsilateral brain areas engaged in the processing of somatosensory information. Hum. Brain Mapp. *32*, 127–140.

Klingner, C.M., Hasler, C., Brodoehl, S., and Witte, O.W. (2014). Excitatory and inhibitory mechanisms underlying somatosensory habituation. Hum. Brain Mapp. *35*, 152–160.

Kurth, R., Villringer, K., Mackert, B.M., Schwiemann, J., Braun, J., Curio, G., Villringer, A., and Wolf, K.J. (1998). fMRI assessment of somatotopy in human Brodmann area 3b by electrical finger stimulation. Neuroreport *9*, 207–212.

Lipton, M.L., Fu, K.-M.G., Branch, C.A., and Schroeder, C.E. (2006). Ipsilateral hand input to area 3b revealed by converging hemodynamic and electrophysiological analyses in macaque monkeys. J. Neurosci. *26*, 180–185.

Mancini, F., Haggard, P., Iannetti, G.D., Longo, M.R., and Sereno, M.I. (2012). Fine-grained nociceptive maps in primary somatosensory cortex. J. Neurosci. *32*, 17155–17162.

McGlone, F., Kelly, E.F., Trulsson, M., Francis, S.T., Westling, G., and Bowtell, R. (2002). Functional neuroimaging studies of human somatosensory cortex. Behav Brain Res *135*, 147–158.

Miyamoto, J.J., Honda, M., Saito, D.N., Okada, T., Ono, T., Ohyama, K., and Sadato, N. (2006). The representation of the human oral area in the somatosensory cortex: a functional MRI study. Cereb Cortex *16*, 669–675.

Mullinger, K.J., Mayhew, S.D., Bagshaw, A.P., Bowtell, R., and Francis, S.T. (2014). Evidence that the negative BOLD response is neuronal in origin: a simultaneous EEG-BOLD-CBF study in humans. Neuroimage *94*, 263–274.

Nair, D.G. (2005). About being BOLD. Brain Res. Brain Res. Rev. *50*, 229–243.

Nelson, A.J., and Chen, R. (2008). Digit somatotopy within cortical areas of the postcentral gyrus in humans. Cereb Cortex *18*, 2341–2351.

Nelson, R.J., Sur, M., Felleman, D.J., and Kaas, J.H. (1980). Representations of the body surface in postcentral parietal cortex of Macaca fascicularis. J Comp Neurol *192*, 611–643.

Newton, J.M., Sunderland, A., and Gowland, P.A. (2005). fMRI signal decreases in ipsilateral primary motor cortex during unilateral hand movements are related to duration and side of movement. Neuroimage *24*, 1080–1087.

Nihashi, T., Naganawa, S., Sato, C., Kawai, H., Nakamura, T., Fukatsu, H., Ishigaki, T., and Aoki, I. (2005). Contralateral and ipsilateral responses in primary somatosensory cortex following electrical median nerve stimulation--an fMRI study. Clin. Neurophysiol. *116*, 842–848.

Nir, Y., Hasson, U., Levy, I., Yeshurun, Y., and Malach, R. (2006). Widespread functional connectivity and fMRI fluctuations in human visual cortex in the absence of visual stimulation. Neuroimage *30*, 1313–1324.

Orlov, T., Makin, T.R., and Zohary, E. (2010). Topographic representation of the human body in the occipitotemporal cortex. Neuron *68*, 586–600.

Overduin, S.A., and Servos, P. (2008). Symmetric sensorimotor somatotopy. PLoS One *3*, e1505.

Pasley, B.N., Inglis, B.A., and Freeman, R.D. (2007). Analysis of oxygen metabolism implies a neural origin for the negative BOLD response in human visual cortex. Neuroimage *36*, 269–276.

Penfield, W., and Brodley, E. (1937). Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain *60*, 359–443.

Penfield, W., and Jasper, H. (1954). Epilepsy and the functional anatomy of the human brain. (Boston: MA: Little Brown).

Penfield, W., and Rasmussen, T. (1950). The Cerebral Cortex of Man (New York: MacmillanMacmillan).

Perez, M.A., and Cohen, L.G. (2008). Mechanisms underlying functional changes in the primary motor cortex ipsilateral to an active hand. J. Neurosci. *28*, 5631–5640.

Picard, N., Lepore, F., Ptito, M., and Guillemot, J.P. (1990). Bilateral interaction in the second somatosensory area (SII) of the cat and contribution of the corpus callosum. Brain Res. *536*, 97–104.

Ragert, P., Nierhaus, T., Cohen, L.G., and Villringer, A. (2011). Interhemispheric interactions between the human primary somatosensory cortices. PLoS One *6*, e16150.

Robinson, C.J., and Burton, H. (1980). Organization of somatosensory receptive fields in cortical areas 7b, retroinsula, postauditory and granular insula of M. fascicularis. J Comp Neurol *192*, 69–92.

Rothemund, Y., Qi, H.X., Collins, C.E., and Kaas, J.H. (2002). The genitals and gluteal skin are represented lateral to the foot in anterior parietal somatosensory cortex of macaques. Somat. Mot Res *19*, 302–315.

Di Russo, F., Committeri, G., Pitzalis, S., Spitoni, G., Piccardi, L., Galati, G., Catagni, M., Nico, D., Guariglia, C., and Pizzamiglio, L. (2006). Cortical plasticity following surgical extension of lower limbs. Neuroimage *30*, 172–183.

Sanchez-Panchuelo, R.M., Francis, S., Bowtell, R., and Schluppeck, D. (2010). Mapping human somatosensory cortex in individual subjects with 7T functional MRI. J. Neurophysiol. *103*, 2544–2556.

Schäfer, K., Blankenburg, F., Kupers, R., Grüner, J.M., Law, I., Lauritzen, M., and Larsson, H.B.W. (2012). Negative BOLD signal changes in ipsilateral primary somatosensory cortex are associated with perfusion decreases and behavioral evidence for functional inhibition. Neuroimage *59*, 3119–3127.

Schweizer, R., Voit, D., and Frahm, J. (2008). Finger representations in human primary somatosensory cortex as revealed by high-resolution functional MRI of tactile stimulation. Neuroimage *42*, 28–35.

Sereno, M.I., and Huang, R.S. (2006). A human parietal face area contains aligned head-centered visual and tactile maps. Nat Neurosci *9*, 1337–1343.

Sereno, M.I., Dale, A.M., Reppas, J.B., Kwong, K.K., Belliveau, J.W., Brady, T.J., Rosen, B.R., and Tootell, R.B. (1995). Borders of multiple visual areas in humans revealed by functional magnetic resonance imaging. Science *268*, 889–893.

Servos, P., Zacks, J., Rumelhart, D.E., and Glover, G.H. (1998). Somatotopy of the human arm using fMRI. Neuroreport *9*, 605–609.

Sherman, S.M. (2007). The thalamus is more than just a relay. Curr. Opin. Neurobiol. *17*, 417–422.

Shmuel, A., Yacoub, E., Pfeuffer, J., Van de Moortele, P.-F., Adriany, G., Hu, X., and Ugurbil, K. (2002). Sustained Negative BOLD, Blood Flow and Oxygen Consumption Response and Its Coupling to the Positive Response in the Human Brain. Neuron *36*, 1195–1210.

Shmuel, A., Augath, M., Oeltermann, A., and Logothetis, N.K. (2006). Negative functional MRI response correlates with decreases in neuronal activity in monkey visual area V1. Nat. Neurosci. *9*, 569–577.

Shoham, D., and Grinvald, A. (2001). The cortical representation of the hand in macaque and human area S-I: high resolution optical imaging. J Neurosci *21*, 6820–6835.

Silver, M.A., Ress, D., and Heeger, D.J. (2005). Topographic maps of visual spatial attention in human parietal cortex. J. Neurophysiol. *94*, 1358–1371.

Smith, A.T., Williams, A.L., and Singh, K.D. (2004). Negative BOLD in the visual cortex: evidence against blood stealing. Hum. Brain Mapp. *21*, 213–220.

Smith, S.M., Fox, P.T., Miller, K.L., Glahn, D.C., Fox, P.M., Mackay, C.E., Filippini, N., Watkins, K.E., Toro, R., Laird, A.R., et al. (2009). Correspondence of the brain's functional architecture during activation and rest. Proc. Natl. Acad. Sci. U. S. A. *106*, 13040–13045.

Stefanovic, B., Warnking, J.M., and Pike, G.B. (2004). Hemodynamic and metabolic responses to neuronal inhibition. Neuroimage *22*, 771–778.

Striem-Amit, E., Hertz, U., and Amedi, A. (2011). Extensive cochleotopic mapping of human auditory cortical fields obtained with phase-encoding FMRI. PLoS One *6*, e17832.

Striem-Amit, E., Ovadia-Caro, S., Caramazza, A., Margulies, D.S., Villringer, A., and Amedi, A. (2015). Functional connectivity of visual cortex in the blind follows retinotopic organization principles. Brain *138*, 1679–1695.

Sutherland, M.T. (2006). The hand and the ipsilateral primary somatosensory cortex. J. Neurosci. *26*, 8217–8218.

Talairach, J., and Tournoux, P. (1988). Co-Planar Stereotaxic Atlas of the Human Brain (New York: Thieme).

Tootell, R.B.., Hadjikhani, N., Hall, E.K., Marrett, S., Vanduffel, W., Vaughan, J.T., and Dale, A.M. (1998). The Retinotopy of Visual Spatial Attention. Neuron *21*, 1409–1422.

Wade, A.R., and Rowland, J. (2010). Early suppressive mechanisms and the negative blood oxygenation level-dependent response in human visual cortex. J. Neurosci. *30*, 5008–5019.

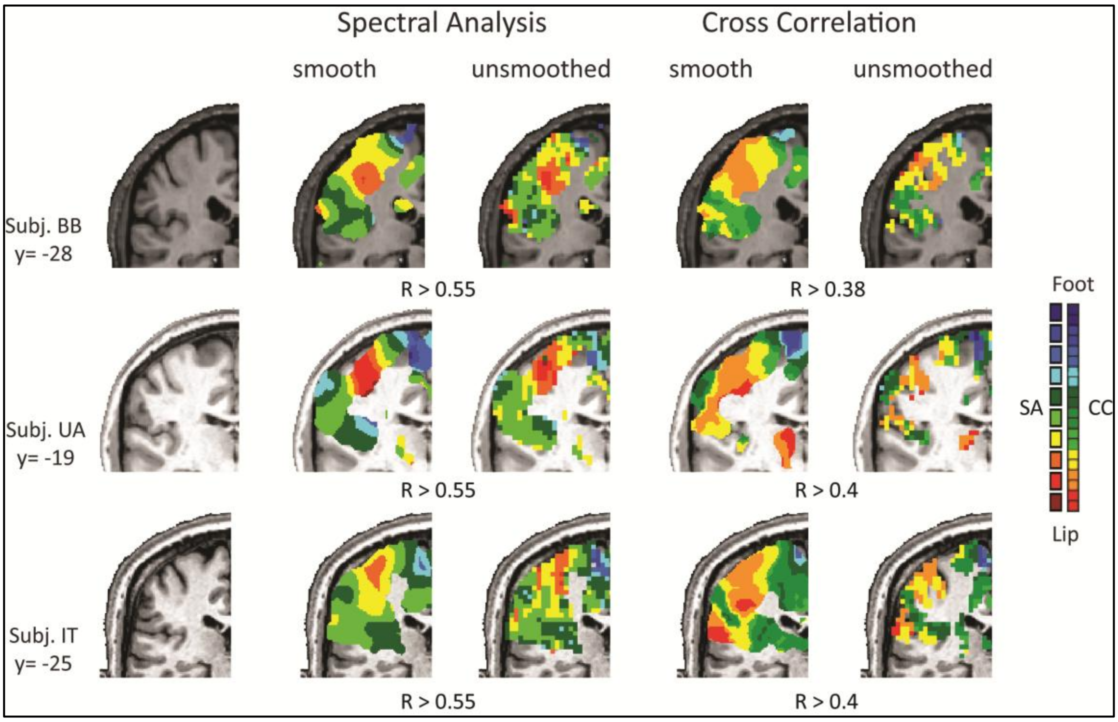
Wandell, B.A., and Winawer, J. (2011). Imaging retinotopic maps in the human brain. Vision Res. *51*, 718–737.

Yeo, B.T.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., Roffman, J.L., Smoller, J.W., Zöllei, L., Polimeni, J.R., et al. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J. Neurophysiol. *106*, 1125–1165.

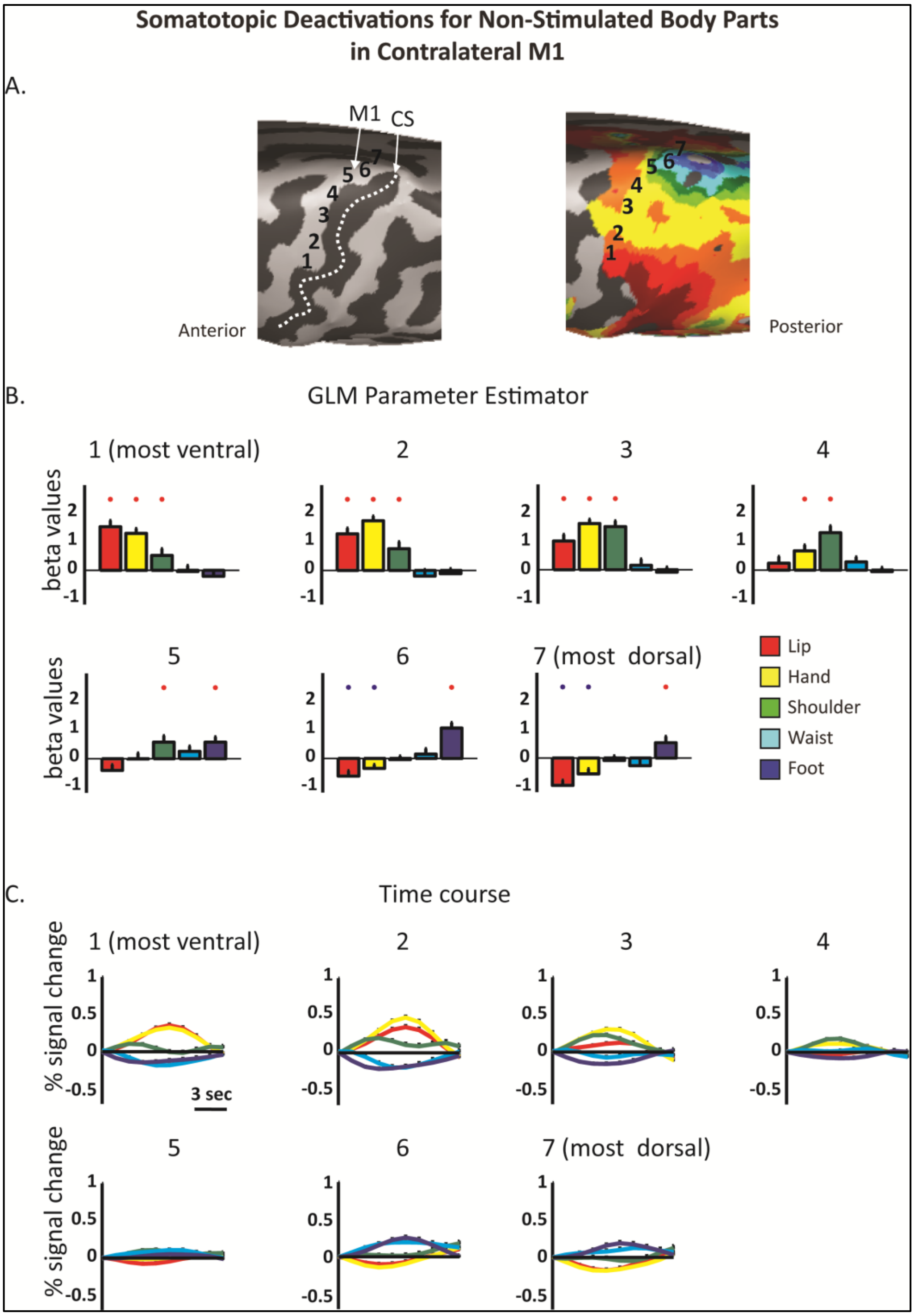
Zeharia, N., Hertz, U., Flash, T., and Amedi, A. (2012). Negative blood oxygenation level dependent homunculus and somatotopic information in primary motor cortex and supplementary motor area. Proc. Natl. Acad. Sci. U. S. A. *109*, 18565–18570.

Zeharia, N., Hertz, U., Flash, T., and Amedi, A. (2015). New whole-body sensory-motor gradients revealed using phase-locked analysis and verified using multivoxel pattern analysis and functional connectivity. J. Neurosci. *35*, 2845–2859.

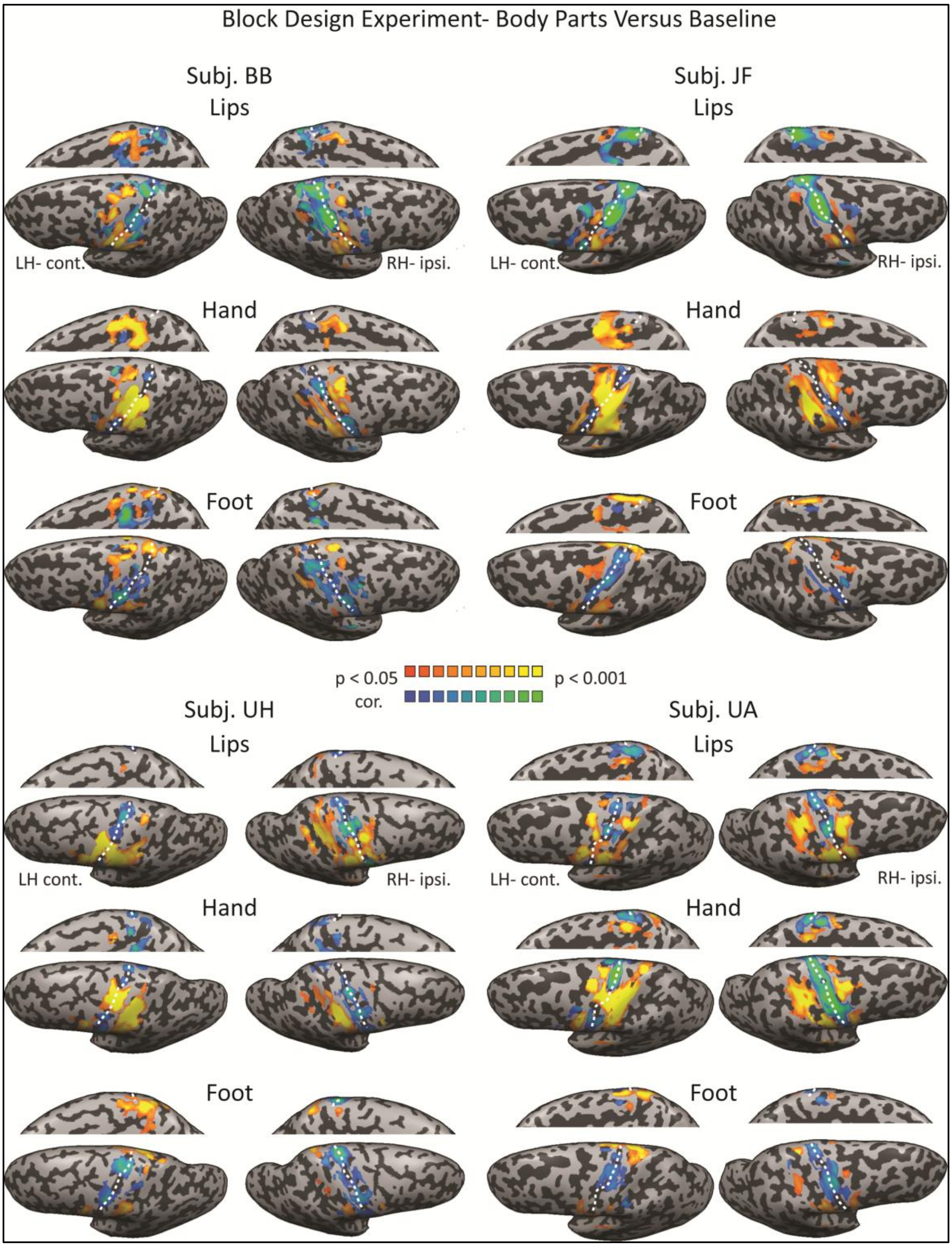
2.6 Supplementary Figures



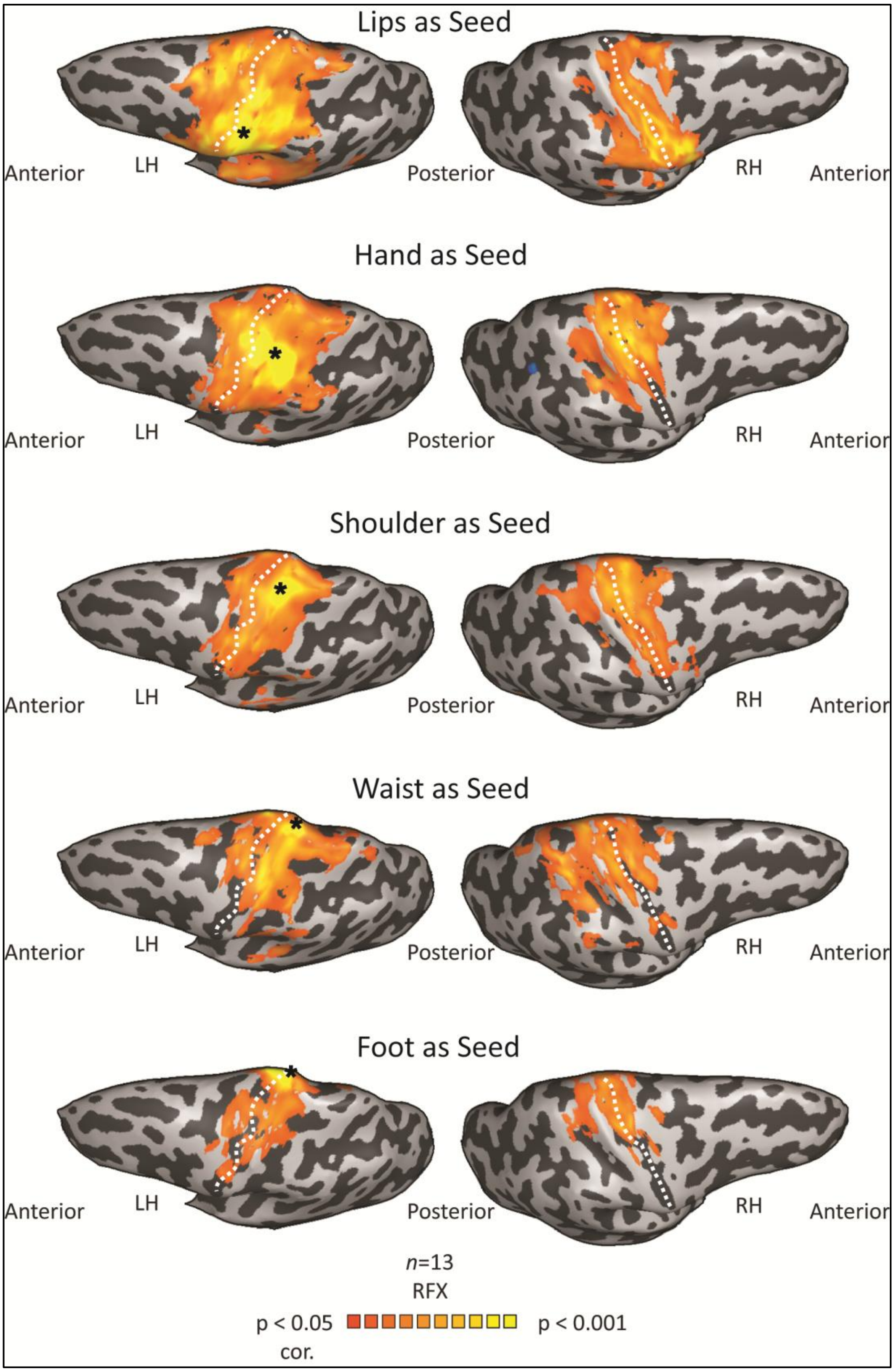
Supplementary Figure 2.1: phase-locked mapping of the primary somatosensory homunculus in single subjects. Spectral analysis and cross-correlation mapping of spatially smoothed and unsmoothed data in three single subjects. The results show that the S1 gradients are not the result of spatial smoothing.



Supplementary Figure 2.2: ROI GLM analysis of positive and negative BOLD responses in contralateral M1. A. Consecutive region-of-interests (ROI) were defined along the contralateral hemisphere from the ventral to the dorsal precentral gyrus. **B.** GLM parameter estimators extracted from the contrast of each body segment vs. baseline rest. Red and blue asterisks denote significant activation and deactivations, respectively ($p<0.05$). **C.** Average time courses in the same ROIs.



Supplementary Figure 2.3: Single subject results on the block-design experiment. Statistical parametric maps of the positive and negative BOLD responses as obtained by GLM analysis of the block-design experiment in single subjects. Responses to lips, hand and foot tactile stimulation are presented in lateral and medial views, and an anatomical mask was applied to the sensory-motor cortex. Note that in the medial view representations, the hemispheres were flipped for illustrative purposes and alignment with the maps on the lateral view.



Supplementary Figure 2.4: Full maps of the functional connectivity analysis. Statistical parametric maps presenting the functional connectivity patterns obtained from the five body segment seeds in the contralateral hemisphere. These maps are similar to the maps presented in Figure 2.5, but here they are presented at lower thresholds ($p<0.05$) to demonstrate the full functional network and not only the peak in the ipsilateral hemisphere.

3. Passive touch and the visual system: bodily topographical biases of cross-modal responses in tool selective areas

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Abstract

Recent evidence suggests that visual areas are task-oriented and sensory modality input independent rather than sensory-specific to vision. Specifically, visual areas are thought to retain their functional selectivity when using non-visual inputs (touch or sound) even without having any visual experience. However, this theory is still controversial since it is not clear whether this also characterizes the sighted brain, and whether the reported results in the sighted reflect basic fundamental a-modal processes or are an epiphenomenon to a large extent. In the current study, we addressed these questions using a series of fMRI experiments aimed to explore visual cortex responses to passive touch on various body parts and the coupling between the parietal and visual cortex during rest. We show that passive touch robustly activated the tool selective parts of the Lateral-Occipital (LO) cortex while deactivating almost all other occipital-retinotopic-areas. Furthermore, passive touch responses in the visual cortex were specific to hand and upper trunk stimulation. Resting state analysis showed that tactile LO but not other tested visual areas were connected specifically to the hand representation in the primary somatosensory cortex (S1). We suggest that LO is a fundamental hub that serves as a node between visual-tool selective areas and S1 hand representation, even in the resting state, probably due to the critical evolutionary role of touch in tool recognition and manipulation. These results might also point to a more general principle suggesting that recruitment or deactivation of the visual cortex by other sensory input depends on the ecological relevance of the information conveyed by this input to the task/computations carried out by each area or network. This is likely to rely on the unique and differential pattern of connectivity for each visual area with the rest of the brain.

3.1 Introduction

Recent studies in blind subjects suggest that the visual cortex of the blind can be taken over by other sensory modalities in very specific manner; namely, cross-modal recycling of each visual area, in a task specific manner even in the absence of any visual experience (Amedi et al., 2007; Merabet and Pascual-Leone, 2010; Ptito et al., 2012; Reich et al., 2011; Renier et al., 2010; Striem-Amit and Amedi, 2014; Striem-Amit et al., 2012a). For instance, it was shown that Braille reading activates the visual word form area (VWFA, Reich et al., 2011), and that haptic object recognition by touch or using visual-to-auditory substitution recruits the object related lateral occipital complex (LOC, Amedi et al., 2007, 2010), leading to the suggestion that this area is dedicated to deciphering the 3D shape of objects regardless of sensory modal input (Amedi et al., 2001). This has led to various complementary theories suggesting that the entire visual system (or even the entire brain) might be a metamodal/supramodal sensory independent task machine even under normal sensory experience during brain development (Amedi et al., 2001; Pascual-Leone and Hamilton, 2001). In other words, the driving force for the recruitment of specific cortical area is not the sensory modality input but rather the task and computations carried out by each area or network. For example it was suggested that the main task of the (‘visual’) word form area is assigning a phonological value to different shape symbols (i.e. letters) which can be delivered by any sensory modality (Reich et al., 2011). This role might be supported by the maintenance of functional connectivity between shape selective areas in the visual cortex and phonological areas in both blind and sighted subjects (Striem-Amit and Amedi, 2014; Striem-Amit et al., 2012a). Similarly, the role of LOC might be to decipher the geometric 3D shape of objects regardless of sensory input modality (Amedi et al., 2001). Under normal conditions, such information is delivered through vision and touch, but recent evidence has revealed that even sound can recruit LOC if it contains specific geometric information, for example when the blind or sighted are using Sensory Substitution Devices (SSDs, Amedi et al., 2007) or echolocation (Arnott et al., 2013).

However, this intriguing theory raises a set of fundamental questions that are highly controversial within the neuroscience community at large, especially in the context of contradictory results:

(1) It is not clear whether and to what extent such cross-modal task selective activations also characterize the sighted brain or whether they are specific to cross-modal plasticity following visual deprivation. Several studies have reported a-modal multisensory activation in the traditional visual cortical areas of sighted individuals (Amedi et al., 2001; Beauchamp et al., 2007; Costantini et al., 2011; Mahon et al., 2009). Other studies have hinted at the reverse phenomenon by showing that cross-modal stimuli (i.e. tactile, auditory or cognitive tasks) deactivate visual areas in normally sighted subjects while activating these areas in blind individuals (Azulay et al., 2009; Kawashima et al., 1995; Sadato et al., 1996). Therefore, it is not clear whether the lack (or reduction) of visual experience leads to the creation of new functional and anatomical connections or whether these results represent a more general pattern that is evident in the sighted as well.

(2) There is still a vigorous debate regarding the interpretation and the source of such cross-modal and task-selective responses, since it is not clear whether the reported results in the sighted reflect basic a-modal processing or could be attributed to different confounding factors such as visual mental imagery (Peltier et al., 2007; Sathian and Zangaladze, 2001; Sathian et al., 1997).

(3) For example, in all the studies reporting on tactile object selectivity in the LOC, the tactile activations emerged from active tool manipulation which in all cases includes to a certain extent also motor movements, semantic input, object recognition and mental visual imagery (Amedi et al., 2001, 2002; James et al., 2002; Reed et al., 2004; Zhang et al., 2004, but see Prather et al., 2004 for results on passive touch). Another set of basic questions relates to the functional networks which might support the creation and maintenance of such a-modal effects. Specifically, little is known about the role of functional and anatomical connectivity patterns between visual areas and somatosensory or auditory areas in the creation of these task selectivity responses.

(4) Beyond the issue of whether visual areas process tactile or auditory stimuli to a similar extent, it is also worth inquiring whether there are any topographical biases in the somatosensory evoked responses in visual areas.

All visual retinotopic and even several non-retinotopic areas such as the VWFA and PPA (Parahippocampal place area, Epstein and Kanwisher, 1998) show clear topographic selectivity to visual eccentricity. Similarly, Penfield's somatosensory homunculi and other high order somatosensory areas show topographic biases to body parts (Huang et al., 2012). However, it is not clear whether body-specific somatosensory biases also characterize cross-modal responses in the visual cortex (and vice versa). Most of the previous literature has focused on one part of the body surface (hands during active touch of objects) to study interactions between the somatosensory and the visual cortices. However, the pattern of visual cortex responses following tactile stimulation of various body parts has never been tested. Similarly, previous studies have suggested that the extent of multisensory processing and connectivity of early visual areas is modulated by their topographic organization (Borra and Rockland, 2011; Falchier et al., 2002; Gleiss and Kayser, 2013; Rockland and Ojima, 2003). Thus there is potentially much to learn from studying whether such topographical biases, such as eccentricity (fovea-periphery organization) also characterize visual responses to passive somatosensory stimuli.

In order to study this set of fundamental questions we focused on the interactions between touch and vision in the normally sighted brain, using the following extensive and complementary approaches: (1) we used a passive rather than active paradigm in the tested somatosensory modality; (2) we compared passive somatosensory input from various body parts; (3) we used various visual localizers to separate early vs. high order and center vs. peripheral areas in the visual cortex, with (4) special attention to tool selective areas which might have a higher likelihood of being functionally connected and driven by the somatosensory system; (5) finally we used a resting state experiment to identify functional connectivity between the classically occipital-visual and parietal-somatosensory areas.

3.2 Material and Methods

Subjects: A total of 16 healthy right-handed subjects (6 females) aged 24–37 (mean age 29) with no neurological deficits were scanned in the current study. All the participants were scanned in the somatosensory and visual experiments, with different subsets of subjects participating in three additional experiments (see below). The Tel Aviv Sourasky Medical Center ethics committee approved the experimental procedure and written informed consent was obtained from each subject before the scanning procedure.

Experiments and stimuli: Our goal was to explore the cross-modal effects of passive somatosensory stimuli in the visual cortex. Five experiments were conducted: a passive somatosensory experiment, an auditory control experiment which served as a control for the somatosensory experiment, two visual experiments mapping early retinotopic and higher functional areas in the visual cortex, and a resting-state fMRI. Except for the visual experiments, the subjects were blindfolded throughout all scans.

1. Somatosensory experiment (n=16): This experiment was made up of two scanning sessions, with two conditions in each session – tactile perception and tactile imagery. In the tactile perception condition, in each block, the body surface was stimulated sequentially by brushing the right side of the subjects' skin surface from the lips, and then continuously from the fingers and palm through the shoulder, waist, knee, and down to the foot and toes. This stimulation order was reversed in the second scanning session, so each body segments was brushed backwards (i.e. toes to knee, knee to waist). The stimulus was passive and the subjects were just asked to concentrate on the tactile sensation. We chose this paradigm of continuance stimulation since it has been shown to be an optimal method for topographical mapping (Engel, 2012; Engel et al., 1997; Sereno et al., 1995) with relatively short scanning sessions. The natural tactile stimuli were delivered using a four-centimeter-wide paint brush by the same experimenter, who was well-trained prior to the scans to maintain a constant pace and pressure during the sessions. In the imagery condition, the subjects were instructed to imagine the same tactile sensation as was experienced during the tactile perception condition. Precise timing of stimuli (tactile or imagery) was achieved by auditory cues (the name of the body part to be stroked) delivered to the experimenter and the subjects through fMRI-compatible electrodynamic headphones (MR-Confon, Germany). The length of each stimulation cycle was 15 s (from lips to toes or vise versa), which was followed by a 12 s rest baseline. Each scanning session included 8 blocks of tactile perception and 8 blocks of tactile imagery, which were presented pseudorandomly. 30 seconds of silence were added before and after the 8 cycles of tactile stimulation for baseline.

2. Visual localizer experiment (n=16): This experiment was aimed at localizing functional visual areas in the extrastriate cortex and was designed in a block paradigm, including 5 visual categories - tools, body parts, faces, houses and textures. Visual stimuli were generated on a PC and presented via an LCD projector (Epson MP 7200) onto a translucent screen. Subjects viewed the gray scale stimuli through a tilted (~45°) mirror positioned above each subject’s forehead. 9 images from the same visual category were presented in each epoch; each image was presented for 800 ms and was followed by a 200 ms blank screen. Each epoch lasted 9 seconds followed by a 6 s blank screen. A central red fixation point was present throughout the experiment. Each experimental condition was repeated 7 times, in pseudorandom order. During the experiment, one or two consecutive repetitions of the same image occurred in each epoch. The subjects’ task was to covertly report whether the presented stimulus was identical to the previous stimulus or not.

3. Auditory control (n=15): This experiment served as a control experiment for the somatosensory experiment and was composed of the same auditory stimuli as in the somatosensory experiment. The subjects passively listened to a list of the names of the body parts in the same set up as in the somatosensory experiment. Each stimulation block, lasting 15 s, included one presentation of the list and was followed by a 12 second rest. 30 seconds of silence were added before and after the 8 cycles of auditory stimulation for baseline. In half of the scanning sessions the order of the auditory stimuli was reversed, starting from the foot to the lips.

4. Visual eccentricity experiment (n=13): The visual stimulus was adapted from standard retinotopy mapping (Engel et al., 1994, 1997; Sereno et al., 1995). An annulus was presented, expanding from 0° to 34° of the subject's visual field in 30 s. This cycle was repeated 10 times. 30 seconds of silence were added before and after the 8 cycles of tactile stimulation for baseline.

5. Resting-state fMRI (n=13): A dataset of spontaneous blood oxygen level-dependent (BOLD) fluctuations for the investigation of intrinsic (rest state; Biswal et al., 1995) functional connectivity was collected while the subjects lay supine in the scanner without any external stimulation or task. Functional connectivity MRI (fcMRI) uses slow (<0.1 Hz) spontaneous (not task-related, e.g. during rest) fluctuations in the BOLD signal which were discovered nearly two decades ago (Biswal et al., 1995), and which have since been convincingly and repeatedly shown to correlate between areas that are parts of the same functional network (Smith et al., 2009, see review in: Deco et al., 2011; Fox and Raichle, 2007), closely mimicking anatomical (although not necessarily monosynaptic; Vincent et al., 2007) connectivity.

Functional and Anatomical MRI Acquisition: The BOLD fMRI measurements were obtained in a whole-body, 3–T Magnetom Trio scanner (Siemens, Germany). The scanning session included anatomical and functional imaging. The functional protocols were based on multi-slice gradient echoplanar imaging (EPI) and a standard head coil. The functional data were collected under the following timing parameters: TR = 1.5 s (TR = 2 s in the visual localizer and resting state fMRI experiments), TE = 30 ms, FA = 70°, imaging matrix = 80 ×80, FOV = 24 × 24 cm (i.e., in-plane resolution of 3 mm). 27-35 slices with slice thickness = 4.1-4.3 mm and 0.4-0.5 mm gap (46 slices with slice thickness = 3 mm and 0.3 mm gap in the visual localizer experiment) were oriented in the axial position, for complete coverage of the whole cortex. The first ten images (during the first baseline rest condition) were excluded from the analysis because of non-steady state magnetization. High resolution three-dimensional anatomical volumes were collected using a 3D-turbo field echo (TFE) T1-weighted sequence (equivalent to MP-RAGE). Typical parameters were: Field of View (FOV) 23cm (RL) x 23cm (VD) x 17cm (AP); Foldover- axis: RL, data matrix: 160x160x144 zero-filled to 256 in all directions (approx 1mm isovoxel native data), TR/TE=9ms/6ms, flip angle = 8°. Cortical reconstruction included the segmentation of the white matter using a grow-region function embedded in the BrainVoyager QX 2.0.8 software package (Brain Innovation, Maastricht, Netherlands). The cortical surface was then inflated. Group results were superimposed on a 3D cortical reconstruction of a Talairach normalized brain (Talairach and Tournoux, 1988).

Preprocessing of fMRI Data: Data analysis was initially performed using the BrainVoyager QX 2.0.8 software package (Brain Innovation, Maastricht, Netherlands). fMRI data went through several preprocessing steps which included head motion correction, slice scan time correction, and high-pass filtering (cutoff frequency: 2 cycles/scan). No data included in the study showed translational motion exceeding 2 mm in any given axis, or had spike-like motion of >1 mm in any direction. The time courses were de-trended to remove linear drifts, and in the experiments in which stimulation was periodic (somatosensory, auditory control and visual eccentricity), a temporal smoothing (4 s) in the frequency domain was also applied, in order to remove drifts and to improve the signal-to-noise ratio. For group analysis functional data also underwent spatial smoothing (spatial Gaussian smoothing, full width at half maximum = 6 mm) in order to overcome inter-subject anatomical variability within and across experiments. Functional and anatomical datasets for each subject were aligned and fit to the standardized Talairach space (Talairach and Tournoux, 1988).

Resting-state BOLD fMRI: Ventricles and white matter signals were sampled using a grow-region function embedded in the Brain Voyager from a seed in each individual brain. Using MATLAB (MathWorks, Natick, MA) ventricle and white matter time courses were regressed out of the data and the resulting time course was filtered to the frequency band-width of 0.1-0.01 Hz (in which typical spontaneous BOLD fluctuations occur). The resulting data were then imported back onto BrainVoyager for group analyses. Single subject data were spatially smoothed with a three-dimensional 6 mm half-width Gaussian in order to reduce inter-subject anatomical variability.

Data analysis:

GLM analysis: To compute statistical parametric maps we applied a general linear model (GLM) using predictors convolved with a typical hemodynamic response function. Cross- subject statistical parametric maps were calculated using hierarchical random-effects model analysis (Friston et al., 1999). A statistical threshold criterion of P < 0.01 was set for all results. This threshold was corrected for multiple comparisons using a cluster-size threshold adjustment for multiple comparisons, based on a Monte Carlo simulation approach extended to 3D datasets, using the threshold size plug-in BrainVoyager QX (Forman et al., 1995).

In the somatosensory experiment, the raw time course of each cycle of response to the continuous full body tactile stimuli was divided into five brushing segments corresponding to stimulation of cortically adjacent body parts according to Penfield's classic homunculus (lip, hand, shoulder and upper trunk, hip to knee and knee to toes). This division of the continual stimulus into five segments roughly reflected the dermatomal arrangement of the skin surface: lips (trigeminal cranial nerve), arm and trunk (cervical dermatomes) and hip and leg (thoracic and lumber dermatomes). The responses to brushing the five segments were averaged from the two sessions with lip-to-toes and toes-to-lip strokes to avoid order and attention effects. Error bars display the standard error across subjects and sessions.

Regions of interest analysis: In order to test the somatotopic preference of the tactile-activated area in LO, we defined two regions-of interest (ROIs) in the left and right LO, identified from the contrast between visual tools and all other visual categories. We then used these ROI as an external localizer to test the body-part specificity in the somatosensory experiment. The time course of activation from these ROI was sampled from the somatosensory experiment, and a ROI based random effect GLM analysis was conducted for the two scanning sessions, across all subjects.

Visual eccentricity analysis: In order to delineate retinotopic visual areas and their center-periphery preference, we applied a cross-correlation analysis. A boxcar function 2 TRs (Time Repetition) long was convolved with a two gamma

Hemodynamic Response Function (HRF) to derive predictors for the analysis. This predictor and the time course of each voxel were cross-correlated, allowing for 20 lags with one TR interval time to account for the stimulation duration of each cycle. For each voxel we obtained the lag value giving the highest correlation coefficient between the time course and one of the 20 predictors and the value of this correlation coefficient itself. On the group level, to run the random effect analysis, we used GLM parameter estimators derived from a complementary analysis as follows. First, a GLM analysis was carried out at the single-subject level using the predictor model described above. The resulting GLM parameter estimator values were then used in a second-level analysis for the group random effect. Finally, the random effect results were corrected for multiple comparisons using the Monte Carlo method (1,000 iterations, $\alpha < 0.05$) with an a-priori threshold of $P < 0.05$. The cross-correlation maps of the individual subjects were averaged to create a mean lag values map. The lag maps were thresholded by both the averaged correlation coefficient and the random effect corrected for multiple comparison maps.

Resting-state analysis: Several ROIs were defined in the visual and somatosensory cortices of the left hemisphere, and served as seeds for whole-brain or cross-correlation functional connectivity analysis. The seed were defined according to the following specified contrasts: (1) Tactile-LO was defined by contrasting all body stimulation versus baseline. (2) Visual-LO was defined from the contrast between visual tools and all other visual categories (as in the ROI GLM analysis). (3) A third ROI in the visual cortex was defined from the peak deactivation evoked by passive touch (which was localized to BA18) and served to test the functional connectivity between the early visual cortex and the somatosensory cortex. (4) Following Malach et al. (2002), we defined an additional control ROI in the ventral occipito-temporal cortex (VOT). This area included anterior ventral object selective regions, such as the FFA (Fusiform Face Area) and PPA (Parahippocampal Place Area) and thus we defined this ROI from the contrast between all object categories versus textures ($t(15)=3$, $p<0.01$, corrected for multiple comparison in all ROIs). (5+6) Two additional ROIs were defined from the peak responses in the primary somatosensory cortex to the hand or foot stimulation versus other body parts ($t(15)=5$, $p<0.01$, corrected for multiple comparison in these two ROIs). Individual time courses for these seed ROIs were sampled from each of the participants, z-normalized and used as individual predictors in a group analysis employing a general linear model (GLM) with hierarchical random effects. The minimum significance level of the results was set to $p<0.01$ corrected for multiple comparisons.

3.3 Results

In this study we explored the cross-modal effects of passive somatosensory inputs from the body on the visual cortex. The study included a set of fMRI experiments on the same group of subjects:(1) a somatosensory experiment designed to search for somatosensory evoked responses in visual areas, and to further assess their topographical biases. This experiment included two conditions-perception of passive tactile stimulation of the subjects' bodies, and mental imagery of the same stimuli, (2) a visual experiment presenting the stimuli from several visual categories, which served as a localizer to define functional areas in the visual cortex and specifically, tool selective areas. We also conducted three additional experiments: (3) resting state BOLD fMRI (4) visual eccentricity mapping to localize foveal and peripheral visual retinotopic areas, (5) an auditory control experiment of passive listening to the names of body parts which served as a control for the somatosensory experiment.

We analyzed the data on several levels and with a series of approaches, both at the group and single subject level. First, in order to discover the large-scale pattern of activation and deactivation in the visual cortex we performed a whole-brain analysis of the passive touch somatosensory responses. Next, to define the somatosensory activated and deactivated areas in the visual cortex we analyzed the visual experiment mapping of the early retinotopic and higher functional visual areas. We then tested whether the tactile evoked areas in the visual cortex showed somatotopic preferences for specific body parts using regions-of-interest (ROI) analysis. Finally, we compared the functional connectivity patterns of visual- and tactile-activated areas in the visual and somatosensory cortices using both ROIs and a whole brain approach.

Figure 3.1 presents the statistical parametric map of the whole-brain GLM analysis in response to tactile stimulation of the right side of the body (all body parts compared to baseline, t (15)= 3, p< 0.01, random effect analysis for all shown group results and corrected for multiple comparisons). As predicted, tactile stimulation of the body resulted in extensive bilateral activation in the parietal somatosensory areas, the insular cortex, and the motor cortex including the premotor and supplementary motor areas. However, an interesting pattern of responses was observed in the visual cortex. We found that in addition to the negative BOLD responses in the posterior and prefrontal areas, which comprise the default mode network (Greicius and Menon, 2004; Raichle et al., 2001), passive touch on the body resulted in a massive and overall deactivation of the visual cortex. Additional foci of deactivation included the dorsal part of the central sulcus in the right hemisphere. Comparing the deactivated areas in the visual system with a visual eccentricity map delineating retinotopic areas (**Figure S3.1, A-C**) showed that the deactivated areas included (i.e. massively overlapped) both the retinotopic and non-retinotopic areas, in both the ventral and dorsal visual streams. This massive deactivation in response to passive touch was also evident and overlapped retinotopic eccentricity mapping at the single subject level (**Figure S3.1D**). Interestingly, we did not find any positive BOLD in the peripheral primary visual (V1) or other peripheral visual areas as might have been expected based on some of the literature (see **Introduction** and **Discussion**).

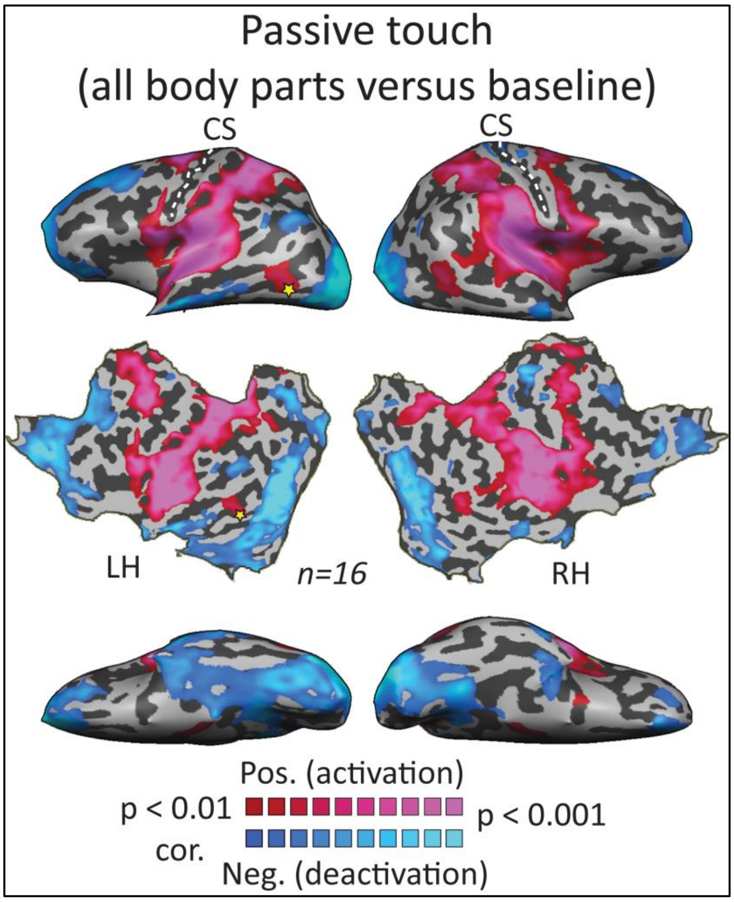


Figure 3.1: Passive touch evokes massive deactivation in the visual cortex with a unique activation in the lateral occipital cortex. Statistical parametric map for whole-body passive touch (all body parts versus baseline) is presented on inflated and flattened brain reconstructions. Following the tactile stimulation, most of the visual cortex was deactivated except a specific activation in the LOC.

The one and only exception for this robust deactivation was observed in the lateral occipital cortex, which showed positive responses to passive touch stimulation. This tactile activated area overlapped the previously reported area that was activated by haptic active exploration of objects (Amedi et al., 2001, the Lateral Occipital tactile visual area- LOtv, denoted by an asterisk). In order to test the hypothesis that the unique passive touch response in the visual system is related to visual tool selectivity, and hence to the specific computation or task performed by this area, we analyzed the visual localizer experiment to map tool selective areas (**Figure 3.2**). The results showed that visual tool selective areas overlapped with the passive touch responses. **Figure 3.2A** presents the positive BOLD response to passive touch on the whole body (the same map as presented in Figure 3.1). **Figure 3.2B** presents the statistical parametric map of the contrast between visual tools and other visual categories (see Material and Methods; t (15)= 3, $p < 0.01$, corrected for multiple comparisons). Visual tool selective areas were observed in two bilateral clusters, the LO and a more dorsal cluster at the precuneus/ posterior Intraparietal Sulcus (IPS). The overlay of the somatosensory and visual (**Figure 3.2C**, pink and orange clusters, respectively) maps clearly shows that the response to tactile stimulation of the body overlapped with the dorsal part of the tool selective area within LO. We termed this the tactile-evoked activation Tactile-LO (peak Talairach coordinates [x, y, z]: -47, -61, -3; very similar to the previously reported LOtv: -45, -62, -9). But note that in contrast to the previous experiments showing LOtv activation to haptic object exploration, the current study did not include hand movement and more importantly did not include any object recognition component. In view of that, we could not determine the exact overlap between these functional areas, but using ROI analysis we suggest estimation for this parameter. For that, we defined ROI from the peak coordinates of LOtv (using a 9mm sphere, in order to create a similar volume as the Tactile-LO ROI). Calculating the overlap between these ROIs resulted with a cluster of 1108 voxels (anatomical resolution- $1mm^3$), which roughly represent overlap of about a third of the ROIs volume. Thus, although using the current data we could not reach a conclusive estimation, we suggest that if these areas will be defined on the same group of participants, they will be highly overlapping.

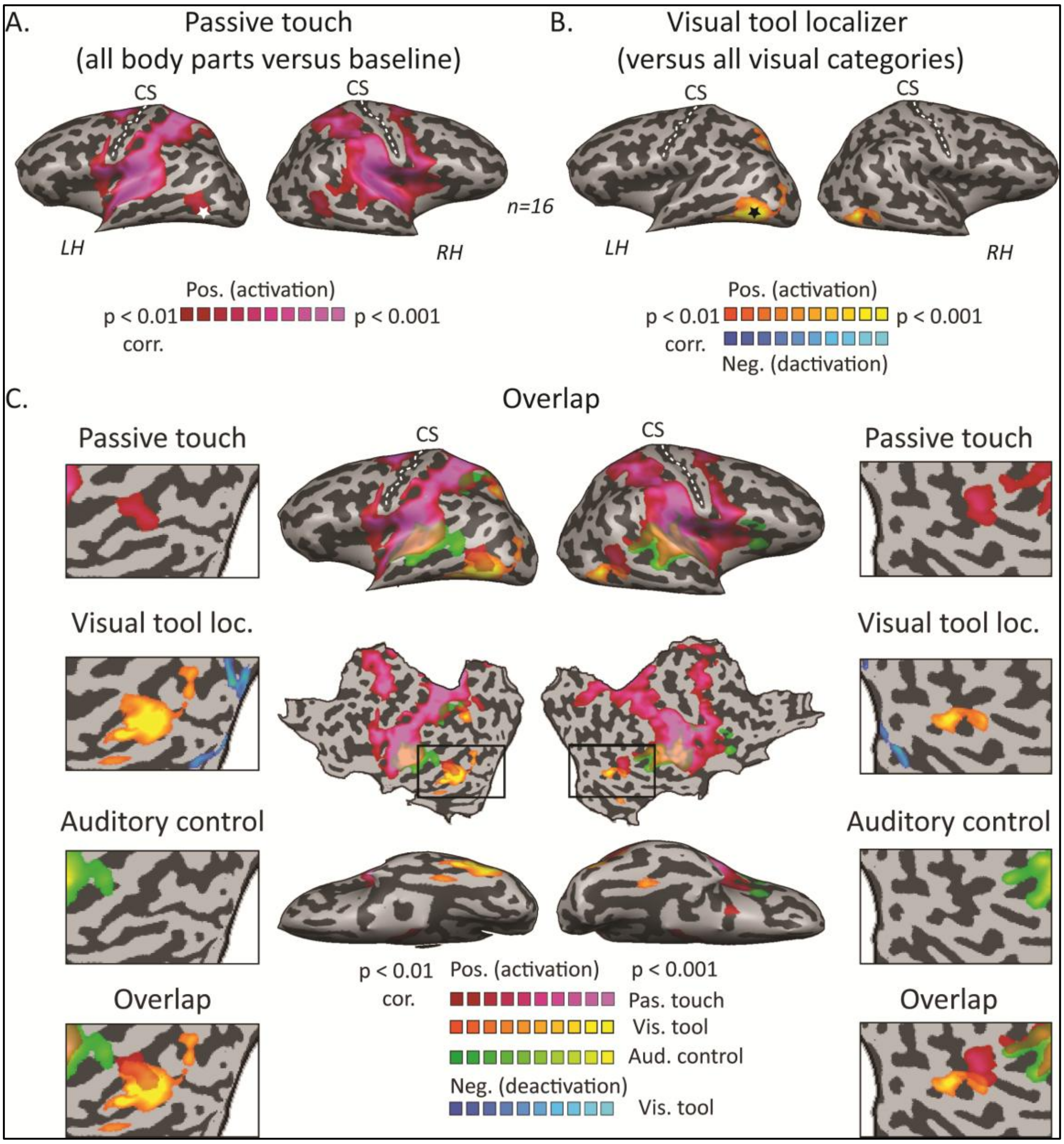


Figure 3.2: Passive touch on the body activates the visual selective area in LOC. **A.** Statistical parametric map for whole-body passive touch **B.** Statistical parametric map for the visual tool localizer shows bilateral LO activation. **C.** Overlap of the activations in response to passive touch (pink), visual-tool (orange) and auditory control (green) stimuli. The results show that tactile but not auditory activated areas overlap bilaterally with the dorsal part of visual tool selectivity in LOC. This tactile activated area overlapped the previously reported (Amedi 2001) tactile object recognition area, the LOtv (denoted by an asterisk).

We also tested whether simply listening to the names of body part would result in similar LO activations due to auditory input or automatic mental imagery processes. For this purpose we conducted a separate auditory control experiment (that preceded the somatosensory experiment) in which the subjects passively listened to the names of the different body parts. The green clusters in **Figure 3.2C** represent the activated areas in response to these auditory stimuli, and show that the responses to the names of body parts were confined to the auditory cortex with an additional cluster in the parietal lobe (further investigation of this effect is beyond the scope of the current paper). This result thus shows that the LO activation observed in the somatosensory experiment could not be attributed to the auditory stimulation and suggests the passive somatosensory input without any object recognition component can activate the visual cortex selectively. Moreover, the responses to the auditory stimulation do not explain the massive visual cortex deactivation observed in the somatosensory condition, as most of the auditory evoked deactivations were localized to the medial prefrontal cortex and posterior cingulate gyrus, which are part of the default mode network (**Figure S3.2**). Thus, passive touch on the body produces much more dramatic deactivation responses than listening to the names of these body parts (the full foci of activated clusters for the somatosensory, visual and auditory experiments are presented in **Table 3.1)**.

Passive Touch	**LH**						**RH**				
Area	**BA**	**x**	**y**	**z**	**t val.**	**p val.**	**x**	**y**	**z**	**t value**	**p val.**
Inferior temporal gyrus	19	-47	-61	-3	4.2	0.00085	47	-54	1	4.7	0.00029
Transverse temporal gyrus	41	-51	-22	12	17.4	$2.6*10^{-11}$	50	-20	10	16.4	$1.9*10^{-11}$
inferior parietal lobule	40	-32	-43	46	12.2	$4.0*10^{-9}$	34	-47	45	7.4	0.000002
superior parietal lobule	7	-23	-50	55	11.2	$1.3*10^{-8}$	17	-54	57	6.6	0.000012
precentral sulcus	6	-57	-2	35	6.1	0.000027	49	-6	7	8.8	$2.7*10^{-7}$
middle frontal gyrus	6	-21	-17	59	9.2	$1.7*10^{-7}$	21	-12	55	5.8	0.000038
medial frontal gyrus	6	-2	-11	55	7.5	0.000002					
insula	13	-37	-26	16	13.5	$1.0*10^{-9}$					
thalamus		-12	-19	3	6.5	0.000013	11	-22	13	6.3	0.000022
basal ganglia		-24	-2	10	4.8	0.00024	23	2	9	5.3	0.0001
cerebellum		-37	-37	-32	3.9	0.0016	27	-43	-27	5.6	0.00073

Visual Tool Localizer	LH						RH				
Area	**BA**	**x**	**y**	**z**	**t val.**	**p val.**	**x**	**y**	**z**	**t val.**	**p val.**
Fusiform gyrus	37	-47	-62	-10	8.7	$3.9*10^{-7}$	46	-63	-10	5.5	0.000074
Precuneus	19	-26	-74	39	5.1	0.000183					
Cerebellum							27	-40	-17	4	0.0014
middle occipital gyrus	19	-36	-81	3	4.3	0.00067					
Fusiform gyrus	20	-31	-38	-18	4.3	0.0018					

Auditory control	LH						RH				
Area	**BA**	**x**	**y**	**z**	**t val.**	**p val.**	**x**	**y**	**z**	**t val.**	**p val**
superior temporal gyrus	22/41	-46	-22	5	13	$4.2*10^{-9}$	47	-24	6	11	$3.2*10^{-8}$
inferior parietal lobule	40	-36	-54	40	3.9	0.0018					
Insula	13						32	19	11	4.5	0.0006

Table 3.1: Peak Talairach coordinates of the activated areas for the somatosensory, visual and auditory experiments.

Next, we characterized the somatotopic preferences of the tactile activated area in LO and assessed whether this general somatosensory activation was driven by specific parts of the body or whether it should be considered a general phenomenon to passive touch on any body part. We used the visual localizer experiment to define visual tool selective regions of interest (ROIs) within the ventral visual stream using the contrast between visual tools and all other categories **(Figure 3.3A**). We then tested the responses to the somatosensory stimuli of the different body parts using ROI-GLM analysis. **Figure 3.3B** presents the estimated statistics for each of the five body segments, compared to baseline and shows a clear bilateral and specific activation to passive touch on the hand and as well as a left lateralized response to the shoulder and upper trunk. The other body segments evoked a non-significant response or were even significantly deactivated in the visual tool selective areas. **Figure 3.3C** presents the contrast between each body segment and all the other body parts independently and further suggests that there is a specific tuning of the responses in the hand and upper trunk. In other words, the responses to passive touch in the visual tool selective areas were specific to the hand and upper trunk stimulation. Some studies have suggested that tactile evoked responses in visual areas during tactile object recognition do not emerge from specific cross-modal input, but rather result from higher cognitive functions, such as naming or mental imagery (Sathian and Zangaladze, 2001; Sathian et al., 1997; Zhang et al., 2004). To test this hypothesis directly, we compared the perception and mental imagery responses from the somatosensory experiment. First, when conducting ROI-GLM analysis in LO we did not find significant activation for tactile imagery in any of the different body parts (p values ranged from0.09 and 0.9 in both left and right ROIs). Second, we defined the specific contrast between passive touch on the hand and upper trunk and mental imagery of the same stimulation. The resulting map (**Figure S3.3**) shows indeed that the passive touch evoked activations in LO emerged from the tactile stimulation per-se, and were not the result of mental imagery processes.

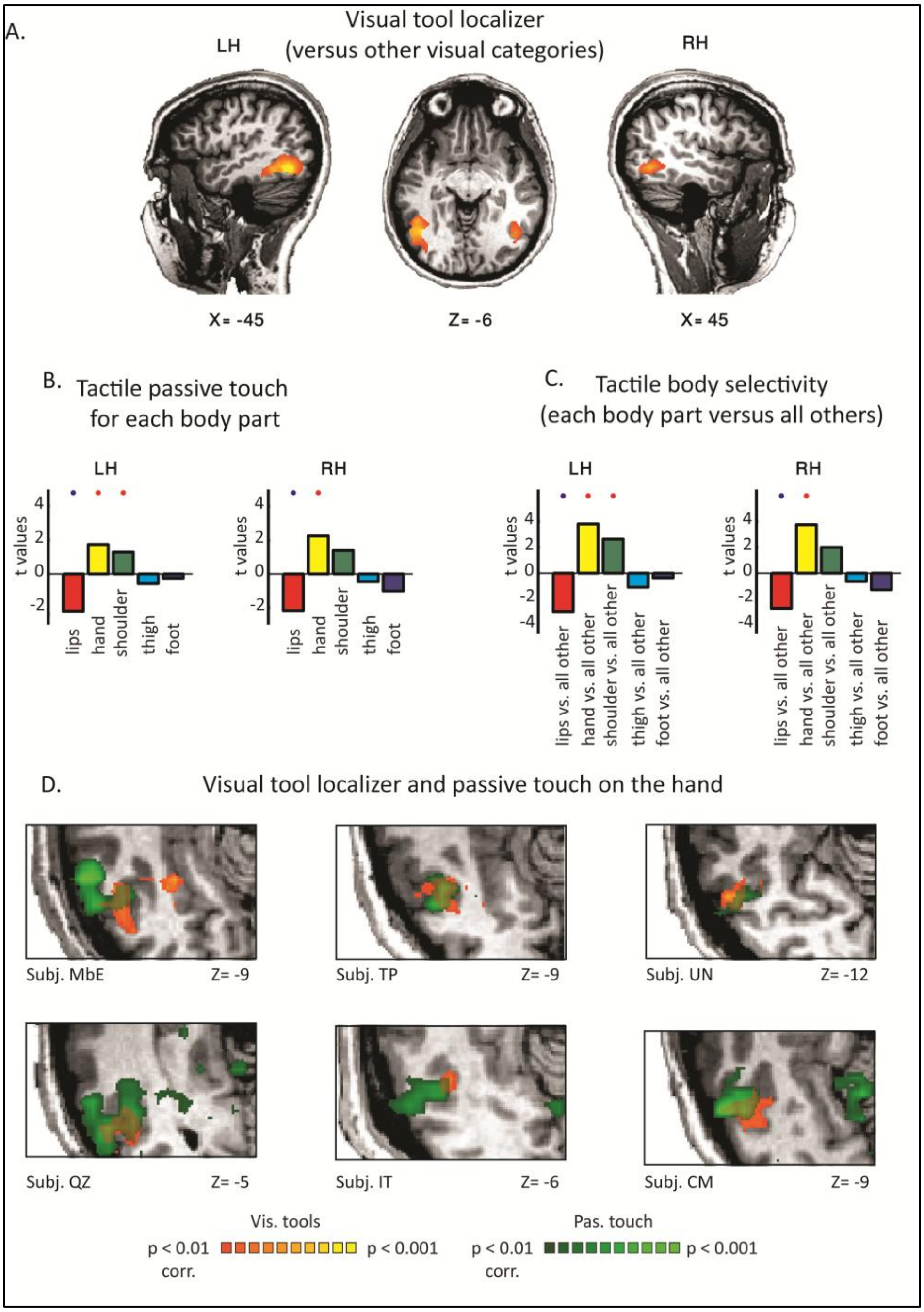


Figure 3.3: **Tactile LO activation shows a high level of selectivity for the hand, and upper trunk. A.** Regions of interest (ROIs) were defined from Visual-LO using the contrast between visual tools and all other visual categories. **B&C.** ROI GLM analysis of the somatosensory responses in Visual-LO for the five body segments versus baseline (**B**), and for the contrast of each body segments versus all the others (**C**). This analysis showed a clear somatotopic preference for the hand in the right hemisphere, and the hand and upper trunk in the left hemisphere. * denotes P < 0.05, for significant activation (red) or deactivation (blue). **D.** Single subject analysis. Overlay of the maps of passive touch to the hand and visual tool selsectivity is presented for six representative single subjects.

In order to further assess this somatotopic preference for passive touch on the hand in LO we also analyzed the responses at the single subject level. For this, the responses to tactile hand stimulation and visual tool selectivity were depicted for each subject individually, based on the non-smooth BOLD signal (i.e. no spatial smoothing). Next, we calculated the extent of overlap between these two maps, for each subject individually using probabilistic analysis (see **Material and Methods**). Out of the sixteen subjects who participated in the somatosensory and visual experiments, fourteen had a significant overlap between passive touch on the hand and visual tools (one subject did not exhibit significant passive touch responses and one had passive touch responses which did not overlap with the visual responses). In other words, over 95% of the subjects showed significant passive touch responses in LO. **Table 3.2** presents the peak Talairach coordination of the overlap between these maps of all the subjects. **Figure 3.3D** further shows this activation at the single subject level using whole brain flat maps. These results clearly show that the overlap between the tactile and visual activations is not simply an artifact due to smoothing effects or data pooling over the group, but rather supports a mechanism of low-level inputs from the hand to a very specific tool sensitive areas in the visual cortex.

Subject	X	Y	Z	# of voxels
1. BL		-		-
2. CM	-46.80	-62.81	-5.80	2493
3. IT	-42.16	-59.20	-5.37	426
4. MbE	-51.43	-64.36	-8.77	1032
5. MvE	-46.06	-61.75	2.85	110
6. NE	-49.68	-58.48	-7.66	399
7. PS	-40.52	-66.46	-0.09	116
8. QZ	-47.93	-73.43	-5.90	2163
9. ThO	-45.61	-59.06	-6.91	202
10. TH	-51.56	-66.95	-11.65	638
11. TN	-45.17	-64.44	-11.53	112
12. TP	-42.15	-60.97	-7.76	1127
13. TZ	-48.18	-66.01	-11.69	2074
14. UH	-45.99	-56.58	-8.70	138
15. UN	-46.26	-59.44	-14.50	1066
16. XB				-

Table 3.2: Peak Talairach coordinates of the overlap between tactile hand stimulation and visual tool selectivity

Our results so far have shown that on top of the visual-haptic object selectivity in the LO passive low level somatosensory information reaches this area from the hand and upper trunk, whereas the rest of the visual cortex is deactivated by passive touch. Our next goal was to explore whether this pattern was supported by functional connectivity as manifested in the resting state BOLD fMRI. This was done at two levels. First, we conducted a whole brain analysis using four representative ROIs in the visual cortex (**Figure 3.4A**). Tactile-LO, Visual-LO, VOT (ventral occipito-temporal region which includes other object selective areas such as the FFA and PPA, see **Material and Methods** for a detailed description of the definition of these ROIs) and the Tactile-deactivation peak (which resides in the retinotopic visual cortex, BA18) ROIs were used as seeds for a whole brain functional connectivity analysis. The results showed that these four visual ROIs differ substantially in their functional connectivity patterns. Whereas the connectivity patterns of the VOT and Tactile-deactivation area were mostly confined to visual areas (two left panels in **Figure 3.4A**), the Visual-LO showed a different pattern of connectivity, in which significant correlation values were observed in the dorsal and ventral visual stream cortical areas, as well as in the posterior parietal cortex. Finally, the Tactile-LO exhibited a similar pattern of connectivity to the Visual-LO, with one important exception. The Tactile-LO (right panel **Figure 3.4A**) was widely connected to the somatosensory and motor cortices (including the left dorsal and ventral premotor areas) and to the left posterior parietal lobe. Importantly, the Tactile-LO was the only ROI that showed connectivity to the primary somatosensory cortex (S1), and specifically to the hand representation.

In order to further characterize and quantify these patterns, we calculated the specific correlation of the resting state BOLD fMRI between the visual ROIs and the hand and leg representations in S1 (**Figure 3.4B**). The correlation analysis yielded several interesting results. First, significant correlations were found between the ROIs of a given modality (visual or somatosensory) and between spatially close ROIs. The only important exception was that the Tactile-LO was functionally connected to the somatosensory cortex, and specifically to the hand area in S1. **Figure 3.4C** presents a simple box-car model diagram summarizing all these results. This diagram suggests that the Tactile-LO serves as a node between object-related areas in the visual cortex and the somatosensory cortex, through the hand representation.

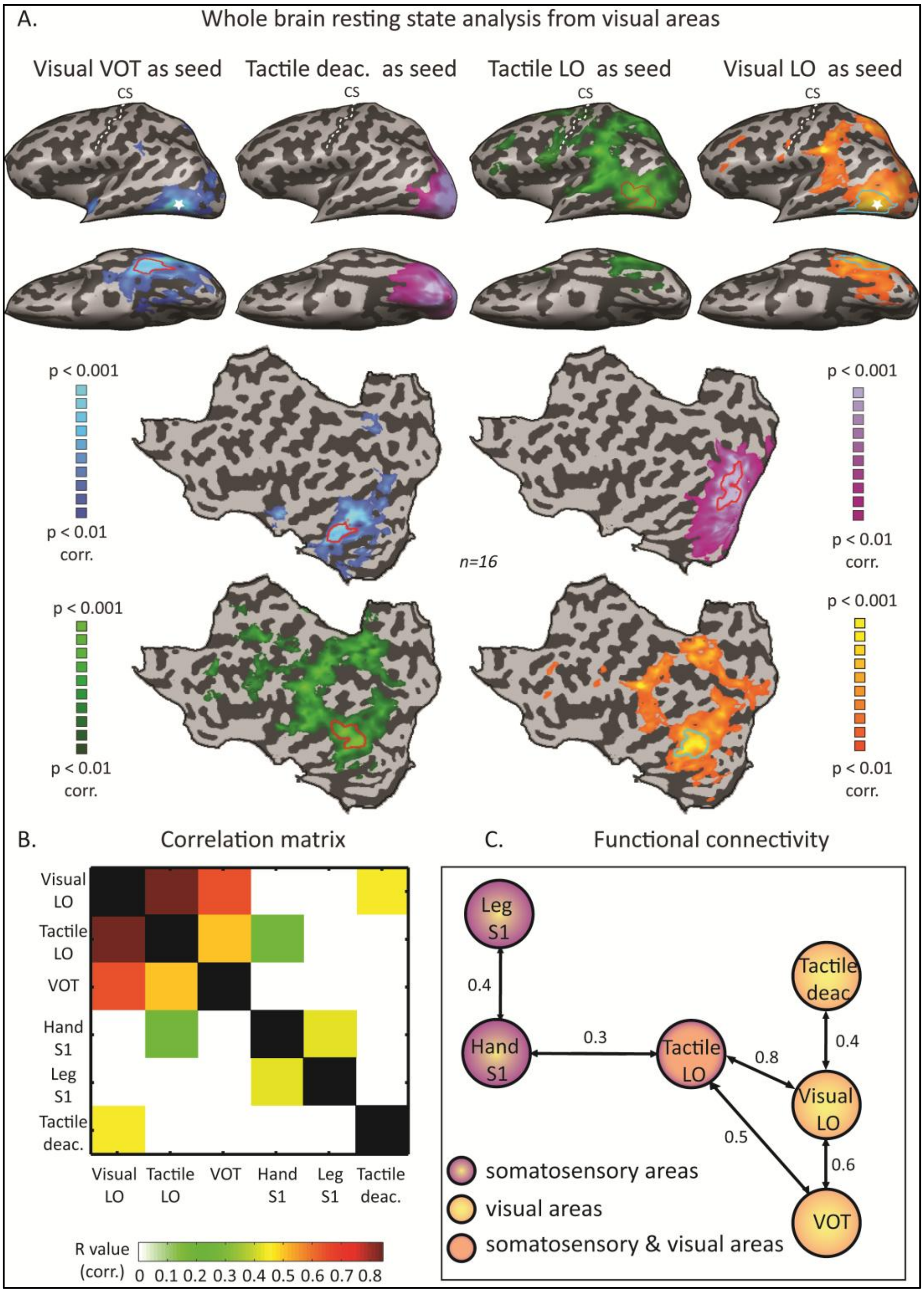


Figure 3.4: Resting state analysis. A. Whole brain resting state analysis with Visual VOT, peak of tactile deactivation, Visual-LO and Tactile-LO as seeds (seed outlines marked on the surface). **B.** Correlation coefficient matrix of the resting state BOLD signal between somatosensory and visual ROIs. High correlation values were observed within somatosensory areas (hand and leg) and within visual object related areas (LO and VOT). A significant correlation was also found between Tactile LO and the hand representation area within the primary somatosensory area. **C**. Functional connectivity box-car model presenting the significant correlation values between visual and somatosensory ROIs. This diagram

shows that Tactile-LO serves as a node between the visual and somatosensory cortical networks, through the somatosensory hand representation.

3.4 Discussion

3.4.1 Summary of the results and general conclusions

In this work we studied the cross-modal effects of passive somatosensory inputs from the body on the visual cortex. Our results revealed a unique combination of positive and negative BOLD responses in the visual cortex of normally sighted individuals. We showed that passive touch on the body triggers an island of activation in the visual tool selective area (area LO) of the lateral occipital complex (LOC). This activation was surrounded by massive negative BOLD, occupying the retinotopic and non-retinotopic and ventral and dorsal visual areas (**Figures 3.1**, **3.2**, **S3.1**, **Table 3.1**). Specifically, the deactivation characterized both fovea and peripheral areas, because we did not observe a significant activation in the delineated retinotopic areas**.** This was shown at the group and single subject levels, as well as in ROI functional connectivity (**Figures 3.1**, **3.4**, **S3.1)**. This is the first demonstration of LO activation following passive tactile stimulation of body parts in which the subjects performed no task, in contrast to studies on haptic or visual-to-auditory shape conserving object recognition. We further showed that the responses in the visual cortex were due to the passive somatosensory stimulation per se, and did not emerge from auditory stimuli or mental imagery (**Figures 3.2**, **3.3).** Our results show that traditional visual cortical areas can be recruited (or deactivated) by passive cross-modal inputs and suggest that such metamodal processing is a fundamental principle even in the sighted brain. We further showed that the activation of LO by passive touch is specific to stimulation of the hand and upper trunk, compared to all other body parts. (**Figure 3.3**, **Table 3.2**). This specific activation of LO was further supported by the resting state functional connectivity analysis which showed that Tactile-LO was connected specifically to the hand representation in the primary somatosensory cortex. All other visual areas (including Visual-LO, VOT and the peak deactivation for passive touch located in BA18) showed much weaker or lacked connectivity to the parietal cortex, and none was significantly connected to S1 (**Figure 3.4**). We suggest that Tactile-LO is a fundamental hub which serves as a node between object-related areas in the visual cortex and the somatosensory hand (and shoulder) representation, even at rest, perhaps due to the critical evolutionary role of touch in tool recognition and manipulation.

Thus, taken together, we suggest a general framework with specific predictions and potential mechanisms to study interactions within and between the senses. We suggest that even passive low-level sensory inputs from one modality can significantly and robustly influence most of the cortical areas of a different sensory modality. The nature and the specificity of these responses is determined by the functional relevance of the cross-modal inputs: if the information relayed by these inputs (passive touch on the hand in our case) is relevant to the task or computation carried out by a specific area (i.e. tool selectivity in LO) it will be activated, while the same inputs will widely deactivate all the rest of the cortical areas that are not pertinent to this function. This prediction needs to be tested and validated across modalities (sound, touch and vision) in different cortical areas (temporal, occipital and parietal) and across functional domains and topographical maps.

3.4.2 Even passive touch stimulation without any task can drive the visual system: a putative framework/model

Increasing lines of evidence have challenged the classic view that the brain is organized according to parallel streams of discrete and modality-specific areas. This evidence for example, has emerged from studies of blind participants which show that various visual areas can be recruited in a task specific manner by non-visual inputs (Amedi et al., 2007; Matteau et al., 2010; Merabet and Pascual-Leone, 2010; Ptito et al., 2012; Reich et al., 2011; Renier et al., 2010; Striem-Amit and Amedi, 2014; Striem-Amit et al., 2012a). These findings have led to several complementary theories suggesting that the brain operates as a sensory-independent task machine and that many (if not all) areas which were considered unisensory can be driven by any sensory modality (Amedi et al., 2001; Pascual-Leone and Hamilton, 2001).

However, these theories are still controversial, mainly since it is not clear whether such task-oriented and functional specialization characterizes the sighted brain as well, and whether the cross-modal responses reported in sighted reflect basic a-modal/multisensory processes or are epiphenomena.

Here, we addressed this array of questions in one of the most well studied cases of cross-modal recruitment of visual area – the lateral occipital (LO) area, but under a novel context which enabled us to explore some of these questions directly. LO was one of the first full examples of a brain area that is clearly task-specific and sensory independent. It was shown to be activated by tactile and visual object recognition in the sighted (Amedi et al., 2001). In particular, the LO was activated by visual and tactile shape recognition tasks but not by auditory object recognition using sound associations (Amedi et al., 2002). Further research into the multisensory nature of LO revealed that vision and touch share shape information within the LO (James et al., 2002), recognition of familiar tactile objects (Lacey et al., 2010) and activation for tactile shape over texture (Stilla and Sathian, 2008). This strengthens the notion that LO deciphers geometric shape information, irrespective of the sensory modality used to acquire it. However, it has been suggested that activation of visual areas during tactile tasks such as object recognition or tactile orientation discrimination does not reflect a-modal properties but is rather mediated through top-down processing arising from mental imagery during haptic exploration (Sathian and Zangaladze, 2001; Sathian et al., 1997; Zhang et al., 2004).

One way to test this alternative explanation directly is to study cross-modal activation of visual areas in the congenitally blind. Recent evidence has shown that in some cases the same functional specialization emerges even without any visual experience or memories (Amedi et al., 2007; Collignon et al., 2011; Fiehler et al., 2009; Mahon et al., 2009; Matteau et al., 2010; Ptito et al., 2012; Reich et al., 2011; Striem-Amit et al., 2012a), thus ruling out visual mental imagery as an exclusive driving mechanism and suggesting that cortical functional specialization can be attributed at least partially to innately determined constraints (Striem-Amit et al., 2012a, 2012b). Another intriguing addition to this body of research is the recently reported preference for visual numerals (over letters or false fonts) in the right inferior temporal gyrus (rITG), a region therefore labeled the visual number-form area (VNFA, Shum et al., 2013). However, some symbols may represent both letters and numerals, such as the symbol for zero and the letter 'O' in English, since only a cultural convention makes them different. In fact, some cultures use the exact same symbol as a number with an assigned quantity and as a letter with an assigned phoneme, for example the symbols 'V', 'I' and 'X' in Roman script. Thus, the emergence of an area with a preference for the task of deciphering visual number symbols which is distinct from the area with a preference for the task of deciphering visual letters cannot be explained by the visual features of such symbols. In a recent study by Abboud et al (2015) blind subjects were presented with such Roman script shapes encoded to sounds by a novel visual-to-music sensory-substitution device developed in our lab (EyeMusic, Abboud et al., 2014). The results show higher activation in the rITG when these symbols were processed as numbers compared to other control tasks on the same stimuli. Using resting-state fMRI in the blind and sighted, the same group further showed that different areas in the ventral visual cortex, including the numeral, letter and body image areas (rITG, VWFA and EBA, respectively) exhibited distinct patterns of functional connectivity (Abboud et al., 2015; Striem-Amit and Amedi, 2014). These findings suggest that specificity in the ventral ‘visual’ stream can emerge independently of sensory modality and visual experience, and is under the influence of unique connectivity patterns.

Here, we chose another approach to control for some potential confounding factors in the sighted. In all of the aforementioned studies of tactile object recognition in LO, the tactile activations emerged from active tool manipulation. Under these circumstances the sensory inputs are not isolated but are rather coupled and integrated to a certain extent with motor movements, semantic input and object recognition (in addition to visual mental imagery). Therefore, it is still unclear whether this reflects pure tactile, low level bottom-up processing (e.g. passive tactile stimulation), high level somatosensory processing, or top-down effects stemming from attentional demands of the task. Our results show for the first time that passive somatosensory stimulation of the body activates the visual cortex of sighted individuals, and overlaps the visual tool selective area in LO.

Moreover, our experimental paradigm allowed us to test the somatotopic preference of these passive tactile responses and showed that they are specific to the hand and upper trunk over all other body part stimulations. We showed that passive touch without any task evokes significant activation in LO, whereas mental imagery of the same stimuli did not produce the same effect. This suggests that at least in our case, low-level and bottom-up cross-modal stimuli can drive the visual cortex even more strongly than high level cognitive and top down processes such as mental imagery. Finally, the functional connectivity analysis of the resting state BOLD fMRI enabled us to further decipher the potential source of tactile evoked activation of the visual cortex. Our results on the functional resting state connectivity between LO and the somatosensory cortex concur with previous effective connectivity studies (Deshpande et al., 2008; Peltier et al., 2007) which showed that the LOC is connected to somatosensory areas in the PCG and posterior insula. Here, we showed that these connections are specific solely to the sub-region of LOC that process tactile information. Although the three object selective areas in the lateral and ventral occipital cortex (Tactile-LO, Visual-LO and VOT) are highly interconnected, only Tactile-LO showed extensive connectivity with parietal areas, and was the only connecting link in this complex to the hand areas in the primary somatosensory cortex.

The framework we suggest here might help resolve some conflicting results regarding the effects of cross-modal stimuli on the visual cortex. For example, there are inconsistencies in the literature regarding whether visual areas in the normally sighted are recruited or deactivated by cross-modal stimuli (see for example- Burton et al., 2004; Laurienti et al., 2002; Sadato et al., 1996; Weisser et al., 2005) and thus whether these areas might be considered as multisensory. We argue that the main concern here is not inquiring whether we should consider LO, VOT or V1 as pure multisensory areas or not. Rather, the crucial factor determining the cross-modal responses is the ecological relevance of the information conveyed by these inputs. We propose that even in the absence of a specific task (i.e. passive stimulation or during the resting state) an area can show a-modal characteristics if the cross-modal stimulus contains information pertinent to the task or computation performed by the specified area. When the input is not relevant to the ecological function or the computation carried out by a given area, the result is lack of activation or as we show here, emergence of cross-modal deactivation. At least in the case of passive touch described here, this essentially characterizes most of the somatosensory and visual cortex interactions.

3.4.3 Negative BOLD and cross-modal deactivations

In recent years there has been growing interest in the phenomenon of negative BOLD responses or deactivations. Negative BOLD responses, which have been shown to reflect decreased neural activity and/or inhibition (Boorman et al., 2010; Devor et al., 2007; Shmuel et al., 2002, 2006) have been studied mainly in the context of the default mode network (DMN, Greicius and Menon, 2004; Raichle and Snyder, 2007; Raichle et al., 2001). In contrast to goal-directed and externally oriented cognition, the DMN was suggested to be involved in self-referential processing, and to be relatively sensory modality and task-independent (Buckner et al., 2008). Beyond the DMN, negative BOLD is usually associated with task- or stimulus-specific responses, and related to processes directing attentional resources away from the deactivated brain area (Amedi et al., 2005; Azulay et al., 2009; Mozolic et al., 2008).

Several studies have reported negative BOLD responses in visual areas following cross-modal stimuli; however these results were generally found in the context of active tactile tasks (Kawashima et al., 1995; Merabet and Swisher, 2007; Sadato et al., 1996; Weisser et al., 2005) or focused on top-down effects such as attentional shift or task difficulty in cognitive performance (Hairston et al., 2008; Johnson and Zatorre, 2005; Laurienti et al., 2002; Mozolic et al., 2008). Here we provide another example of deactivation outside the DMN which is unique in the extent of the deactivation encompassing major parts of ventral and dorsal, retinotopic and non retinotopic areas, in particular since the stimulation was passive. This suggests that cross-modal effects are much more dramatic in contexts that have been less well explored; namely, the passive stream of input. Previous works reporting on cross modal effects in the visual system could also be interpreted in light of this framework. Merabet and Swisher (2007) explored the involvement of early visual cortical areas in tactile discrimination tasks. They found that perceiving roughness or inter-dot spacing of tactile patterns resulted in significant activation in the primary visual cortex and deactivation of extrastriate cortical regions, including part of the LOC. Critically, this result shows that the context and information carried by the tactile inputs determine which areas will be recruited or deactivated. This framework could also apply to higher cognitive tasks influencing the visual cortex such as verbal memory. Azulay and colleagues (2009) studied verbal memory processing in a group of sighted and blind individuals and showed that cross-modal deactivation triggered by top-down processes is task-related. During memory retrieval, both auditory and visual areas were robustly deactivated in the sighted. In contrast, in the blind participants, only the auditory cortex was deactivated whereas visual areas, shown previously to be relevant to this task (Amedi et al., 2003; Raz et al., 2005), presented a positive BOLD signal. Thus, there is a task-dependent balance of activation and deactivation that might allow maximization of resources and the filtering out of non- relevant information to enable allocation of attention to the required task.

Taken together, we suggest that the balance between positive and negative BOLD might be crucial to our understanding of a large variety of intrinsic and extrinsic tasks including high-level cognitive functions, sensory processing and multisensory integration, and might reflect a fundamental interaction between the senses.

3.4.4 Concluding remarks

In this work we showed that passive touch on the hand and shoulder triggers a specific activation in the tool selective part of the lateral occipital complex within the visual cortex. How did visual tool selectivity develop in the huge cortical portion that is devoted to vision? According to the neural recycling hypothesis (Dehaene and Cohen, 2007), a novel cultural ability encroaches onto a pre-existing brain system, resulting in an extension of existing cortical networks to address the novel functionality. This hypothesis was used to explain the cortical network dedicated to reading, and show how novel cultural objects rely on older brain circuits used for objects and face recognition (Dehaene et al., 2005). In the context of this framework, once tools were introduced during evolution, the brain machinery had to be developed to support tool recognition and tool use abilities. One cortical region which was associated to knowledge and the use of tools is a subarea of left anterior parietal cortex (Culham and Valyear, 2006). A recent study implementing a monkey model of tool use (Iriki, 2005) showed that the presumably homological area in the monkey has the capacity to be recycled for tool use. We speculate that such recycling processes could also support the specialization of the LO in tool recognition among the different object categories within the ventral visual stream. Compared to other visual object categories (such as houses, faces, visual script) tools are unique as they are haptically manipulated during their everyday use. Thus, functional specialization for tool recognition would potentially involve cortical areas that process touch (and motor movement of) on body parts that are mainly used to manipulate tools as well as high level visual object recognition centers and the connection between them. The unique pattern of positive BOLD of only the hand and shoulder and only in visual tool selective areas are in line with these assumptions. The functional connectivity reported here either existed or then was developed / strengthened by the growing need to use tools during evolution (even today most people use tools extensively during a large part of their waking hours). Our work is the first to highlight and provide concrete evidence to support this missing link between passive touch on the hand and shoulder and visual tool selectivity including the pathway supporting it. Further research is needed to test this framework under different contextual circumstances and in different functional selective areas in the visual system and the entire brain.

3.5 References

Abboud, S., Hanassy, S., Levy-Tzedek, S., Maidenbaum, S., and Amedi, A. (2014). EyeMusic: Introducing a “visual” colorful experience for the blind using auditory sensory substitution. Restor. Neurol. Neurosci. *32*, 247–257.

Abboud, S., Maidenbaum, S., Dehaene, S., and Amedi, A. (2015). A number-form area in the blind. Nat. Commun. *6*, 6026.

Amedi, A., Malach, R., Hendler, T., Peled, S., and Zohary, E. (2001). Visuo-haptic object-related activation in the ventral visual pathway. Nat. Neurosci. *4*, 324–330.

Amedi, A., Jacobson, G., Hendler, T., Malach, R., and Zohary, E. (2002). Convergence of visual and tactile shape processing in the human lateral occipital complex. Cereb. Cortex *12*, 1202–1212.

Amedi, A., Raz, N., Pianka, P., Malach, R., and Zohary, E. (2003). Early “visual” cortex activation correlates with superior verbal memory performance in the blind. Nat. Neurosci. *6*, 758–766.

Amedi, A., Malach, R., and Pascual-Leone, A. (2005). Negative BOLD differentiates visual imagery and perception. Neuron *48*, 859–872.

Amedi, A., Stern, W.M., Camprodon, J.A., Bermpohl, F., Merabet, L., Rotman, S., Hemond, C., Meijer, P., and Pascual-Leone, A. (2007). Shape conveyed by visual-to-auditory sensory substitution activates the lateral occipital complex. Nat. Neurosci. *10*, 687–689.

Amedi, A., Raz, N., Azulay, H., Malach, R., and Zohary, E. (2010). Cortical activity during tactile exploration of objects in blind and sighted humans. Restor. Neurol. Neurosci. *28*, 143–156.

Arnott, S.R., Thaler, L., Milne, J.L., Kish, D., and Goodale, M.A. (2013). Shape-specific activation of occipital cortex in an early blind echolocation expert. Neuropsychologia *51*, 938–949.

Azulay, H., Striem, E., and Amedi, A. (2009). Negative BOLD in sensory cortices during verbal memory: a component in generating internal representations? Brain Topogr. *21*, 221–231.

Beauchamp, M.S., Yasar, N.E., Kishan, N., and Ro, T. (2007). Human MST but not MT responds to tactile stimulation. J. Neurosci. *27*, 8261–8267.

Biswal, B., Zerrin Yetkin, F., Haughton, V.M., and Hyde, J.S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar mri. Magn. Reson. Med. *34*, 537–541.

Boorman, L., Kennerley, A.J., Johnston, D., Jones, M., Zheng, Y., Redgrave, P., and Berwick, J. (2010). Negative blood oxygen level dependence in the rat: a model for investigating the role of suppression in neurovascular coupling. J. Neurosci. *30*, 4285–4294.

Borra, E., and Rockland, K.S. (2011). Projections to early visual areas v1 and v2 in the calcarine fissure from parietal association areas in the macaque. Front. Neuroanat. *5*, 35.

Buckner, R.L., Andrews-Hanna, J.R., and Schacter, D.L. (2008). The brain's default network: anatomy, function, and relevance to disease. Ann. N. Y. Acad. Sci. *1124*, 1–38.

Burton, H., Sinclair, R.J., and McLaren, D.G. (2004). Cortical activity to vibrotactile stimulation: an fMRI study in blind and sighted individuals. Hum Brain Mapp *23*, 210–228.

Collignon, O., Vandewalle, G., Voss, P., Albouy, G., Charbonneau, G., Lassonde, M., and Lepore, F. (2011). Functional specialization for auditory-spatial processing in the occipital cortex of congenitally blind humans. Proc. Natl. Acad. Sci. U. S. A. *108*, 4435–4440.

Costantini, M., Urgesi, C., Galati, G., Romani, G.L., and Aglioti, S.M. (2011). Haptic perception and body representation in lateral and medial occipito-temporal cortices. Neuropsychologia *49*, 821–829.

Culham, J.C., and Valyear, K.F. (2006). Human parietal cortex in action. Curr. Opin. Neurobiol. *16*, 205–212.

Deco, G., Jirsa, V.K., and McIntosh, A.R. (2011). Emerging concepts for the dynamical organization of resting-state activity in the brain. Nat. Rev. Neurosci. *12*, 43–56.

Dehaene, S., and Cohen, L. (2007). Cultural recycling of cortical maps. (Cambridge).

Dehaene, S., Cohen, L., Sigman, M., and Vinckier, F. (2005). The neural code for written words: a proposal. Trends Cogn. Sci. *9*, 335–341.

Deshpande, G., Hu, X., Stilla, R., and Sathian, K. (2008). Effective connectivity during haptic perception: a study using Granger causality analysis of functional magnetic resonance imaging data. Neuroimage *40*, 1807–1814.

Devor, A., Tian, P., Nishimura, N., Teng, I.C., Hillman, E.M.C., Narayanan, S.N., Ulbert, I., Boas, D.A., Kleinfeld, D., and Dale, A.M. (2007). Suppressed neuronal activity and concurrent arteriolar vasoconstriction may explain negative blood oxygenation level-dependent signal. J. Neurosci. *27*, 4452–4459.

Engel, S.A. (2012). The development and use of phase-encoded functional MRI designs. Neuroimage *62*, 1195–1200.

Engel, S.A., Rumelhart, D.E., Wandell, B.A., Lee, A.T., Glover, G.H., Chichilnisky, E.J., and Shadlen, M.N. (1994). fMRI of human visual cortex. Nature *369*, 525.

Engel, S.A., Glover, G.H., and Wandell, B.A. (1997). Retinotopic organization in human visual cortex and the spatial precision of functional MRI. Cereb Cortex *7*, 181–192.

Epstein, R., and Kanwisher, N. (1998). A cortical representation of the local visual environment. Nature *392*, 598–601.

Falchier, A., Clavagnier, S., Barone, P., and Kennedy, H. (2002). Anatomical Evidence of Multimodal Integration in Primate Striate Cortex. J. Neurosci. *22*, 5749–5759.

Fiehler, K., Burke, M., Bien, S., Röder, B., and Rösler, F. (2009). The human dorsal action control system develops in the absence of vision. Cereb. Cortex *19*, 1–12.

Forman, S.D., Cohen, J.D., Fitzgerald, M., Eddy, W.F., Mintun, M.A., and Noll, D.C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. Magn. Reson. Med. *33*, 636–647.

Fox, M.D., and Raichle, M.E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat. Rev. Neurosci. *8*, 700–711.

Friston, K.J., Holmes, A.P., and Worsley, K.J. (1999). How many subjects constitute a study? Neuroimage *10*, 1–5.

Gleiss, S., and Kayser, C. (2013). Eccentricity dependent auditory enhancement of visual stimulus detection but not discrimination. Front. Integr. Neurosci. *7*, 52.

Greicius, M.D., and Menon, V. (2004). Default-mode activity during a passive sensory task: uncoupled from deactivation but impacting activation. J. Cogn. Neurosci. *16*, 1484–1492.

Hairston, W.D., Hodges, D.A., Casanova, R., Hayasaka, S., Kraft, R., Maldjian, J.A., and Burdette, J.H. (2008). Closing the mind’s eye: deactivation of visual cortex related to auditory task difficulty. Neuroreport *19*, 151–154.

Huang, R.-S., Chen, C., Tran, A.T., Holstein, K.L., and Sereno, M.I. (2012). Mapping multisensory parietal face and body areas in humans. Proc. Natl. Acad. Sci. U. S. A. *109*, 18114–18119.

Iriki, A. (2005). A prototype of Homo-Faber: A silent precursor of human intelligence in the tool-using monkey brain. In From Monkey Brain to Human Brain: A Fyssen Foundation Symposium, S. Dehaene, J.R. Duhamel, M. Hauser, and G. Rizzolatti, eds. (Cambridge, MA: MIT Press), pp. 133–157.

James, T.W., Humphrey, G.K., Gati, J.S., Servos, P., Menon, R.S., and Goodale, M.A. (2002). Haptic study of three-dimensional objects activates extrastriate visual areas. Neuropsychologia *40*, 1706–1714.

Johnson, J.A., and Zatorre, R.J. (2005). Attention to simultaneous unrelated auditory and visual events: behavioral and neural correlates. Cereb. Cortex *15*, 1609–1620.

Kawashima, R., O'Sullivan, B.T., and Roland, P.E. (1995). Positron-emission tomography studies of cross-modality inhibition in selective attentional tasks: closing the "mind's eye". Proc. Natl. Acad. Sci. U. S. A. *92*, 5969–5972.

Lacey, S., Flueckiger, P., Stilla, R., Lava, M., and Sathian, K. (2010). Object familiarity modulates the relationship between visual object imagery and haptic shape perception. Neuroimage *49*, 1977–1990.

Laurienti, P.J., Burdette, J.H., Wallace, M.T., Yen, Y.-F., Field, A.S., and Stein, B.E. (2002). Deactivation of sensory-specific cortex by cross-modal stimuli. J. Cogn. Neurosci. *14*, 420–429.

Mahon, B.Z., Anzellotti, S., Schwarzbach, J., Zampini, M., and Caramazza, A. (2009). Category-specific organization in the human brain does not require visual experience. Neuron *63*, 397–405.

Malach, R., Levy, I., and Hasson, U. (2002). The topography of high-order human object areas. Trends Cogn. Sci. *6*, 176–184.

Matteau, I., Kupers, R., Ricciardi, E., Pietrini, P., and Ptito, M. (2010). Beyond visual, aural and haptic movement perception: hMT+ is activated by electrotactile motion stimulation of the tongue in sighted and in congenitally blind individuals. Brain Res. Bull. *82*, 264–270.

Merabet, L., and Swisher, J. (2007). Combined activation and deactivation of visual cortex during tactile sensory processing. J. … 1633–1641.

Merabet, L.B., and Pascual-Leone, A. (2010). Neural reorganization following sensory loss: the opportunity of change. Nat. Rev. Neurosci. *11*, 44–52.

Mozolic, J.L., Joyner, D., Hugenschmidt, C.E., Peiffer, A.M., Kraft, R.A., Maldjian, J.A., and Laurienti, P.J. (2008). Cross-modal deactivations during modality-specific selective attention. BMC Neurol. *8*, 35.

Pascual-Leone, A., and Hamilton, R. (2001). The metamodal organization of the brain. Prog. Brain Res. *134*, 427–445.

Peltier, S., Stilla, R., Mariola, E., LaConte, S., Hu, X., and Sathian, K. (2007). Activity and effective connectivity of parietal and occipital cortical regions during haptic shape perception. Neuropsychologia *45*, 476–483.

Prather, S.C., Votaw, J.R., and Sathian, K. (2004). Task-specific recruitment of dorsal and ventral visual areas during tactile perception. Neuropsychologia *42*, 1079–1087.

Ptito, M., Matteau, I., Zhi Wang, A., Paulson, O.B., Siebner, H.R., and Kupers, R. (2012). Crossmodal recruitment of the ventral visual stream in congenital blindness. Neural Plast. *2012*, 304045.

Raichle, M.E., and Snyder, A.Z. (2007). A default mode of brain function: a brief history of an evolving idea. Neuroimage *37*, 1083–1090; discussion 1097–1099.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., and Shulman, G.L. (2001). A default mode of brain function. Proc. Natl. Acad. Sci. U. S. A. *98*, 676–682.

Raz, N., Amedi, A., and Zohary, E. (2005). V1 activation in congenitally blind humans is associated with episodic retrieval. Cereb. Cortex *15*, 1459–1468.

Reed, C.L., Shoham, S., and Halgren, E. (2004). Neural substrates of tactile object recognition: an fMRI study. Hum. Brain Mapp. *21*, 236–246.

Reich, L., Szwed, M., Cohen, L., and Amedi, A. (2011). A ventral visual stream reading center independent of visual experience. Curr. Biol. *21*, 363–368.

Renier, L.A., Anurova, I., De Volder, A.G., Carlson, S., VanMeter, J., and Rauschecker, J.P. (2010). Preserved functional specialization for spatial processing in the middle occipital gyrus of the early blind. Neuron *68*, 138–148.

Rockland, K.S., and Ojima, H. (2003). Multisensory convergence in calcarine visual areas in macaque monkey. Int. J. Psychophysiol. *50*, 19–26.

Sadato, N., Pascual-Leone, A., Grafman, J., Ibañez, V., Deiber, M.P., Dold, G., and Hallett, M. (1996). Activation of the primary visual cortex by Braille reading in blind subjects. Nature *380*, 526–528.

Sathian, K., and Zangaladze, A. (2001). Feeling with the mind's eye: the role of visual imagery in tactile perception. Optom. Vis. Sci. *78*, 276–281.

Sathian, K., Zangaladze, A., Hoffman, J.M., and Grafton, S.T. (1997). Feeling with the mind's eye. Neuroreport *8*, 3877–3881.

Sereno, M.I., Dale, A.M., Reppas, J.B., Kwong, K.K., Belliveau, J.W., Brady, T.J., Rosen, B.R., and Tootell, R.B. (1995). Borders of multiple visual areas in humans revealed by functional magnetic resonance imaging. Science *268*, 889–893.

Shmuel, A., Yacoub, E., Pfeuffer, J., Van de Moortele, P.-F., Adriany, G., Hu, X., and Ugurbil, K. (2002). Sustained Negative BOLD, Blood Flow and Oxygen Consumption Response and Its Coupling to the Positive Response in the Human Brain. Neuron *36*, 1195–1210.

Shmuel, A., Augath, M., Oeltermann, A., and Logothetis, N.K. (2006). Negative functional MRI response correlates with decreases in neuronal activity in monkey visual area V1. Nat. Neurosci. *9*, 569–577.

Shum, J., Hermes, D., Foster, B.L., Dastjerdi, M., Rangarajan, V., Winawer, J., Miller, K.J., and Parvizi, J. (2013). A brain area for visual numerals. J. Neurosci. *33*, 6709–6715.

Smith, S.M., Fox, P.T., Miller, K.L., Glahn, D.C., Fox, P.M., Mackay, C.E., Filippini, N., Watkins, K.E., Toro, R., Laird, A.R., et al. (2009). Correspondence of the brain's functional architecture during activation and rest. Proc. Natl. Acad. Sci. U. S. A. *106*, 13040–13045.

Stilla, R., and Sathian, K. (2008). Selective visuo-haptic processing of shape and texture. Hum. Brain Mapp. *29*, 1123–1138.

Striem-Amit, E., and Amedi, A. (2014). Visual cortex extrastriate body-selective area activation in congenitally blind people "seeing" by using sounds. Curr. Biol. *24*, 687–692.

Striem-Amit, E., Cohen, L., Dehaene, S., and Amedi, A. (2012a). Reading with sounds: sensory substitution selectively activates the visual word form area in the blind. Neuron *76*, 640–652.

Striem-Amit, E., Dakwar, O., Reich, L., and Amedi, A. (2012b). The large-scale organization of "visual" streams emerges without visual experience. Cereb. Cortex *22*, 1698–1709.

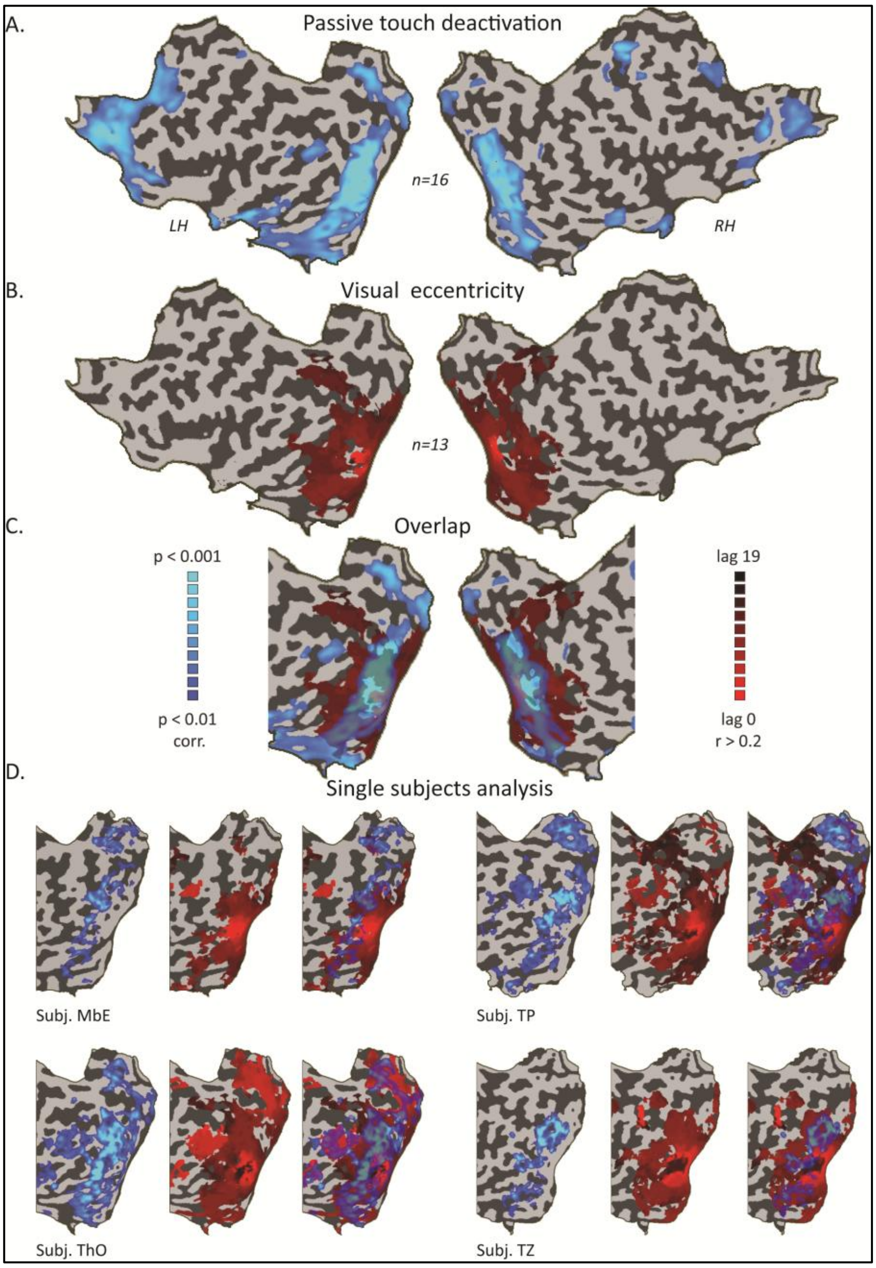
Talairach, J., and Tournoux, P. (1988). Co-Planar Stereotaxic Atlas of the Human Brain (New York: Thieme).

Vincent, J.L., Patel, G.H., Fox, M.D., Snyder, A.Z., Baker, J.T., Van Essen, D.C., Zempel, J.M., Snyder, L.H., Corbetta, M., and Raichle, M.E. (2007). Intrinsic functional architecture in the anaesthetized monkey brain. Nature *447*, 83–86.

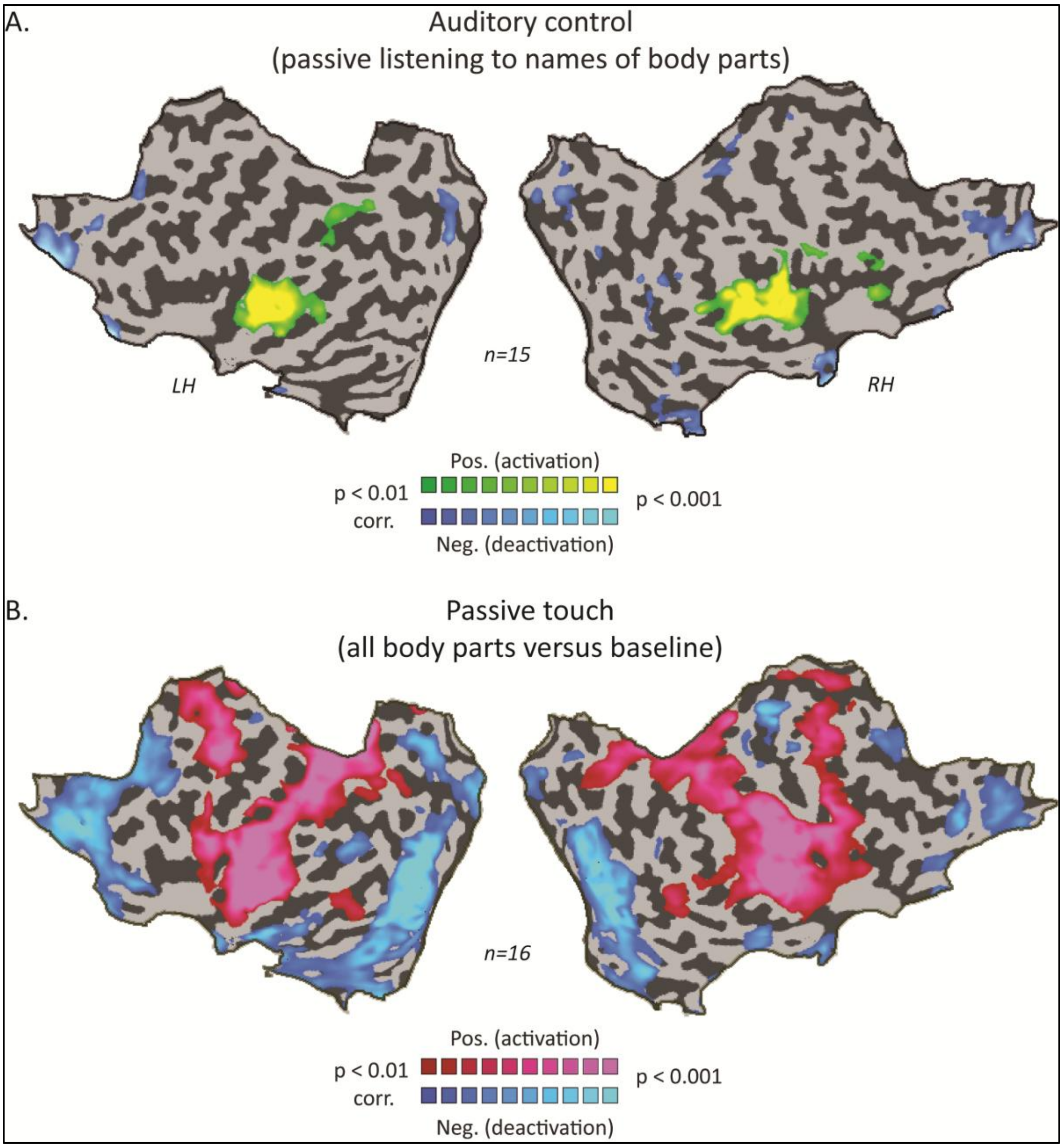
Weisser, V., Stilla, R., Peltier, S., Hu, X., and Sathian, K. (2005). Short-term visual deprivation alters neural processing of tactile form. Exp. Brain Res. *166*, 572–582.

Zhang, M., Weisser, V.D., Stilla, R., Prather, S.C., and Sathian, K. (2004). Multisensory cortical processing of object shape and its relation to mental imagery. Cogn. Affect. Behav. Neurosci. *4*, 251–259.

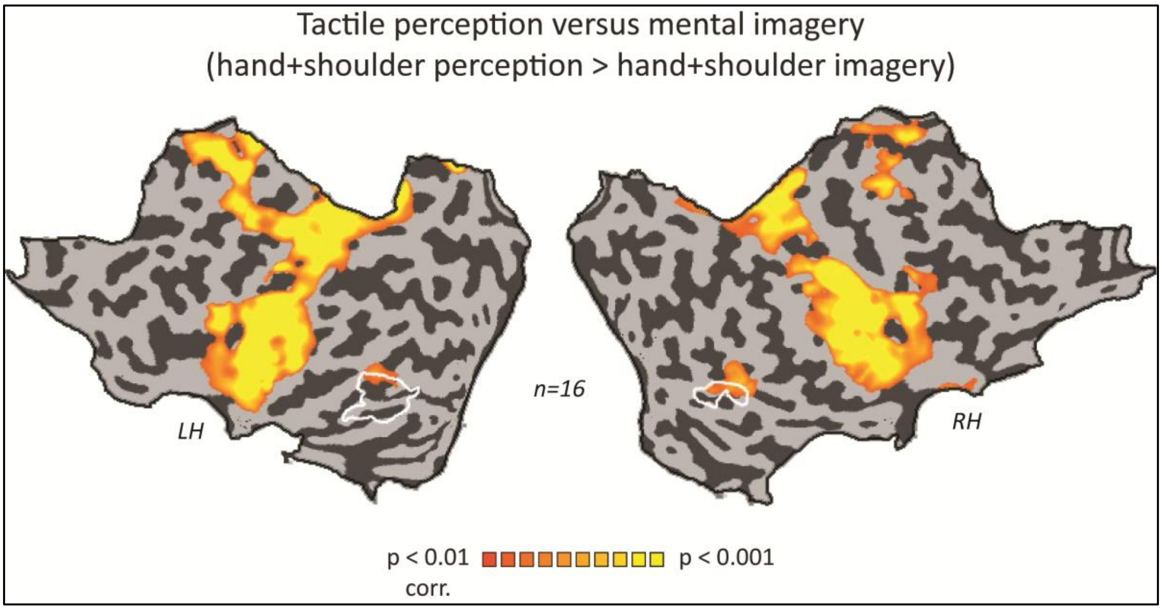
3.6 Supplementary Figures



Supplementary Figure 3.1: Passive touch evokes massive deactivation of the visual cortex. A. Statistical parametric map presenting the negative BOLD responses to whole-body passive tactile stimulation. **B.** Group visual eccentricity map delineating retinotopic areas in the visual cortex. **C.** Overlap of the maps shows that the deactivated areas include both retinotopic and non-retinotopic areas, in both the ventral and dorsal visual streams. **D.** Tactile evoked negative BOLD responses and visual eccentricity mapping are presented on the inflated left hemisphere of four representative subjects, showing that the massive deactivation in response to passive touch was also evident at the single subject level.



Supplementary Figure 3.2: Auditory control. Statistical parametric map of the GLM analysis applied to the auditory control experiment. The results show that the auditory stimulus activated the bilateral auditory cortex and the left inferior parietal lobule, whereas deactivation was mostly confined to areas of the default mode network. Therefore, the auditory condition did not evoke any response in the visual cortex.



Supplementary Figure 3.3: Mental imagery control. Statistical parametric map of the contrast between hand and upper trunk passive tactile stimulation and mental imagery of the same stimuli. This direct contrast shows that the LO activations were specific to passive touch stimulation and could not be explained by mental imagery processes.

4. Discussion and conclusion

4.1 Summary of the findings

In this thesis I used the somatosensory system as a model to explore the topographical biases of passive somatosensory inputs from the different body parts. This was tested by inspecting positive and negative BOLD signals, both within and outside the somatosensory cortex. The main findings of this dissertation include:

(1) Topographical biases of the positive BOLD responses

In the primary somatosensory cortex: By utilizing a combination of a continuous and periodic unilateral tactile stimulation of the entire body and applying phase-locked analysis methods, I was able to verify the well-known contralateral topographical organization of S1, demonstrate the gradual shift in the representation of different body parts, and further suggest a modification of Penfield's homunculus at the medial wall (See **Figures 2.1**, **2.2**, **S2.1** and section 2.4.1).

In the visual cortex: Passive touch responses were not confined to the somatosensory cortex, but rather revealed a complex pattern in the visual cortex. I showed that passive touch robustly activated the tool selective parts of Lateral-Occipital (LO) cortex while deactivating almost all other occipital-retinotopic-areas (**Figures 3.1**, **3.2**, **S3.1**). Furthermore, these passive touch responses in the visual cortex were specific to hand and upper trunk stimulation at both group and single subject levels. (**Figures 3.3**, **S3.3** and section 3.4.2).

Thus, both within and outside the somatosensory system, positive BOLD signals exhibited topographic biases to stimulation of different body parts.

(2) Topographical biases of the negative BOLD responses

In the primary somatosensory cortex: I found that Penfield's homunculi are characterized by a combination of positive and negative BOLD patterns which differ between the contralateral and ipsilateral hemispheres. In the contralateral hemisphere, the homunculus contains a sharpening contrast mechanism in which a combination of positive and negative BOLD was evoked for each of the tested body segments. The negative BOLD responses were found in the cortical areas of the non-stimulated body segments, and were somatotopically organized, giving rise to a negative homunculus (see **Figures 2.2**, **2.4**, **S2.3** and section 2.4.2). In the ipsilateral cortex, quite surprisingly, the deactivation was not focused only (or even peaking) in the ipsilateral homologue of the various stimulated parts but rather was widespread across many parts of ipsilateral Penfield's homunculus (see **Figures 1.3**, **2.4**, **S2.3** and section 2.4.5). Taken together, my results indicate a complex pattern of baseline and activity dependent responses in which negative BOLD responses characterize the primary somatosensory area both contralateral and ipsilateral to the stimulation, and suggest that they are an important component in sharpening the tuning curves of populations of neurons.

In the visual cortex: Passive touch on the body triggered a massive negative BOLD occupying the retinotopic and non-retinotopic and ventral and dorsal visual areas (see **Figures 3.1**, **3.2**, **S3.1**). This was shown at the group and single subject levels, as well as in ROI functional connectivity (see **Figures 3.1**, **3.2**, **3.4**, **S3.1** and section 3.4.3). Specifically, within the retinotopic areas, the deactivation characterized both fovea and peripheral areas, and thus the results show that negative BOLD responses in the visual cortex to passive somatosensory stimuli are not topographically biased according to eccentricity organization. However, topographical biases to passive touch responses were found within the LO area, in which only the hand and shoulder elicited positive responses whereas all other body parts evoked a non-significant response or deactivation.

(3) Topographical biases of the resting state BOLD signal:

In the primary somatosensory cortex: Using resting state analysis I found that the peak ipsilateral functional connectivity from different body segments in the contralateral hemisphere were somatotopically localized to the homological areas in S1 (see **Figures 2.5**, **S2.4** and section 2.4.7). I found that the topographical gradient of ipsilateral S1 could be reconstructed by the connectivity patterns from seeds in the contralateral hemisphere. Thus, the resting- state functional connectivity patterns showed strong bilateral consistency that resulted in highly symmetrical and topographic networks.

In the visual cortex: Resting state analysis showed that the Tactile-LO but not the other tested visual areas was connected specifically to the hand representation in the primary somatosensory cortex (see **Figure 3.4**, section 3.4.4). This suggests that the LO is a fundamental hub which serves as a node between visual-tool-selectivity and the S1 hand representation, even in resting state, probably due to the critical evolutionary role of touch in tool recognition and manipulation.

In a more general perspective, the results presented in this thesis suggest that the balance between the positive and negative BOLD signal and the ecological relevance of the input at each point in time might be crucial to a better understanding of a range of intrinsic and extrinsic tasks including low level sensory processing, high-level cognitive functions and multisensory integration. Furthermore, the combination of both positive and negative responses reflects topographical biases in which within a given sensory cortex (i.e. somatosensory or visual), each body part activates only functionally relevant subareas, while deactivating the surrounding non-relevant areas.

In the next sections I will address all these topics in more depth and discuss their relevance in the context of the current literature and theories of brain organization.

4.2 Mapping topographic gradients in sensory cortices

Topographic gradients are characterized by a gradual progression of the neuronal representation of the estimated parameter (in this case, the stimulated body segment) as well as an overlap in representations of nearby values (i.e. an overlap in the representation of adjacent body parts). In this study, I used three complementary methods for somatotopic mapping of tactile gradients in S1: a general linear model (GLM) analysis and two phase-locking approaches (cross-correlation and spectral analysis). In order to understand their additive value it is important to note the differences and limitations of these different paradigms in delineating different features of the gradients.

GLM is a classical analysis method in fMRI studies that has been applied for somatotopic mapping using a block-design paradigm for a limited number of body parts (e.g. Kell et al., 2005; McGlone et al., 2002; Miyamoto et al., 2006; Nelson and Chen, 2008). Since in GLM analysis the time course of activation in each voxel is modeled by a combination of the separate predictors (different predictor for each stimulated body part), it can provide an estimate of the partial contribution of each body part to the BOLD signal. Thus, GLM serves to identify the peak activations of the different body parts compared to rest baseline, as well as the contrasts between different body parts (i.e. finding the areas in which the stimulation of one body part elicits a significantly stronger BOLD signal compared to other body part(s)). Importantly, this analysis is used to define negative BOLD responses that could not be detected by phase-locking methods. However, GLM analysis is less optimal for delineating maps that contain continuous representations of a certain parameter in a topographic manner (Engel, 2012). This difficulty is related to the overlap in representation, where the relative signal of each represented feature (e.g. each body part) is often low. Therefore, the activation of a given feature relative to the rest baseline or a contrast between the activations of different features cannot always be detected.

On the other hand, phase-locking approaches are considered the classical way of defining early visual areas (Engel et al., 1994, 1997; Sereno et al., 1995; Wandell and Winawer, 2011). Characterizing the responses within specific visual field maps is essential to understanding the cortical organization of visual functions and provides useful information about the likely perceptual function of a specific cortical region (Wandell et al., 2007). Thus, the very first step in most studies of the visual cortex involves a detailed mapping of the targeted visual cortical fields, including the 8 basic retinotopic representations (V1-V8). Additional multiple maps have also been found in other visual areas including the lateral occipital cortex (LO-1, LO-2), ventral occipital cortex (VO-1, VO-2) and dorsal maps in the IPS (IPS-1/2/3/4; for an extensive review see Wandell et al., 2007). Topographically organized visual maps were also found in the frontal cortex (Hagler and Sereno, 2006), beyond the classical visual cortex. These approaches were also introduced (but to a much lesser extent and more recently) to map other topographically organized sensory (Hertz and Amedi, 2010; Orlov et al., 2010; Striem-Amit et al., 2011) and motor (Zeharia et al., 2012, 2015) gradients. They yield a highly robust topographic mapping and can pinpoint gradients undetected by standard GLM analysis (Engel, 2012; Zeharia et al., 2015). Here I applied these approaches for the first time to systematically map the entire body gradients and as expected found them to be extremely useful and fruitful for a better understanding of the way the brain processes passive somatosensory inputs.

To understand why this is so, certain properties of phase-locked analyses need to be detailed. In contrast to GLM, these methods are more efficient in mapping topographic gradients even if the amplitude of the response is relatively low in a certain voxel. Both methods rely on the continuity of the stimulus cycle to calculate the correlation between a periodic predictor and the BOLD time course. The phase or lag value (for spectral analysis and cross-correlation, respectively) with the highest correlation coefficient serves as a measure of the body segment that activated each voxel. The main difference between spectral analysis and cross-correlation methods has to do with the different models they use as the predictor. While cross-correlation takes into account the HRF model, spectral analysis uses a pure cosine (in the stimulus repetition frequency) as the predictor of activation. Since spectral analysis is not confined to a specific HRF model or shape of response, it can identify various activation shapes, including broadly tuned voxels or highly selective voxels. Cross correlation analysis is more sensitive to the shape of the hemodynamic response and to the degree of overlap in representation. Despite these differences, both these methods are applicable for mapping gradients that contain a relatively small number of overlapping representations such as the primary somatosensory cortex. I showed here that both methods yielded similar results for the group as well as for single subjects (**Figures 2.1**, **S2.1**). However, despite the power of these phase-locked methods in non-invasive mapping of topographic gradients, they are ill suited to inferring the exact locus of representation of each body part along the topographic gradient (although this kind of localization is possible, see Besle et al., 2013). Such a validation of the results could be achieved using other methods such as GLM analysis, which enables a direct contrast between the responses to different body parts.

Taken together, my results demonstrate that a natural tactile stimulus combined with phase-locked analysis provides a powerful and sensitive tool for the mapping of whole-body somatosensory gradients, at the group and single-subject levels, and should be the gold standard to map whole body gradients in both basic research and in the clinic. Furthermore, beyond improved resolution and clearer gradients, this periodic experimental design has some practical benefits in that it requires a shorter scanning time and fewer repetitions compared to other experimental designs, a feature which is even more important in clinical setting (see below a discussion on the potential clinical implications and Appendix A for a preliminary clinical work that shows how my approach and the results presented here can be applied in clinical settings).

4.2.1 Future directions and clinical implications of studying somatosensory gradients

In this study I focused on the topographic organization of the primary somatosensory homunculus. However, the methodological approaches (and some of the results) presented here could also be used to study somatotopic gradients beyond S1. As discussed above, these approaches have been used to reveal additional retinotopic, cochleotopic and somatotopic-motor maps beyond the primary areas. Delineating multiple topographical maps could be utilized for studying parallel and divergent functional somatotopic regions and their hierarchical connections. Moreover, understanding the topographical structure of the somatosensory cortex, in particular high-order areas, could lead to a better understanding of multisensory processes ascribed to these areas such as sensorimotor and visual integration or perceptual tasks such as shape and texture discrimination or object localization (Reed et al., 2005; Roland et al., 1998). Several somatosensory-activated areas have been identified in addition to the primary somatosensory cortex in the parietal operculum including the second somatosensory cortex, (Burton et al., 1997, 2008; Disbrow et al., 2000; Eickhoff et al., 2006a, 2006b; Young et al., 2004), the insular cortex (Burton et al., 1993; Mazzola et al., 2006; Ostrowsky et al., 2002; Penfield and Faulk, 1955), the posterior parietal lobe (Golaszewski et al., 2006; Huang et al., 2012; Sereno and Huang, 2006; Young et al., 2004), and in the prefrontal cortex (Burton et al., 1997; Golaszewski et al., 2006), but their exact number and the extent to which they represent the whole body remains unclear.

In a recent study, Huang and colleagues (2012) mapped multisensory tactile - visual areas in the posterior parietal cortex. The main finding of this study was the existence of a tactile homunculus in the posterior parietal lobe which overlapped with retinotopic maps. Inspection of the visual polar-angle maps revealed that the median of the visual polar-angle representations gradually shifted from near the horizontal meridian in the face area to the lower visual field in the lag area. Thus, it was suggested that these areas fuse multisensory information in the peri-personal space to protect the individual from head to toe. It is important to note that the spatial arrangement of the observed parietal face, lip, and finger areas was different from the organization of the S1 homunculus since the fingers were found to be located ventral and lateral to the lips and face representations. In this study the tactile experiments used full-body air puff stimulation to deliver stimulation to 64 sites on six body parts in a set of block-design scans. However, even with this high number of stimulation sites, the tactile maps were quite coarse, and the single-subject maps further suggested that multiple representations of a body part existed in the superior parietal lobe. This highlights the need for a high-density stimulation on different body parts to verify the location and the precise topographic organization of this homunculus (Huang et al., 2012). Although this was beyond the scope of the work presented here, and thus was not tested directly, my data (see Figures 2.1, 2.4) indicate that the tactile evoked responses extended to the posterior parietal lobe, and show a trend for somatotopic organization in this area, which is parallel to Penfield's homunculus in the primary somatosensory cortex. These preliminary results should be further investigated and verified at the single subject level as well. I suggest that by applying the cyclic experimental design and phase-locked analysis methods described above, this homunculus (and probably others) and their topographic organization could be mapped in greater detail.

Higher somatosensory cortices are characterized by neurons with large and overlapping receptive fields (Disbrow et al., 2000; Mazzola et al., 2006; Robinson and Burton, 1980), leading to wider tuning curves of the population of neurons within each voxel, which can create problems when portraying topographic gradients in these areas. As discussed above, such higher cortex gradients can be detected by spectral analysis of the BOLD signal which is less sensitive to the specific width of the response. An alternative and highly promising technique that has been recently proposed uses a model-driven approach to estimate neuronal population receptive fields as the basis for generating topographic maps. This approach, first described for early visual mapping (Dumoulin and Wandell, 2008), fits a model of the population's receptive field to each voxel that best explains the measured fMRI responses. Then, these best-fit models are used to estimate the preferred stimulus driving the voxels' response, similar to phase-encoded methods of spectral analysis mapping. This method has been used recently to show the topographic representation of numerosity in the human parietal cortex (Harvey et al., 2013), thus extending topographic principles to the representation of higher-order abstract features in the associative cortex. Thus, it would be of great interest to apply this in the somatosensory domain as well, to reveal and characterize additional somatotopic gradients both within as well as beyond the classical somatosensory cortex.

Finally, ample studies have established the existence of topographical gradients in both sensory and motor cortices as well as in high associative areas, and highlight the notion of topography as a fundamental principle of brain organization. The functional significance of these gradients can be tested under different pathological conditions. Various pathologies along the somatosensory pathway in both animals and humans show a cortical imprint which is reflected in the reorganization of the somatosensory cortex (Chen et al., 2012; Hahamy et al., 2015; Moore et al., 2000). For example, after spinal cord injury and amputations there was an expansion of adjacent body-parts representation (Corbetta et al., 2002; Flor et al., 1995; Henderson et al., 2011). However, the role of topographic gradient continuity and the functional correlatives of their disturbances remain unclear. This question was addressed recently in a clinical work I collaborated on which applied a phase-locked approach to study plastic reorganization of the somatosensory homunculi. In this work, we examined the role of continuity and discontinuity in somatosensory processing in patients with cervical partial (sensory) Brown-Séquard syndrome. This syndrome is characterized by injury to only one half of the spinal cord, which disturbes sensory signal conduction from the body to the brain (Kobayashi et al., 2003; Tattersall and Turner, 2000). Importantly, this syndrome is unique, as it involves a unilateral representation of the whole body but in patients without brain pathology, and thus can serve as an ideal model to compare physiological and pathological cortical patterns from the disturbed and non-disturbed body sides within the same subjects. The results showed that for each individual patient, gradient continuity was disturbed in the hemisphere contralateral to the disturbed body side; gradients in the patients' hemisphere contralateral to the non-disturbed body side were similar to controls (the results of this study are detailed in the Appendix). These results suggest that gradient continuity may play a central role in somatotopic organization, and its disruption may characterize pathological signal processing.

4.3 Negative BOLD as an important component of the neuronal correlates of sensory processing

In this thesis I showed that passive stimuli arising from one sensory modality (i.e. passive touch on the body) evoke a mixed pattern of positive and negative BOLD responses both within the related sensory cortex as well as in cortical areas of different sensory modalities (i.e. the visual cortex). While these unisensory and cross-modal negative responses might be mediated by different mechanisms, the conjunction of these results provides strong evidence against the "blood stealing" explanation for this phenomenon, since in all cases, the positive and negative BOLD responses extended to cortical areas which are supplied by different arteries. In addition several studies have recorded direct electrophysiological activity or different features of blood flow and metabolic rate which further support a neurological source for the negative BOLD responses (Boorman et al., 2010; Mullinger et al., 2014; Shmuel et al., 2002, 2006; Stefanovic et al., 2004; reviewed in Logothetis and Wandell, 2004; Nair, 2005).

In the contralateral primary somatosensory cortex, this negative BOLD might serve to create a sharper somatotopic tuning curve across the entire S1 homunculus via the involvement of intercortical connections. This mechanism might be similar to the more local role of inhibition in creating the directional tuning curve in S1, as observed in spatiotemporal interactions via local lateral connections in areas BA3 and BA1 (Friedman et al., 2008; Reed et al., 2010). Such findings support the hypothesis that area 3b is involved in widespread stimulus integration. The functional role or potential readout of such somatotopic tuning curve is still an open question. In the visual domain, stimulation of central visual field evoked negative BOLD responses which were coupled to decreased local field potentials and multiunit activity in the surrounding peripheral areas (Shmuel et al., 2006). Such a precise pattern of deactivation has been shown to contain stimulus-specific distributed information and was suggested to play an important role in the resulting visual percept (Bressler et al., 2007). Furthermore, in the motor domain, multivoxel pattern analysis showed that positive and negative BOLD in M1 contain somatotopic information, enabling prediction of the moving body part from inside and outside its somatotopic location (Zeharia et al., 2012). Future studies are needed to explain the relations of negative BOLD to somatotopic percept and the underlying mechanism. The combined positive and negative BOLD responses from the entire homunculus could be integrated in higher somatosensory areas, with larger (and perhaps bilateral) receptive field. Another potential explanation is related to attentional process. In the visual domain, several studies have shown that directing attention to a specific location is associated with an increase in neuronal activity at the attended region and a decrease in the BOLD signal of the unattended areas (see for example - (Müller and Kleinschmidt, 2004; Slotnick et al., 2003; Tootell et al., 1998). Thus, feedback connections from attention related areas is thought to enhance the relevant signal and to reduce the contribution of noise from the surrounding areas, allowing improved resolution of position coding (Bressler et al., 2007).

Converging evidence from animal and human studies further support a neuronal mechanism underlying the negative BOLD responses in the ipsilateral somatosensory cortex (Boorman et al., 2010; Lipton et al., 2006; Mullinger et al., 2014). Moreover, negative BOLD responses in the ipsilateral hemisphere have been associated to behavioral changes in the tactile perceptual threshold. For example, Kastrup and colleagues (2008) tested the perceptual threshold to electrical stimulation of the left index finger (current perception threshold, CPT) during concomitant electrical stimulation of the right median nerve as a quantitative measure of sensory function. They found that the ipsilateral negative BOLD signal correlated highly with an increase in the CPT of the contralateral, unstimulated finger, thus supporting the notion that the ipsilateral negative BOLD response reflects functionally effective inhibition in the somatosensory system. In another study (Schäfer et al., 2012) it was shown that while CPTs of the ipsilateral finger were elevated during median nerve stimulation (as described above), the perceptual threshold for hallux stimulation did not change, suggesting that the increased CPTs of the finger were not caused by refocused attention on the opposite median nerve. These findings seem to contradict my results which found negative BOLD responses in the ipsilateral foot area during hand stimulation. However, as discussed previously (see section 2.4.5), the results of this study (Schäfer et al., 2012) and others (Gröschel et al., 2013; Kastrup et al., 2008) showed in fact that the ipsilateral pattern of the negative BOLD was more extensive than the area of the hand representation and in some cases also included the ipsilateral foot . Additional studies directly testing the perceptual threshold for various body parts corresponding to the somatotopically deactivated areas would resolve this issue, and further support the notion that the negative BOLD is related to a functional inhibition mechanism.

Finally, cross-modal deactivations have been reported in various sensory modalities, but the consistency, spatial pattern and the factors mediating these cross-modal effects are still uncertain (Shulman et al., 1997). In this thesis I showed that passive touch on the body results in a coherent combination of cross-modal positive and negative BOLD in the visual cortex, and that this pattern is task and body specific. Previous studies have suggested that cross modal effects may be imposed by top-down control to refine sensory inputs in a variety of scenarios (Corbetta and Shulman, 2002; Talsma et al., 2010). These may serve as a mechanism that filters non-relevant sensory inputs, thus allowing for more efficient processing higher in the hierarchy (Corbetta and Shulman, 2002; Gazzaley and D'Esposito, 2007). This is in line with the deactivations reported in sensory cortices during demanding cognitive tasks such as visual imagery, linguistic tasks and intrinsic tasks (Amedi et al., 2005; Azulay et al., 2009; Goldberg et al., 2006). Specifically, deactivation in non-relevant sensory cortices has been found to be related to task difficulty and cognitive task performance (Hairston et al., 2008). The fact that the visual area which showed peak deactivation to passive touch (corresponding to V2/V3) was not functionally connected to the somatosensory cortex further supports the hypothesis that the cross-modal inhibition reported in this work stems from large-scale top-down processing rather than from direct bottom-up somatosensory inputs. Potential sources for this top-down effect include the IPS (which was also activated by the tactile stimulus), as this area involves in both attention and multisensory processing (Grefkes et al., 2002; Merabet and Swisher, 2007), and the prefrontal gyrus which is involved in inhibiting the processing of irrelevant information in posterior sensory areas (Johnson and Zatorre, 2006; Miller and Cohen, 2001). Here I provide another example of cross-modal deactivation which is unique in the extent of the deactivation encompassing major parts of ventral and dorsal, retinotopic and non retinotopic areas, and especially given that the stimulation was passive. This suggests that cross-modal effects are much more dramatic in a context less explored so far; namely the passive stream of input.

To conclude these sections, my findings so far suggest that while negative BOLD responses could arise from reciprocal, bottom-up or top-down sources, the balance between positive and negative BOLD responses is a fundamental property of the brain's reaction to many (if not all) sensory or cognitive tasks, thus reflecting the functional inhibition of dynamic processing of cortical networks. The functional role of such inhibitory processes could be further studied under different pathological conditions. For example, as discussed above (see section 4.2.1 and Appendix A) we found a disturbance in the somatotopic continuity of the contralateral S1 homunculus in patients with unilateral cervical damage. In the future, it would be intriguing to test whether such a disturbance also occurs in the negative BOLD responses, both within and outside the somatosensory cortex. This could potentially enhance our understanding of the source of the ipsilateral inhibition in S1. If the ipsilateral deactivation is mediated through transcallosal connections, the disturbed topography in the contralateral hemisphere could also affect the negative BOLD in the ipsilateral homunculus. This would mean that although the sensory deficits are unilateral and thus affect the contralateral hemisphere, they also extend their effect to the ipsilateral hemisphere, in which there is a representation of the non-disturbed body side. Furthermore, comparing the cross-modal positive and negative BOLD responses elicited in the visual cortex after stimulation of the disturbed and non-disturbed body sides might also help to study the sources of such responses.

4.4 Passive tactile responses in sighted visual cortex individuals: the brain as a metamodal task machine

The visual cortex has been traditionally considered to be a stimulus-driven, unimodal system with a hierarchical organization, in which the early visual areas tune general features while the higher-tier ones respond selectively to the specific features of a visual stimulus (Golarai et al., 2007; Wandell et al., 2007). However, recent studies by our group and others have shown that the cortical preference in the ‘visual’ cortex might not be exclusively visual and in fact that specialization might develop independently of visual experience (Amedi et al., 2001; Frasnelli et al., 2011; Pietrini et al., 2004; Prather et al., 2004; Ptito et al., 2012). In addition to the a-modal properties of the LO for tool and object recognition (Amedi et al., 2001, 2007) discussed above during active haptic palpation, other visual areas have been shown to be activated by non-visual task related stimuli. More generally, an overlap in the neural correlates of equivalent tasks has been repeatedly shown between the blind and sighted using different sensory modalities (Collignon et al., 2011; Mahon et al., 2009; Matteau et al., 2010; Ptito et al., 2012; Renier et al., 2014, 2010; Ricciardi et al., 2007; Sathian, 2005; Striem-Amit et al., 2012).The most recent addition to the literature of task-selective areas was a study that explored the processing of number symbols and letters in the congenitally blind using visual-to-music sensory substitution (Abboud et al., 2014). This study (Abboud et al., 2015) found that the VNFA (visual number form area) was selectively activated by Roman scripts, but only if they were processed as numbers (compared to letters or color).

Two main neural mechanisms have been proposed to explain the involvement of the visual cortex in the processing of non-visual signals. One hypothesis is that of cross-modal plasticity, in which atypical connections and networks are generated in the blind that convey non-visual information to the occipital cortex, as a result of significant plastic reorganization in the blind brain. A clear example is the cross modal plasticity to process language and memory in the visual system (Amedi et al., 2003; Bedny et al., 2011; Raz et al., 2005). Another hypothesis, which not completely mutually exclusive, holds that the visual cortex is supramodal in nature, which means that in many cases (or to an extreme in all cases) there is a common representation of the perceived stimuli irrespective of their perceptual sensory (Amedi et al., 2001; Pascual-Leone and Hamilton, 2001; Reich et al., 2012). This newly suggested model of the brain as a metamodal task-specific machine has far-reaching implications for the understanding of sensory perception and cortical processing. It might also have clinical relevance (which is beyond the scope of the current thesis).

One line of evidence supporting the notion of the brain as a task-selective rather than a sensory specific operator comes from studies in sighted individuals. Several areas in the visual cortex have also been shown to be activated by non-visual modalities in sighted people, and thus ruling out the hypothesis that such processing is unique and relates to reorganization of the visually deprived brain (Amedi et al., 2001, 2007; Beauchamp et al., 2007; Costantini et al., 2011; Kilgour et al., 2005).

However, while these studies have shown that visual areas can be elicited by non-visual modalities in the sighted and thus are not solely dependent on plastic reorganization, they also introduce other potential confounding factors. The main alternative explanation for the observed results in the sighted argues that the activation of visual areas by other sensory modalities does not reflect pure cross-modal responses, but rather that they result from top-down mechanisms such as mental imagery processing that build up a mental visual representation of the stimuli (see review in Sathian, 2005).

The results presented in my thesis contribute to this debate on several levels. First, this is the first study that shows that even totally passive stimuli can recruit visual areas in the sighted and with a clear topographical bias. Second, the cross-modal activations were selective in two ways: they were specific to the LO area, and were also selective to the hand versus all other body parts or compared to mental imagery (see results section 3.3 and **Figures 3.3**, **3.4**, **S3.3**). Third, this specific pattern also emerged in the functional connectivity analysis in the resting brain, which emphasizes the important role of somatosensory inputs in object recognition (**Figure 3.4**). This suggests that at least in our case, low-level and bottom-up cross-modal stimuli can drive the visual cortex even more strongly than high cognitive and top-down processes such as mental imagery. Thus, my findings contribute to novel converging evidence supporting the theory that the brain has a sensory-independent, task-selective supramodal organization rather than a sensory-specific one, and further suggest that this organization can be elicited even by passive stimuli. In the future, it would be interesting to test whether other areas in the visual cortex (or in other sensory cortices) could be activated by cross-modal inputs carrying task-selective information even under passive conditions and whether this will rely on unique and differential pattern of connectivity between the relevant brain areas.

Resting state analysis has been especially useful in the detection of altered functional connectivity in different populations such as consciousness disorders (Ovadia-Caro et al., 2012), neuronal disorders (Gavrilescu et al., 2010) or developmental deficits such as congenital hand absence (Hahamy et al., 2015). The latter study found that compensatory arm usage maintains symmetric sensorimotor functional connectivity in one-handers, supporting the hypothesis that individual ecological behavior is imprinted in the connectivity patterns (Harmelech and Malach, 2013). Thus, implementation of resting state analysis, which is extremely fast and efficient for sensory and motor mapping, can be important in clinical cases when the use of phase-locked analysis is not possible, or to complement it by an alternative approach.

On the basis of these findings on functional connectivity combined with the result of unique functional connectivity between the tactile-LO and the hand representation in S1, the connectivity pattern of the tactile-LO might be altered when the ecological relevance of the somatosensory inputs from the hand vary. For example, blind individuals who mostly rely on somatosensory inputs for object and tool recognition might exhibit enhanced connectivity between the visual cortex and the hand area, compared to normally sighted individuals. Conversely, upper limb amputees have been found to show reduced inter-hemispheric connectivity in the hand area (Makin et al., 2013) and might as well show such a reduction in connectivity to the LO. A case study of amputees with extraordinary foot movement skill found that toe tapping movements in these individuals activated the bilateral (missing) hand area in S1 (Yu et al., 2006). It could be hypothesized that under these circumstances in which the amputees regularly use their feet to manipulate objects, the relevant somatosensory inputs which activate the LO would be foot stimulation, reflected in the functional connectivity pattern of these areas.

4.5 Conclusion

In this thesis I studied new views of brain organization which suggest that brain function is characterized by sets of metamodal task-oriented but sensory independent operators, that topography is a fundamental basis for brain architecture and function and that the balance between large scale activation and deactivations that give rise to negative and positive BOLD are crucial to our understanding of sensory processing within and between the senses. Using the somatosensory system as a model, I provide evidence that support and expand these views. First, cross-modal responses in the visual system were specific to the task-relevant area under passive conditions, and such task-relevance connections were found even without any stimulus. Second, topographical biases in the responses to somatosensory stimulation were found in both early and high-order sensory cortices and they characterized both positive and negative BOLD responses since within a given sensory cortex (i.e. somatosensory or visual), each body part only activated the functionally relevant subareas, while deactivating the surrounding non-relevant areas. Taken together, the results presented in this thesis suggest that the balance between positive and negative BOLD signal and the ecological relevance of the input at each point in time might be crucial to our understanding of a large variety of intrinsic and extrinsic tasks including low level sensory processing, high-level cognitive functions and multisensory integration.

4.6 References

Abboud, S., Hanassy, S., Levy-Tzedek, S., Maidenbaum, S., and Amedi, A. (2014). EyeMusic: Introducing a “visual” colorful experience for the blind using auditory sensory substitution. Restor. Neurol. Neurosci. *32*, 247–257.

Abboud, S., Maidenbaum, S., Dehaene, S., and Amedi, A. (2015). A number-form area in the blind. Nat. Commun. *6*, 6026.

Amedi, A., Malach, R., Hendler, T., Peled, S., and Zohary, E. (2001). Visuo-haptic object-related activation in the ventral visual pathway. Nat. Neurosci. *4*, 324–330.

Amedi, A., Raz, N., Pianka, P., Malach, R., and Zohary, E. (2003). Early “visual” cortex activation correlates with superior verbal memory performance in the blind. Nat. Neurosci. *6*, 758–766.

Amedi, A., Malach, R., and Pascual-Leone, A. (2005). Negative BOLD differentiates visual imagery and perception. Neuron *48*, 859–872.

Amedi, A., Stern, W.M., Camprodon, J.A., Bermpohl, F., Merabet, L., Rotman, S., Hemond, C., Meijer, P., and Pascual-Leone, A. (2007). Shape conveyed by visual-to-auditory sensory substitution activates the lateral occipital complex. Nat. Neurosci. *10*, 687–689.

Azulay, H., Striem, E., and Amedi, A. (2009). Negative BOLD in sensory cortices during verbal memory: a component in generating internal representations? Brain Topogr. *21*, 221–231.

Beauchamp, M.S., Yasar, N.E., Kishan, N., and Ro, T. (2007). Human MST but not MT responds to tactile stimulation. J. Neurosci. *27*, 8261–8267.

Bedny, M., Pascual-Leone, A., Dodell-Feder, D., Fedorenko, E., and Saxe, R. (2011). Language processing in the occipital cortex of congenitally blind adults. Proc. Natl. Acad. Sci. U. S. A. *108*, 4429–4434.

Besle, J., Sánchez-Panchuelo, R.-M., Bowtell, R., Francis, S., and Schluppeck, D. (2013). Single-subject fMRI mapping at 7 T of the representation of fingertips in S1: a comparison of event-related and phase-encoding designs. J. Neurophysiol. *109*, 2293–2305.

Boorman, L., Kennerley, A.J., Johnston, D., Jones, M., Zheng, Y., Redgrave, P., and Berwick, J. (2010). Negative blood oxygen level dependence in the rat: a model for investigating the role of suppression in neurovascular coupling. J. Neurosci. *30*, 4285–4294.

Bressler, D., Spotswood, N., and Whitney, D. (2007). Negative BOLD fMRI response in the visual cortex carries precise stimulus-specific information. PLoS One *2*, e410.

Burton, H., Videen, T.O., and Raichle, M.E. (1993). Tactile-vibration-activated foci in insular and parietal-opercular cortex studied with positron emission tomography: mapping the second somatosensory area in humans. Somat. Mot Res *10*, 297–308.

Burton, H., MacLeod, A.M., Videen, T.O., and Raichle, M.E. (1997). Multiple foci in parietal and frontal cortex activated by rubbing embossed grating patterns across fingerpads: a positron emission tomography study in humans. Cereb Cortex *7*, 3–17.

Burton, H., Sinclair, R.J., Wingert, J.R., and Dierker, D.L. (2008). Multiple parietal operculum subdivisions in humans: tactile activation maps. Somat. Mot Res *25*, 149–162.

Chen, L.M., Qi, H.-X., and Kaas, J.H. (2012). Dynamic reorganization of digit representations in somatosensory cortex of nonhuman primates after spinal cord injury. J. Neurosci. *32*, 14649–14663.

Collignon, O., Vandewalle, G., Voss, P., Albouy, G., Charbonneau, G., Lassonde, M., and Lepore, F. (2011). Functional specialization for auditory-spatial processing in the occipital cortex of congenitally blind humans. Proc. Natl. Acad. Sci. U. S. A. *108*, 4435–4440.

Corbetta, M., and Shulman, G.L. (2002). Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. *3*, 201–215.

Corbetta, M., Burton, H., Sinclair, R.J., Conturo, T.E., Akbudak, E., and McDonald, J.W. (2002). Functional reorganization and stability of somatosensory-motor cortical topography in a tetraplegic subject with late recovery. Proc. Natl. Acad. Sci. *99*, 17066–17071.

Costantini, M., Urgesi, C., Galati, G., Romani, G.L., and Aglioti, S.M. (2011). Haptic perception and body representation in lateral and medial occipito-temporal cortices. Neuropsychologia *49*, 821–829.

Disbrow, E., Roberts, T., and Krubitzer, L. (2000). Somatotopic organization of cortical fields in the lateral sulcus of Homo sapiens: evidence for SII and PV. J Comp Neurol *418*, 1–21.

Dumoulin, S.O., and Wandell, B.A. (2008). Population receptive field estimates in human visual cortex. Neuroimage *39*, 647–660.

Eickhoff, S.B., Schleicher, A., Zilles, K., and Amunts, K. (2006a). The human parietal operculum. I. Cytoarchitectonic mapping of subdivisions. Cereb Cortex *16*, 254–267.

Eickhoff, S.B., Amunts, K., Mohlberg, H., and Zilles, K. (2006b). The human parietal operculum. II. Stereotaxic maps and correlation with functional imaging results. Cereb Cortex *16*, 268–279.

Engel, S.A. (2012). The development and use of phase-encoded functional MRI designs. Neuroimage *62*, 1195–1200.

Engel, S.A., Rumelhart, D.E., Wandell, B.A., Lee, A.T., Glover, G.H., Chichilnisky, E.J., and Shadlen, M.N. (1994). fMRI of human visual cortex. Nature *369*, 525.

Engel, S.A., Glover, G.H., and Wandell, B.A. (1997). Retinotopic organization in human visual cortex and the spatial precision of functional MRI. Cereb Cortex *7*, 181–192.

Flor, H., Elbert, T., Knecht, S., Wienbruch, C., Pantev, C., Birbaumers, N., Larbig, W., and Taub, E. (1995). Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. Nature *375*, 482–484.

Frasnelli, J., Collignon, O., Voss, P., and Lepore, F. (2011). Crossmodal plasticity in sensory loss. Prog. Brain Res. *191*, 233–249.

Friedman, R.M., Chen, L.M., and Roe, A.W. (2008). Responses of areas 3b and 1 in anesthetized squirrel monkeys to single- and dual-site stimulation of the digits. J. Neurophysiol. *100*, 3185–3196.

Gavrilescu, M., Rossell, S., Stuart, G.W., Shea, T.L., Innes-Brown, H., Henshall, K., McKay, C., Sergejew, A.A., Copolov, D., and Egan, G.F. (2010). Reduced connectivity of the auditory cortex in patients with auditory hallucinations: a resting state functional magnetic resonance imaging study. Psychol. Med. *40*, 1149–1158.

Gazzaley, A., and D’Esposito, M. (2007). Top-down modulation and normal aging. Ann. N. Y. Acad. Sci. *1097*, 67–83.

Golarai, G., Ghahremani, D.G., Whitfield-Gabrieli, S., Reiss, A., Eberhardt, J.L., Gabrieli, J.D.E., and Grill-Spector, K. (2007). Differential development of high-level visual cortex correlates with category-specific recognition memory. Nat. Neurosci. *10*, 512–522.

Golaszewski, S.M., Siedentopf, C.M., Koppelstaetter, F., Fend, M., Ischebeck, A., Gonzalez-Felipe, V., Haala, I., Struhal, W., Mottaghy, F.M., Gallasch, E., et al. (2006). Human brain structures related to plantar vibrotactile stimulation: a functional magnetic resonance imaging study. Neuroimage *29*, 923–929.

Goldberg, I.I., Harel, M., and Malach, R. (2006). When the brain loses its self: prefrontal inactivation during sensorimotor processing. Neuron *50*, 329–339.

Grefkes, C., Weiss, P.H., Zilles, K., and Fink, G.R. (2002). Crossmodal processing of object features in human anterior intraparietal cortex: an fMRI study implies equivalencies between humans and monkeys. Neuron *35*, 173–184.

Gröschel, S., Sohns, J.M., Schmidt-Samoa, C., Baudewig, J., Becker, L., Dechent, P., and Kastrup, A. (2013). Effects of age on negative BOLD signal changes in the primary somatosensory cortex. Neuroimage *71*, 10–18.

Hagler, D.J., and Sereno, M.I. (2006). Spatial maps in frontal and prefrontal cortex. Neuroimage *29*, 567–577.

Hahamy, A., Sotiropoulos, S.N., Henderson Slater, D., Malach, R., Johansen-Berg, H., and Makin, T.R. (2015). Normalisation of brain connectivity through compensatory behaviour, despite congenital hand absence. Elife *4*, e04605.

Hairston, W.D., Hodges, D.A., Casanova, R., Hayasaka, S., Kraft, R., Maldjian, J.A., and Burdette, J.H. (2008). Closing the mind's eye: deactivation of visual cortex related to auditory task difficulty. Neuroreport *19*, 151–154.

Harmelech, T., and Malach, R. (2013). Neurocognitive biases and the patterns of spontaneous correlations in the human cortex. Trends Cogn. Sci. *17*, 606–615.

Harvey, B.M., Klein, B.P., Petridou, N., and Dumoulin, S.O. (2013). Topographic representation of numerosity in the human parietal cortex. Science *341*, 1123–1126.

Henderson, L.A., Gustin, S.M., Macey, P.M., Wrigley, P.J., and Siddall, P.J. (2011). Functional reorganization of the brain in humans following spinal cord injury: evidence for underlying changes in cortical anatomy. J. Neurosci. *31*, 2630–2637.

Hertz, U., and Amedi, A. (2010). Disentangling unisensory and multisensory components in audiovisual integration using a novel multifrequency fMRI spectral analysis. Neuroimage *52*, 617–632.

Huang, R.-S., Chen, C., Tran, A.T., Holstein, K.L., and Sereno, M.I. (2012). Mapping multisensory parietal face and body areas in humans. Proc. Natl. Acad. Sci. U. S. A. *109*, 18114–18119.

Johnson, J.A., and Zatorre, R.J. (2006). Neural substrates for dividing and focusing attention between simultaneous auditory and visual events. Neuroimage *31*, 1673–1681.

Kastrup, A., Baudewig, J., Schnaudigel, S., Huonker, R., Becker, L., Sohns, J.M., Dechent, P., Klingner, C., and Witte, O.W. (2008). Behavioral correlates of negative BOLD signal changes in the primary somatosensory cortex. Neuroimage *41*, 1364–1371.

Kell, C.A., von Kriegstein, K., Rosler, A., Kleinschmidt, A., and Laufs, H. (2005). The sensory cortical representation of the human penis: revisiting somatotopy in the male homunculus. J Neurosci *25*, 5984–5987.

Kilgour, A.R., Kitada, R., Servos, P., James, T.W., and Lederman, S.J. (2005). Haptic face identification activates ventral occipital and temporal areas: an fMRI study. Brain Cogn. *59*, 246–257.

Kobayashi, N., Asamoto, S., Doi, H., and Sugiyama, H. (2003). Brown-Sèquard syndrome produced by cervical disc herniation: report of two cases and review of the literature. Spine J. *3*, 530–533.

Lipton, M.L., Fu, K.-M.G., Branch, C.A., and Schroeder, C.E. (2006). Ipsilateral hand input to area 3b revealed by converging hemodynamic and electrophysiological analyses in macaque monkeys. J. Neurosci. *26*, 180–185.

Logothetis, N.K., and Wandell, B.A. (2004). Interpreting the BOLD signal. Annu Rev Physiol *66*, 735–769.

Mahon, B.Z., Anzellotti, S., Schwarzbach, J., Zampini, M., and Caramazza, A. (2009). Category-specific organization in the human brain does not require visual experience. Neuron *63*, 397–405.

Makin, T.R., Cramer, A.O., Scholz, J., Hahamy, A., Henderson Slater, D., Tracey, I., and Johansen-Berg, H. (2013). Deprivation-related and use-dependent plasticity go hand in hand. Elife *2*, e01273.

Matteau, I., Kupers, R., Ricciardi, E., Pietrini, P., and Ptito, M. (2010). Beyond visual, aural and haptic movement perception: hMT+ is activated by electrotactile motion stimulation of the tongue in sighted and in congenitally blind individuals. Brain Res. Bull. *82*, 264–270.

Mazzola, L., Isnard, J., and Mauguiere, F. (2006). Somatosensory and pain responses to stimulation of the second somatosensory area (SII) in humans. A comparison with SI and insular responses. Cereb Cortex *16*, 960–968.

McGlone, F., Kelly, E.F., Trulsson, M., Francis, S.T., Westling, G., and Bowtell, R. (2002). Functional neuroimaging studies of human somatosensory cortex. Behav Brain Res *135*, 147–158.

Merabet, L., and Swisher, J. (2007). Combined activation and deactivation of visual cortex during tactile sensory processing. J. … 1633–1641.

Miller, E.K., and Cohen, J.D. (2001). An integrative theory of prefrontal cortex function. Annu. Rev. Neurosci. *24*, 167–202.

Miyamoto, J.J., Honda, M., Saito, D.N., Okada, T., Ono, T., Ohyama, K., and Sadato, N. (2006). The representation of the human oral area in the somatosensory cortex: a functional MRI study. Cereb Cortex *16*, 669–675.

Moore, C.I., Stern, C.E., Dunbar, C., Kostyk, S.K., Gehi, A., and Corkin, S. (2000). Referred phantom sensations and cortical reorganization after spinal cord injury in humans. Proc. Natl. Acad. Sci. *97*, 14703–14708.

Müller, N.G., and Kleinschmidt, A. (2004). The attentional “spotlight”s’ penumbra: center-surround modulation in striate cortex. Neuroreport *15*, 977–980.

Mullinger, K.J., Mayhew, S.D., Bagshaw, A.P., Bowtell, R., and Francis, S.T. (2014). Evidence that the negative BOLD response is neuronal in origin: a simultaneous EEG-BOLD-CBF study in humans. Neuroimage *94*, 263–274.

Nair, D.G. (2005). About being BOLD. Brain Res. Brain Res. Rev. *50*, 229–243.

Nelson, A.J., and Chen, R. (2008). Digit somatotopy within cortical areas of the postcentral gyrus in humans. Cereb Cortex *18*, 2341–2351.

Orlov, T., Makin, T.R., and Zohary, E. (2010). Topographic representation of the human body in the occipitotemporal cortex. Neuron *68*, 586–600.

Ostrowsky, K., Magnin, M., Ryvlin, P., Isnard, J., Guenot, M., and Mauguiere, F. (2002). Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. Cereb Cortex *12*, 376–385.

Ovadia-Caro, S., Nir, Y., Soddu, A., Ramot, M., Hesselmann, G., Vanhaudenhuyse, A., Dinstein, I., Tshibanda, J.-F.L., Boly, M., Harel, M., et al. (2012). Reduction in inter-hemispheric connectivity in disorders of consciousness. PLoS One *7*, e37238.

Pascual-Leone, A., and Hamilton, R. (2001). The metamodal organization of the brain. Prog. Brain Res. *134*, 427–445.

Penfield, W., and Faulk Jr., M.E. (1955). The insula; further observations on its function. Brain *78*, 445–470.

Pietrini, P., Furey, M.L., Ricciardi, E., Gobbini, M.I., Wu, W.-H.C., Cohen, L., Guazzelli, M., and Haxby, J. V (2004). Beyond sensory images: Object-based representation in the human ventral pathway. Proc. Natl. Acad. Sci. U. S. A. *101*, 5658–5663.

Prather, S.C., Votaw, J.R., and Sathian, K. (2004). Task-specific recruitment of dorsal and ventral visual areas during tactile perception. Neuropsychologia *42*, 1079–1087.

Ptito, M., Matteau, I., Zhi Wang, A., Paulson, O.B., Siebner, H.R., and Kupers, R. (2012). Crossmodal recruitment of the ventral visual stream in congenital blindness. Neural Plast. *2012*, 304045.

Raz, N., Amedi, A., and Zohary, E. (2005). V1 activation in congenitally blind humans is associated with episodic retrieval. Cereb. Cortex *15*, 1459–1468.

Reed, C.L., Klatzky, R.L., and Halgren, E. (2005). What vs. where in touch: an fMRI study. Neuroimage *25*, 718–726.

Reed, J.L., Qi, H.X., Zhou, Z., Bernard, M.R., Burish, M.J., Bonds, A.B., and Kaas, J.H. (2010). Response Properties of Neurons in Primary Somatosensory Cortex of Owl Monkeys Reflect Widespread Spatiotemporal Integration. J. Neurophysiol. *103*, 2139–2157.

Reich, L., Maidenbaum, S., and Amedi, A. (2012). The brain as a flexible task machine: implications for visual rehabilitation using noninvasive vs. invasive approaches. Curr. Opin. Neurol. *25*, 86–95.

Renier, L., De Volder, A.G., and Rauschecker, J.P. (2014). Cortical plasticity and preserved function in early blindness. Neurosci. Biobehav. Rev. *41*, 53–63.

Renier, L.A., Anurova, I., De Volder, A.G., Carlson, S., VanMeter, J., and Rauschecker, J.P. (2010). Preserved functional specialization for spatial processing in the middle occipital gyrus of the early blind. Neuron *68*, 138–148.

Ricciardi, E., Vanello, N., Sani, L., Gentili, C., Scilingo, E.P., Landini, L., Guazzelli, M., Bicchi, A., Haxby, J. V, and Pietrini, P. (2007). The effect of visual experience on the development of functional architecture in hMT+. Cereb. Cortex *17*, 2933–2939.

Robinson, C.J., and Burton, H. (1980). Organization of somatosensory receptive fields in cortical areas 7b, retroinsula, postauditory and granular insula of M. fascicularis. J Comp Neurol *192*, 69–92.

Roland, P.E., O'Sullivan, B., and Kawashima, R. (1998). Shape and roughness activate different somatosensory areas in the human brain. Proc Natl Acad Sci U S A *95*, 3295–3300.

Sathian, K. (2005). Visual cortical activity during tactile perception in the sighted and the visually deprived. Dev. Psychobiol. *46*, 279–286.

Schäfer, K., Blankenburg, F., Kupers, R., Grüner, J.M., Law, I., Lauritzen, M., and Larsson, H.B.W. (2012). Negative BOLD signal changes in ipsilateral primary somatosensory cortex are associated with perfusion decreases and behavioral evidence for functional inhibition. Neuroimage *59*, 3119–3127.

Sereno, M.I., and Huang, R.S. (2006). A human parietal face area contains aligned head-centered visual and tactile maps. Nat Neurosci *9*, 1337–1343.

Sereno, M.I., Dale, A.M., Reppas, J.B., Kwong, K.K., Belliveau, J.W., Brady, T.J., Rosen, B.R., and Tootell, R.B. (1995). Borders of multiple visual areas in humans revealed by functional magnetic resonance imaging. Science *268*, 889–893.

Shmuel, A., Yacoub, E., Pfeuffer, J., Van de Moortele, P.-F., Adriany, G., Hu, X., and Ugurbil, K. (2002). Sustained Negative BOLD, Blood Flow and Oxygen Consumption

Response and Its Coupling to the Positive Response in the Human Brain. Neuron *36*, 1195–1210.

Shmuel, A., Augath, M., Oeltermann, A., and Logothetis, N.K. (2006). Negative functional MRI response correlates with decreases in neuronal activity in monkey visual area V1. Nat. Neurosci. *9*, 569–577.

Shulman, G.L., Corbetta, M., Buckner, R.L., Raichle, M.E., Fiez, J.A., Miezin, F.M., and Petersen, S.E. (1997). Top-down modulation of early sensory cortex. Cereb. Cortex *7*, 193–206.

Slotnick, S.D., Schwarzbach, J., and Yantis, S. (2003). Attentional inhibition of visual processing in human striate and extrastriate cortex. Neuroimage *19*, 1602–1611.

Stefanovic, B., Warnking, J.M., and Pike, G.B. (2004). Hemodynamic and metabolic responses to neuronal inhibition. Neuroimage *22*, 771–778.

Striem-Amit, E., Hertz, U., and Amedi, A. (2011). Extensive cochleotopic mapping of human auditory cortical fields obtained with phase-encoding FMRI. PLoS One *6*, e17832.

Striem-Amit, E., Dakwar, O., Reich, L., and Amedi, A. (2012). The large-scale organization of “visual” streams emerges without visual experience. Cereb. Cortex *22*, 1698–1709.

Talsma, D., Senkowski, D., Soto-Faraco, S., and Woldorff, M.G. (2010). The multifaceted interplay between attention and multisensory integration. Trends Cogn. Sci. *14*, 400–410.

Tattersall, R., and Turner, B. (2000). Brown-Séquard and his syndrome. Lancet *356*, 61–63.

Tootell, R.B.., Hadjikhani, N., Hall, E.K., Marrett, S., Vanduffel, W., Vaughan, J.T., and Dale, A.M. (1998). The Retinotopy of Visual Spatial Attention. Neuron *21*, 1409–1422.

Wandell, B.A., and Winawer, J. (2011). Imaging retinotopic maps in the human brain. Vision Res. *51*, 718–737.

Wandell, B.A., Dumoulin, S.O., and Brewer, A.A. (2007). Visual field maps in human cortex. Neuron *56*, 366–383.

Young, J.P., Herath, P., Eickhoff, S., Choi, J., Grefkes, C., Zilles, K., and Roland, P.E. (2004). Somatotopy and attentional modulation of the human parietal and opercular regions. J Neurosci *24*, 5391–5399.

Yu, X., Zhang, S., Liu, H., and Chen, Y. (2006). The activation of the cortical hand area by toe tapping in two bilateral upper-extremities amputees with extraordinary foot movement skill. Magn. Reson. Imaging *24*, 45–50.

Zeharia, N., Hertz, U., Flash, T., and Amedi, A. (2012). Negative blood oxygenation level dependent homunculus and somatotopic information in primary motor cortex and supplementary motor area. Proc Natl Acad Sci U S A *109*, 18565–18570.

Zeharia, N., Hertz, U., Flash, T., and Amedi, A. (2015). New whole-body sensory-motor gradients revealed using phase-locked analysis and verified using multivoxel pattern analysis and functional connectivity. J. Neurosci. *35*, 2845–2859.

5. Appendix

Discontinuity of somatosensory cortical gradients reflects sensory impairment

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Abstract

A crucial principle of neuroplasticity is that when part of the somatosensory cortex is deprived of its corresponding body part, this cortex is reorganized by inputs from nearby body parts. Such deprivation of somatosensory input may manifest in reduced somatotopic-dependent activation or in altered non-somatotopic processing. While many studies have investigated somatotopic reorganization, the role of functional, non-somatotopic cortical reorganization in response to insult is still to be unraveled. We hypothesized that non-somatotopic reorganization is related to loss of continuity of the whole-body representation in the somatosensory cortex.

To test this hypothesis, we compared cortical representations of disturbed and non-disturbed body sides of patients with cervical partial (sensory) Brown-Séquard syndrome (injury to one side of the spinal cord). These patients suffer from decreased sensation in one side of their bodies, which makes it possible to compare the disturbance of the whole body-side representation in the same subject. We used fMRI on five patients and five age-matched healthy controls to compare responses in the primary somatosensory (S1) and supplementary motor area (SMA) cortices to continuous sensory stimulation of both body sides. Spatial changes of cortical activation coinciding with continuous stimulation was defined here as a “gradient”, and its divergence from a continuous pattern was quantified.

For each individual patient, the gradient continuity was disturbed in the hemisphere contralateral to the disturbed body side in both S1 and SMA cortices; gradients in patients’ hemisphere contralateral to the non-disturbed body side were similar to the controls. fMRI percent signal change did not show any significant difference between hemispheres in either patients or controls.

These results suggest that decreased sensation in the patients is related to gradient discontinuity rather than signal reduction. Gradient continuity may play a central

role in somatotopic organization, and its disruption may characterize pathological signal processing.

Introduction

The somatotopic "homunculus" representation in the human cortex is one of the most important discoveries of modern neuroscience (Penfield and Boldrey, 1937; Penfield and Rasmussen, 1950). The early electrophysiological findings of Penfield and colleagues have been confirmed and extended in several neuroimaging studies in healthy individuals (Fox et al., 1987; Nakamura et al., 1998; Narici et al., 1991; Stippich et al., 1999; Yang et al., 1993) and have been further explored in patients and non-human primates with different pathologies using both electrophysiology and neuroimaging (Kaas, 1991, 2000; Kaas et al., 1983, 2008; Nardone et al., 2013; Pons et al., 1991; Wall et al., 2002). The latter elicited changes in the cortical pattern of activity following damage to the somatosensory system, manifested as functional cortical reorganization. Kaas, Merzenich and Killackey suggested that there may be "several types of cortical reorganization, including [1] the somatotopic expansion of previously existing representations of body parts, [2] the development of "new" representations, [3] the activation of large regions of the cortex from a very limited region of a receptive field surface, [4] and a "non-somatotopic" activation of the cortex from scattered receptive fields" (Kaas et al., 1983). Studies in non-human primates have reported an expansion of adjacent body part representations following spinal cord injuries and amputations (Dutta et al., 2014; Florence and Kaas, 1995; Jain et al., 2008; Merzenich et al., 1984; Tandon et al., 2009). Similar results were found in human patients using fMRI (Corbetta et al., 2002; Flor et al., 1995; Henderson et al., 2011; Simões et al., 2012). fMRI in non-human primates after partial section of the dorsal column of the spinal cord at the cervical level showed dispersion of representations of each finger, which were further assembled later (Chen et al., 2012). Co-activation of nonadjacent representations was found as well, suggesting that cortical reorganization is dispersed over the somatosensory cortex (Moore et al., 2000). Although most of these results have investigated somatotopic re-organizations [1-3], non-somatotopic organization [4] remains understudied and unclear, we hypothesized that non-somatotopic reorganization may be associated to the relationship between the representation of the disturbed body part and the whole body representation. In fact, the whole body representation may have particular importance, since somatotopic organization reflects not only adjacency of different body parts, but also the general principle that neural populations that are involved in similar computational tasks are located in close spatial proximity (Kaas, 1997; Silver and Kastner, 2009). Non-somatotopic discontinuity may thus reflect a general pathological principle.

To examine the role of continuity and discontinuity in somatosensory processing, we searched for a model that would enable us to compare processing of physiological and pathological whole-body continuous signals in the same study subject. One such unique model is the cervical partial (sensory) Brown-Séquard syndrome. This syndrome is characterized by injury to only one half of the spinal cord, which disturbs sensory signal conduction from the body to the brain (Kobayashi et al., 2003; Tattersall and Turner, 2000). Patients with Brown-Séquard syndrome experience a reduction in sensation of one side of their body (hemihypoaesthesia). Cervical Brown-Séquard syndrome is unique, involving a unilateral representation of the whole body, but in patients without brain pathology, thus serving as an ideal model to compare physiological and pathological cortical patterns from the disturbed and non-disturbed body sides. We therefore used fMRI in patients with partial (sensory) Brown-Séquard syndrome to compare responses in the primary somatosensory (S1) and supplementary motor area (SMA) cortices to continuous sensory stimulation of the right and left body sides.

To describe a change in cortical activation coinciding with continuous sensory stimulation we use the term “gradient” (Goldberg, 1989; Sereno et al., 1994). We quantified the continuity of gradients by analyzing a one-dimensional series of functional cluster geometric centroids which represents responses to sensory input from different body parts. A somatosensory deficit that results in hypoesthesia may be reflected in signal reduction or discontinuity. We hypothesized that somatotopic representations in the hemisphere contralateral to the sensory deficit would exhibit functional reorganization manifested as gradient discontinuity.

Results

Five patients with partial Brown-Séquard syndrome due to disc protrusion, manifested as hemihypoaesthesia and five age-matched healthy controls were stimulated with a continuous somatosensory stimulation of their right and left body sides under fMRI. We looked for changes in gradient continuity and signal power between the two contralateral responses and relative to healthy controls by quantitative analysis. To characterize somatotopic gradients in the S1 and SMA cortices, we first analyzed the continuous stimulation fMRI data using cross-correlation analysis over 12 different lag-values, corresponding to different body parts sequentially organized from head to toe. This procedure yielded a gradient representation of S1 and SMA homunculi in the contralateral hemisphere for the stimulated body side, corroborating previous studies (Zeharia et al., 2012; **Figure 1**). The exact locations of the gradients were further verified using a block design paradigm (repeated stimulation of cheek, palm and toes) and a general linear model (GLM) analysis.

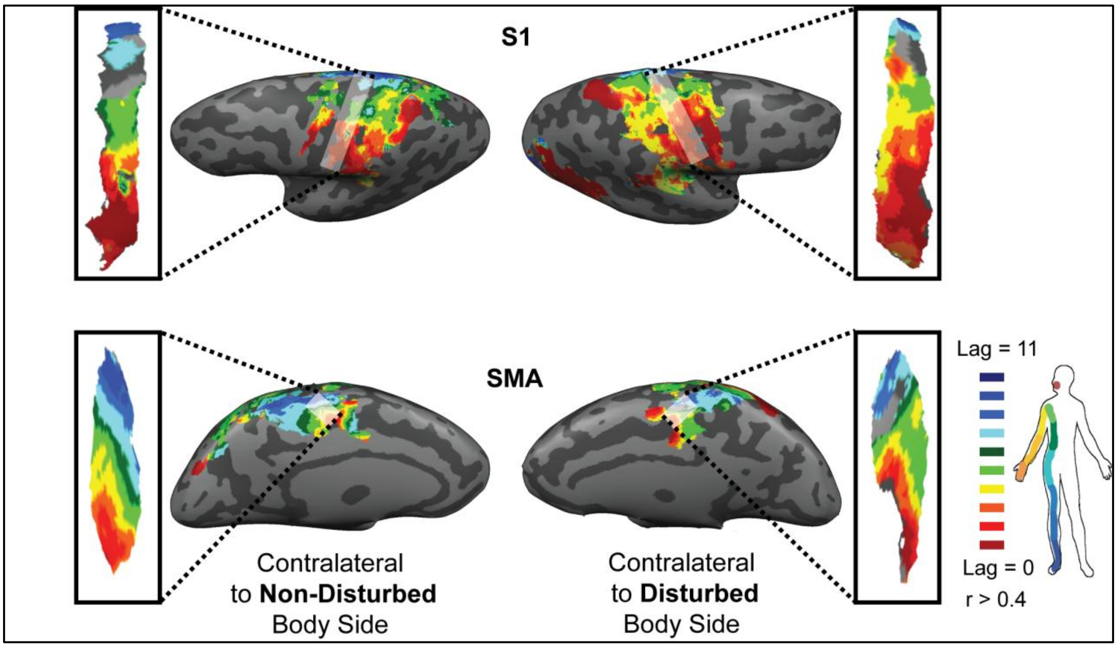

Figure 1. Cross correlation maps corresponding to continuous somatosensory stimulation of a patient with left hemi-hypoaesthesia due to partial Brown-Séquard syndrome. Contralateral S1 (top, lateral view) and SMA (bottom, medial view) are shown for right body stimulation in the left hemisphere (left), and left body stimulation in the right hemisphere (right). Color scale represents body parts from lips (dark red) to toe (dark blue). Extracted gradients (white rectangles) are magnified.

In order to quantify gradient continuity, we developed the following analysis. The different lag-values of each gradient were first segmented into clusters (**Figure 2A**). Geometric centroids were projected on a linear-fit, and lag-values were then organized according to their projection on this fit (**Figure 2B**). The variance of the difference series was defined as the gradient dispersion value (GDV), characterizing the continuity of the gradient (better continuity is reflected in lower variance and therefore lower GDV; for details see Methods). In order to best capture the main axis of the gradient, the linear fit was rotated (±35º) and translated (within 4 intervals between the extrema of vertical axis components) to obtain minimal GDV (**Figure 2C**).

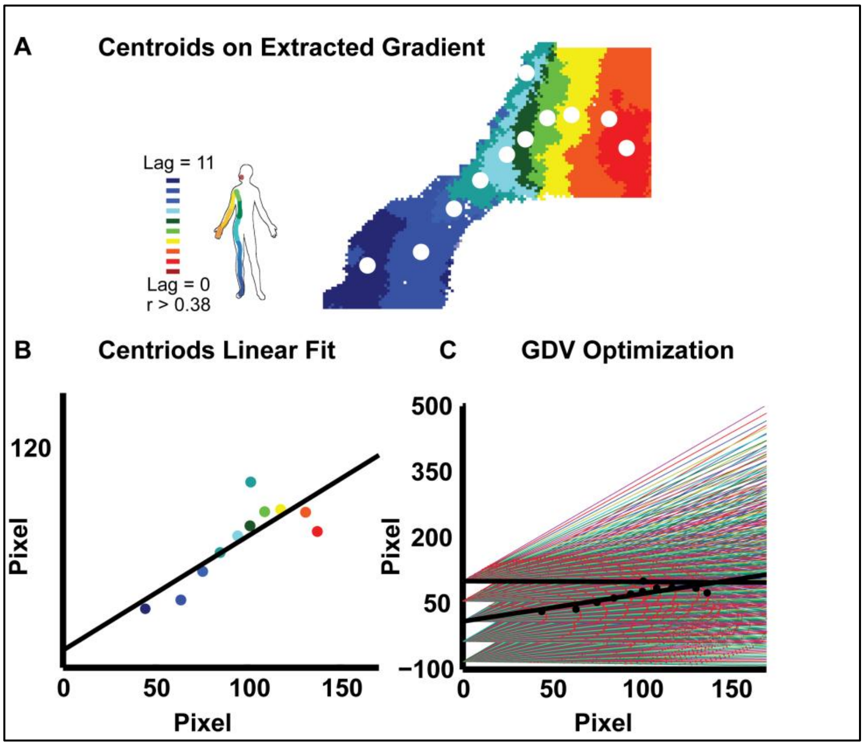

Figure 2. Gradient quantification. A. The original functional image of the gradient is shown, including the centroids corresponding to different lag values; B. Centroids are shown with the corresponding lag color and linear fit; C. Trend line optimization: centroids (black) projected on different trend lines (red dots) varying 35 degrees rotation clock and anti-clock wise and four vertical translations. Black lines represent the original linear fit and the deviation which yielded the lowest gradient disperssion value (GDV).

For each individual patient, gradients contralateral to the disturbed body side showed higher GDV than gradients contralateral to the non-disturbed body side, in both the S1 and the SMA. Statistical analysis at the group level confirmed these results (Wilcoxon rank sum, $p<0.05$). Significant differences were found also in compare of disturbed body-side to control subjects (p<0.05). No difference was found when the non-disturbed body side was compared to control subjects (S1: p=0.547, SMA: p= 0.166) as well as between the right and left sides of the control subjects (S1: p=0.198, SMA: p=0.682, **Figure 3A**).

These results demonstrate that hypoesthesia is reflected in a discontinuity of the corresponding somatosensory cortical gradient. We further inquired whether this disturbance was also reflected in the power of the fMRI signal. For this purpose we analyzed the percent change of the fMRI blood-oxygen-level dependent (BOLD) signal, averaged separately over the different body parts for S1 and SMA. This analysis did not reveal any significant difference between the disturbed and non-disturbed body sides or between the different sides compared to the healthy controls (all p's >0.05, **Figure 3B**).

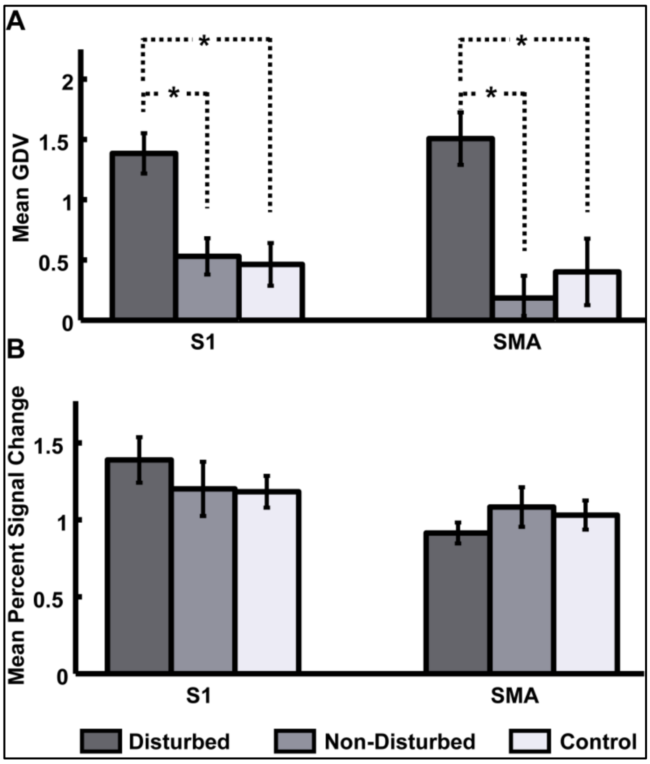

Figure 3. A. Mean GDVs of all patients' gradients contralateral to the disturbed (dark gray) and non-disturbed (light gray) body sides as well as for healthy controls (white, averaged over both hemispheres) are presented for S1 (left) and the SMA (right) separately. Note the difference between disturbed and non-disturbed/control gradients (p<0.05), as well as the similarity between non-disturbed gradients and healthy controls. B. Percent signal change of whole body representation in the abovementioned conditions did not reveal any significant differences. Error bars represent standard error of the mean (SEM).

Discussion

The underlying pathology of Brown-Séquard syndrome involves a disruption of signal conduction from the peripheral sensors to the brain due to spinal cord lesion. In our patients this disruption led to decreased sensation in the affected body side that was reflected in cortical activity. Our results relate this disturbance to a discontinuity of cortical gradients rather than signal reduction, and stress the central role of gradients' continuity in somatosensory sensation. This may further explain non-somatotopic organization in the context of a whole-body representation.

Reorganization of the human somatosensory cortex in response to spinal cord injury has been widely investigated. Nevertheless, there is a lack of consensus with respect to the underlying mechanism. The suggested mechanisms include growth of intracortical connections (Florence et al., 1998), lemniscal and thalamocortical axonal withdrawal (Graziano and Jones, 2009), reorganization of brainstem and thalamic nuclei (Jain et al., 2000; Jones and Pons, 1998; Kambi et al., 2014) and gray matter volume loss (Henderson et al., 2011). The whole-body representation and the gradiental relations between body parts within this representation may shed new light on mechanisms of reorganization.

Gradients enable computation with respect to neighboring values rather than absolute values. This may facilitate computational processes, since neighboring units will present similar values. Gradient discontinuity may be a result of damage as well as an adaptation to damage. In the first case, the brain will lose information due to the damage, while in the second case the brain trades the computational advantage of adjacency in order to gain information.

Topographic representations are ubiquitous in the primary cortices: visual retinotopic maps represent projections of the visual field on the retina, auditory cortex contains tonotopic maps reflecting the representation of sounds frequencies, motor and somatosensory cortices contains homunculus maps corresponding to the representation of body parts (Engel, 1997; Engel et al., 1994; Lauter et al., 1985; Luethke et al., 1989; Meier et al., 2008; Penfield and Boldrey, 1937; Penfield and Rasmussen, 1950; Striem-Amit et al., 2011; Wandell, 1999; Zeharia et al., 2012). Recent studies show that topographic organization characterizes not only the primary cortices but also higher-order cortices, processing functions such as memory, spatial attention and numerosity (Hagler and Sereno, 2006; Harvey et al., 2013; Kastner et al., 2007; Silver et al., 2005). In fact, natural signals perceived by the nervous system from the external world, the internal milieu or the intrinsic system are usually composed of a series of successive elements in time or space (Golland et al., 2007; Hasson et al., 2004). Gradient continuity may therefore be of importance not only to somatotopic organization but to topographic organization in general.

Our study included five patients, encompassing all patients who were treated at our institute with hemihypoaesthesia due to disc protrusion over a period of 18 months and who agreed to participate in the study, met inclusion criteria and were MRI-compatible. Despite the relatively small number of patients, the ability to compare the healthy body side to the damaged one in the same subject strengthens the results. In particular, differences were found not only at the group level but also in each individual patient. Brown-Séquard syndrome may further serve as a powerful model to study somatosensory deficits in humans where the subjective experience of sensory deficit is crucial.

This study was also confronted with a few technical limitations. First, the light touch stimulation was manual; however the protocol was pre-planned and the experimenter followed precise stimulus-locked instructions. Second, the substantial variation among different subjects yielded differences in the extracted gradients. Extraction was verified in three anatomical representations (3D, inflate, flattened) including signal evaluation, and was verified by an additional GLM analysis over a standard block design paradigm. Moreover, all potential trend lines to the extracted gradients in a range of ±35 degrees from the linear fit were examined to identify an optimal gradient. Finally, homunculi differ in size; thus, segmentation to clusters with the same lag had various threshold values for minimum pixels per cluster. However, the threshold settings were always identical for the same homunculi in the two hemispheres.

In conclusion, we showed that a sensory deficit due to spinal injury is reflected in cortical gradient discontinuity, rather than signal power reduction. We suggest that gradient continuity is a crucial property of brain function, and its disruption may be a key feature of pathological signal processing. Further research is needed to investigate gradient organization in other sensory modalities, in higher-order cortices, as well as the role of gradient organization and its potential disruption in brain pathologies.

Methods

Participants. This prospective cohort study was composed of five patients with hemi-hypoaesthesia (unilateral) related to partial Brown-Séquard syndrome due to cervical disc protrusion (four males, 41.8±11.8 years (mean±SD)), and five age-matched healthy volunteers (two males, 41.4±13.1 years). No participant had any other neurological, psychiatric or systemic disorder. Patients underwent a semi-structural interview that documented time of pathology onset, symptoms and their development, past medical history and family and social history. Neurological examination elicited normal muscle strength and moderate to severe hypoesthesia for light touch in the affected body side for all patients. All patients underwent MRI of the cervical spine, including T1, T2 and STIR* contrasts in sagittal and axial views. All participants gave written informed consent and the study was approved by the ethics committee of the Hadassah Hebrew University Medical Center.

Stimuli and procedures. Patients and healthy controls underwent two different stimulation paradigms, continuous (periodic-design) and discrete (block-design). In the continuous stimulation, a whole-body brush movement was applied lip-to-toe and toe-to-lip bilaterally in two different scanning sessions. Each scanning session contained fourteen whole-body stimulation cycles, seven to each body side. The length of each stimulation cycle was 15s, which was followed by a 12s rest baseline. Session started with 30s of silence before the first cycle onset, and ended with 4.5s after the last cycle offset, in addition to 12s of silence between body sides.

In the discrete stimulation paradigm, the right and left toes, palm, and cheek were stimulated in separate blocks (yielding six conditions). Each body part stimulation was repeated four times in a randomized order. Stimulation lasted 6s followed by 9s rest. Session started with 28s of silence before the first cycle onset, and ended with 6s after the last cycle offset. In both stimulation paradigms, the natural tactile stimuli were delivered using a four centimeter wide paint brush by the same experimenter, who was well-trained prior to the scans to maintain a constant pace and pressure during the sessions. The experimenter wore fMRI-compatible electrodynamic headphones which delivered pre-programmed (Presentation®, Neurobehavioral Systems, Berkley, CA) auditory cues signaling the precise timing of the body part sequence which enabled a controlled velocity of tactile stimuli.

Functional MRI image acquisition procedures and preprocessing. Patients and healthy controls were scanned at the same site using a Siemens Trio 3T system (32 channel head coil) with the same imaging sequence. Blood Oxygen Level Dependent (BOLD) fMRI was acquired using a whole-brain, gradient-echo (GE) echoplanar (EPI) (TR/Time Echo (TE) =1500/27ms, flip angle=70, FOV=192×192mm, matrix=64×64, 26 axial slices, slice thickness/gap=4mm/0.8mm, voxel size=3×3×3mm). In addition, high resolution (1×1×1mm) T1-weighted anatomical images were acquired to aid spatial normalization to standard atlas space. The anatomic reference volume was acquired along the same orientation as the functional images (TR/TE=2300/2.97ms, matrix=256×256, 160 axial slices, 1-mm slice thickness, TI = 900ms).

Preprocessing was performed using the Brain Voyager® QX 2.4.2.2070 software package (Brain Innovation, Maastricht, Netherlands), including head motion correction, slice scan time correction and high-pass filtering (cutoff frequency: 2 cycles/scan). Temporal smoothing (FWHM=4s) and spatial smoothing (FWHM=4mm) were applied to the periodic design. Functional and anatomical datasets for each subject were aligned and fit to standardized Talairach space (Talairach and Tournoux, 1988).

Cross-Correlation Analysis. A boxcar function (3s) was convolved with a two gamma hemodynamic response function (HRF), in order to derive predictors for the analysis. These predictors and the time course of each voxel were cross-correlated, allowing for 12 lags with one TR (time repetition) interval time to account for the stimulation duration of each cycle (10 TRs) and two additional TRs to account for the hemodynamic delay. For each voxel, we obtained the lag value with the highest correlation coefficient between the time course and 1 of 12 predictors and the value of this correlation coefficient.

Gradient quantification analysis. The above procedure yielded map values (lag and correlation coefficient), corresponding to vertex coordinates of the brain surface (flat). The correlation threshold was set for each individual subject (S1 and SMA separately, mean: 0.37, SEM: 0.011) which best captured S1 and SMA gradients for each subject while keeping it constant between both sides. Each lag and its corresponding coordinates were represented by a specific color as an RGB matrix. Then, the 3D image matrix was converted into a 2D matrix with corresponding lag values. This 2D matrix was segmented into clusters with the same lag-value (**Figure 2A**). The cluster-size threshold, set according to the gradient size, defined the minimum number of pixels that accounted for a cluster. In a next step, we calculated the coordinates of a geometric centroid for each cluster. Centroids were plotted on an X-Y plane in which the axes preserved the original image scale. In order to further define a vector that best represented the quality of the gradient, centroids were projected on a linear fit (**Figure 2B**). This manipulation yielded a one-dimensional series of lag-values reflecting the cluster organization and order. Continuity of the gradient was defined with respect to the differences between lags, giving rise to a derivative vector. The gradient was characterized according to the variance of this derivative vector (variation from a "perfectly" organized gradient). This value was thus termed the “gradient dispersion value” (GDV). In order to find an optimal fit (lowest GDV) on which centroids were projected, we performed multiple rotations (35 degrees clockwise and counter-clockwise, 1 degree step) and translations (4) of the linear fit which covered the potential line orientation through the scattered centroids (**Figure 2C**). Corresponding GDVs were calculated while the minimal value was extracted to best capture the gradient continuity and monotonicity. To test for significant differences between average groups of GDVs we used the Wilcoxon rank sum test.

Block design analysis. A general linear model (GLM) was applied to the block design data, using predictors (boxcar function, 6s) convolved with a two gamma HRF for each of the six conditions (cheek, palm and toes, bilaterally). Activation maps for each body part were obtained by contrasting each condition versus baseline, in order to verify the gradients' localization. The peak activations for the cheek and toes in the contralateral postcentral gyrus were defined as the start and end point of the S1 homunculus and were compared to the gradient maps obtained from the continuous stimulation. For the SMA homunculi, the localization was verified by the peaks along the medial walls.

Power analysis. In order to test whether the disturbance in somatosensory inputs was also reflected in the power of the fMRI signal we quantified the power of the BOLD signal in each homunculus using the block design data. We extracted a "patch of interest" (POI) of the contralateral S1 and SMA from the inflated presentation of each contrast (cheek, palm and toes) containing the most significant 50 and 10 vertices, respectively. This method therefore does not require correction for multiple comparisons as only the most significant vertices are selected. Percent signal change was calculated as the maximum value of epoch based (-1 to 1 TR around condition onset) event related averaging.

References

Chen, L.M., Qi, H.-X., and Kaas, J.H. (2012). Dynamic reorganization of digit representations in somatosensory cortex of nonhuman primates after spinal cord injury. J. Neurosci. *32*, 14649–14663.

Corbetta, M., Burton, H., Sinclair, R.J., Conturo, T.E., Akbudak, E., and McDonald, J.W. (2002). Functional reorganization and stability of somatosensory-motor cortical topography in a tetraplegic subject with late recovery. Proc. Natl. Acad. Sci. U. S. A. *99*, 17066–17071.

Dutta, A., Kambi, N., Raghunathan, P., Khushu, S., and Jain, N. (2014). Large-scale reorganization of the somatosensory cortex of adult macaque monkeys revealed by fMRI. Brain Struct. Funct. *219*, 1305–1320.

Engel, S. (1997). Retinotopic organization in human visual cortex and the spatial precision of functional MRI. Cereb. Cortex *7*, 181–192.

Engel, S.A., Rumelhart, D.E., Wandell, B.A., Lee, A.T., Glover, G.H., Chichilnisky, E.-J., and Shadlen, M.N. (1994). fMRI of human visual cortex. Nature 369, 525.

Flor, H., Elbert, T., Knecht, S., Wienbruch, C., Pantev, C., Birbaumer, N., Larbig, W., and Taub, E. (1995). Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. Nature *375*, 482–484.

Florence, and Kaas, J.H. (1995). Large-scale reorganization at multiple levels of the somatosensory pathway follows therapeutic amputation of the hand in monkeys. J. Neurosci. *15*, 8083–8095.

Florence, S., Taub, H., and Kaas, J. (1998). Large-scale sprouting of cortical connections after peripheral injury in adult macaque monkeys. Science (80-.). *282*, 1117–1121.

Fox, P.T., Burton, H., and Raichle, M.E. (1987). Mapping human somatosensory cortex with positron emission tomography. J. Neurosurg. *67*, 34–43.

Goldberg, E. (1989). Gradiental approach to neocortical functional organization. J. Clin. Exp. Neuropsychol. *4*, 489–517.

Golland, Y., Bentin, S., Gelbard, H., Benjamini, Y., Heller, R., Nir, Y., Hasson, U., and Malach, R. (2007). Extrinsic and intrinsic systems in the posterior cortex of the human brain revealed during natural sensory stimulation. Cereb. Cortex *17*, 766–777.

Graziano, A., and Jones, E.G. (2009). Early withdrawal of axons from higher centers in response to peripheral somatosensory denervation. J. Neurosci. *29*, 3738–3748.

Hagler, D.J., and Sereno, M.I. (2006). Spatial maps in frontal and prefrontal cortex. Neuroimage *29*, 567–577.

Harvey, B.M., Klein, B.P., Petridou, N., and Dumoulin, S.O. (2013). Topographic representation of numerosity in the human parietal cortex. Science *341*, 1123–1126.

Hasson, U., Nir, Y., Levy, I., Fuhrmann, G., and Malach, R. (2004). Intersubject synchronization of cortical activity during natural vision. Science *303*, 1634–1640.

Henderson, L.A., Gustin, S.M., Macey, P.M., Wrigley, P.J., and Siddall, P.J. (2011). Functional reorganization of the brain in humans following spinal cord injury: evidence for underlying changes in cortical anatomy. J. Neurosci. *31*, 2630–2637.

Jain, N., Florence, S.L., Qi, H.X., and Kaas, J.H. (2000). Growth of new brainstem connections in adult monkeys with massive sensory loss. Proc. Natl. Acad. Sci. U. S. A. *97*, 5546–5550.

Jain, N., Qi, H.-X., Collins, C.E., and Kaas, J.H. (2008). Large-scale reorganization in the somatosensory cortex and thalamus after sensory loss in macaque monkeys. J. Neurosci. *28*, 11042–11060.

Jones, E.G., and Pons, T.P. (1998). Thalamic and Brainstem Contributions to Large-Scale Plasticity of Primate Somatosensory Cortex. Science (80-.). *282*, 1121–1125.

Kaas, J. (1991). Plasticity of Sensory and Motor Maps in Adult Mammals. Ann. Rev. Neurosci. *14*, 137–167.

Kaas, J.H. (1997). Topographic Maps are Fundamental to Sensory Processing. Brain Res. Bull. *44*, 107–112.

Kaas, J.H. (2000). The reorganization of somatosensory and motor cortex after peripheral nerve or spinal cord injury in primates. Prog. Brain Res. *128*, 173–179.

Kaas, J.H., Merzenich, M.M., and Killackey, H.P. (1983). The reorganization of somatosensory cortex following peripheral nerve damage in adult and developing mammals. Annu. Rev. Neurosci. *6*, 325–356.

Kaas, J.H., Qi, H.-X., Burish, M.J., Gharbawie, O.A., Onifer, S.M., and Massey, J.M. (2008). Cortical and subcortical plasticity in the brains of humans, primates, and rats after damage to sensory afferents in the dorsal columns of the spinal cord. Exp. Neurol. *209*, 407–416.

Kambi, N., Halder, P., Rajan, R., Arora, V., Chand, P., Arora, M., and Jain, N. (2014). Large-scale reorganization of the somatosensory cortex following spinal cord injuries is due to brainstem plasticity. Nat. Commun. *5*, 3602.

Kastner, S., DeSimone, K., Konen, C.S., Szczepanski, S.M., Weiner, K.S., and Schneider, K.A. (2007). Topographic maps in human frontal cortex revealed in memory-guided saccade and spatial working-memory tasks. J. Neurophysiol. *97*, 3494–3507.

Kobayashi, N., Asamoto, S., Doi, H., and Sugiyama, H. (2003). Brown-Sèquard syndrome produced by cervical disc herniation: report of two cases and review of the literature. Spine J. *3*, 530–533.

Lauter, J.L., Herscovitch, P., Formby, C., and Raichle, M.E. (1985). Tonotopic organization in human auditory cortex revealed by positron emission tomography. Hear. Res. *20*, 199–205.

Luethke, L.E., Krubitzer, L.A., and Kaas, J.H. (1989). Connections of primary auditory cortex in the New World monkey, Saguinus. J. Comp. Neurol. *285*, 487–513.

Meier, J.D., Aflalo, T.N., Kastner, S., and Graziano, M.S.A. (2008). Complex organization of human primary motor cortex: a high-resolution fMRI study.

Merzenich, M.M., Nelson, R.J., Stryker, M.P., Cynader, M.S., Schoppmann, A., and Zook, J.M. (1984). Somatosensory cortical map changes following digit amputation in adult monkeys. J. Comp. Neurol. *224*, 591–605.

Moore, C.I., Stern, C.E., Dunbar, C., Kostyk, S.K., Gehi, A., and Corkin, S. (2000). Referred phantom sensations and cortical reorganization after spinal cord injury in humans. Proc. Natl. Acad. Sci. U. S. A. *97*, 14703–14708.

Nakamura, A., Yamada, T., Goto, A., Kato, T., Ito, K., Abe, Y., Kachi, T., and Kakigi, R. (1998). Somatosensory homunculus as drawn by MEG. Neuroimage *7*, 377–386.

Nardone, R., Höller, Y., Brigo, F., Seidl, M., Christova, M., Bergmann, J., Golaszewski, S., and Trinka, E. (2013). Functional brain reorganization after spinal cord injury: Systematic review of animal and human studies. Brain Res. *1504*, 58–73.

Narici, L., Modena, I., Opsomer, R.J., Pizzella, V., Romani, G.L., Torrioli, G., Traversa, R., and Rossini, P.M. (1991). Neuromagnetic somatosensory homunculus: a non-invasive approach in humans. Neurosci. Lett. *121*, 51–54.

Penfield, W., and Boldrey, E. (1937). Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation.

Penfield, W., and Rasmussen, T. (1950). The cerebral cortex of man; a clinical study of localization of function. (New York: Hafner).

Pons, T., Garraghty, P., Ommaya, A., Kaas, J., Taub, E., and Mishkin, M. (1991). Massive cortical reorganization after sensory deafferentation in adult macaques. Science (80-.). *252*, 1857–1860.

Sereno, M.I., McDonald, C.T., and Allman, J.M. (1994). Analysis of retinotopic maps in extrastriate cortex. Cereb. Cortex *4*, 601–620.

Silver, M.A., and Kastner, S. (2009). Topographic maps in human frontal and parietal cortex. Trends Cogn. Sci. *13*, 488–495.

Silver, M.A., Ress, D., and Heeger, D.J. (2005). Topographic maps of visual spatial attention in human parietal cortex. J. Neurophysiol. *94*, 1358–1371.

Simões, E.L., Bramati, I., Rodrigues, E., Franzoi, A., Moll, J., Lent, R., and Tovar-Moll, F. (2012). Functional expansion of sensorimotor representation and structural reorganization of callosal connections in lower limb amputees. J. Neurosci. *32*, 3211–3220.

Stippich, C., Hofmann, R., Kapfer, D., Hempel, E., Heiland, S., Jansen, O., and Sartor, K. (1999). Somatotopic mapping of the human primary somatosensory cortex by fully automated tactile stimulation using functional magnetic resonance imaging.

Striem-Amit, E., Hertz, U., and Amedi, A. (2011). Extensive cochleotopic mapping of human auditory cortical fields obtained with phase-encoding FMRI. PLoS One *6*, e17832.

Talairach, J., and Tournoux, P. (1988). Co-planar stereotaxic atlas of the human brain. 3-Dimensional proportional system: an approach to cerebral imaging.

Tandon, S., Kambi, N., Lazar, L., Mohammed, H., and Jain, N. (2009). Large-scale expansion of the face representation in somatosensory areas of the lateral sulcus after spinal cord injuries in monkeys. J. Neurosci. *29*, 12009–12019.

Tattersall, R., and Turner, B. (2000). Brown-Séquard and his syndrome. Lancet *356*, 61–63.

Wall, J.., Xu, J., and Wang, X. (2002). Human brain plasticity: an emerging view of the multiple substrates and mechanisms that cause cortical changes and related sensory dysfunctions after injuries of sensory inputs from the body. Brain Res. Rev. *39*, 181–215.

Wandell, B.A. (1999). Computational neuroimaging of human visual cortex. Annu. Rev. Neurosci. *22*, 145–173.

Yang, T.T., Gallen, C.C., Schwartz, B.J., and Bloom, F.E. (1993). Noninvasive somatosensory homunculus mapping in humans by using a large-array biomagnetometer. Proc. Natl. Acad. Sci. U. S. A. *90*, 3098–3102.

Zeharia, N., Hertz, U., Flash, T., and Amedi, A. (2012). Negative blood oxygenation level dependent homunculus and somatotopic information in primary motor cortex and supplementary motor area. Proc. Natl. Acad. Sci. U. S. A. *109*, 18565–18570.

תהליכי עיבוד תחושתי ורב-חושי של הגוף במוח האנושי

חיבור לשם קבלת תואר דוקטור לפילוסופיה

מאת

זהר טל

הוגש לסנט האוניברסיטה העברית בירושלים

מרץ 2015

עבודה זו נעשתה בהדרכתו של

פרופסור אמיר עמדי

תקציר

במהלך חיי היומיום אנו חווים מגוון אינסופי של קלטים חושיים שונים, המובילים מידע מהסביבה הקרובה והרחוקה וכן מידע ישיר ומתמשך מהגוף ומפני העור. למרות זאת, תפיסת העולם שלנו היא קוהרנטית ואחידה, בעיקר בשל תהליכי אינטגרציה מתמשכים של הקלטים השונים. שני עקרונות בסיסיים לארגון המוח נקשרו באופן קלאסי לתהליכי עיבוד ושילוב של קלטים סנסורים (חושיים). על פי העיקרון הראשון, המוח נחלק לאזורים שונים, אשר לכל אחד מהם התמחות סנסורית נפרדת. ההנחה המקובלת היא כי עיבוד מידע מחושים שונים מתקיים בתחילה באופן עצמאי ובלתי תלוי עבור כל חוש בנפרד, בעוד שתהליכי האינטגרציה נעשים באזורים גבוהים יותר במעלה ההיארכיה המוחית. העיקרון השני עוסק בארגון הטופוגרפי של אזורים סנסוריים ועל פיו מאפיינים סמוכים בשדה הקלט החושי (השדה הרצפטיבי) מיוצגים על ידי קבוצות נוירונים סמוכות בקליפת המוח (הקורטקס), כך שאזורים סנסוריים מאופיינים במפות רטינוטופיות (מיקום בשדה הראייה), קוכליאוטופיות (תדר הצליל), סומטוסנסוריות (מיקום על פני הגוף) ומפות סומטוטופיות מוטוריות (תנועת אפקטורים שונים). ההנחה הרווחת היא שכאשר מתקדמים לעבר אזורים קורטיקלים גבוהים, הארגון הטופוגרפי דועך לטובת ייצוג אבסטרקטי ומורכב יותר, בשל קיומם של שדות רצפטיבים גדולים יותר, המכסים את השדה הסנסורי כולו או חלקים גדולים ממנו.

ראיות מחקריות שנאספו בעשור האחרון קוראות תיגר במידה מסוימת על עקרונות הארגון הקנונים הללו ומציעות שהמוח נחלק ליחידות חישוב בהן נעשים תהליכי העיבוד באופן המוכוון לביצוע מטלה מסויימת, אך ללא תלות בחוש הסנסורי המוביל את המידע אל המוח. יתר על כן, מחקרים מן העת האחרונה מצביעים על כך שהארגון הטופוגרפי הינו עיקרון בסיסי לא רק באזורים סנסוריים ראשוניים אלא מאפיין גם אזורי עיבוד גבוהים יותר. אך למרות זאת, הגישות המתחרות הללו עדיין רחוקות מלהיות מובנות לעומקן והויכוח לגבי תקפותן עדיין מתקיים. לכן, מטרת התזה הזו היא להעמיק את הידע הקיים בשדה מחקר זה ולנסות להרחיבו.

בעבודת התזה שלי התמקדתי במערכת הסומטוסנסורית (המובילה מידע חושי מן העור ואיברי הגוף השונים) של בני אדם כמערכת מודל לחקירת תפיסות חדשות אלו של הארגון המוחי בעזרת דימות מוחי תפקודי (fMRI). בשל העובדה שהמערכת הסומטוסנסורית מעורבת בתהליכי אינטגרציה חושית ומראה מידה גבוהה של ארגון טופוגרפי (לפחות בשלבי העיבוד הראשוניים) היא עשויה לשמש כמודל מוצלח לבחינת התיאוריות החדשות הללו ואף לסייע בהצעת מסגרת תיאורטית כללית להטמעתן. באופן ספציפי, עסקתי בנושאים אלו על ידי חקירת תחום שנלמד במידה פחותה באופן יחסי עד כה, ובחנתי את קיומם של מאפיינים טופוגרפיים בתגובות החיוביות והשליליות של הסיגנל ההמודינמי (blood-oxygenation-level-dependent -BOLD) בקורטקס הסומטוסנסורית ומחוצה לו.

על ידי גירוי מגע רציף ומחזורי של צד אחד של הגוף, בשילוב שיטות אנליזה מתקדמות (phase-locked approaches) אימתי את קיומו הידוע של הארגון הטופוגרפי בקורטקס הסומטוסנסורי הראשוני (ההומונקולוס הסומטוסנסורי) והראיתי את אופן השינוי ההדרגתי בייצוג של איברי הגוף השונים. יתר על כן, התוצאות שהצגתי מציעות כי יש צורך לערוך שינויים בסכימה של ההומונקולוס הסומטוסנסורי הראשוני מכיוון שהוא אינו נמשך לעומקו של הקיר המדיאלי, אלא מסתיים בנקודה הגבוהה ביותר שלו. בנוסף לכך מצאתי כי איברי גוף שונים הובילו לתגובות שליליות של סיגנל ה- BOLD בהמיספרה הקונטרלטרלית וכן בהמיספרה האיפסילטרלית, אך הציגו תבנית מרחבית שונה. בהמיספרה הקונטרלטרלית, נצפה מנגנון ניגוד המחדד את התגובות השונות כך ששילוב תגובות חיוביות ושליליות נצפה עבור כל אחד מאיברי הגוף, באופן שבנה הומונקולוס BOLD שלילי. תגובות BOLD שליליות נמצאו גם בהמיספרה האיפסילטרלית, אך בניגוד לממצאים קודמים ולצד הקונטרלטרלי, הדאקטיבציות לא התמקדו רק באזור ההומולוגי

לאיבר הגוף שגורה, אלא נמשכו לכל אורך ההומונקולוס האיפסילטרלי. התוצאות המוצגות בתזה, אשר חלקן מאששות ומרחיבות ידע קודם וחלקן חדשניות לחלוטין, מצביעות על קיומה של תבנית מורכבת בפעילות המוחית אשר לפיה, תגובות BOLD שליליות מאפיינות את האזורים הסומטוסנסוריים הראשוניים בשתי ההמיספירות ומציעות כי תגובות אלו הן רכיב חשוב בעקומות הכוונון של אוכלוסיות נוירונים כפי שנצפה קודם לכן בקורטקס הראייתי והמוטורי.

בפרספקטיבה רחבה יותר, התוצאות המוצגות בעבודה זו מראות כי שילוב של גירוי מגע טבעי עם שיטות אנליזה ספקטרליות מהווה כלי חזק ורגיש למיפוי של רצפים סומטוסנסוריים של הגוף כולו עבור קבוצות וכן עבור נבדקים בודדים. בשל העובדה ששיטות אלו מתאפיינות בכמה יתרונות מעשיים הן בשדה המחקר הבסיסי והן בעולם הקליני.

בחלקה השני של התזה, התמקדתי באזור שמוגדר על ידי רוב החוקרים כקורטקס ראייתי בראש ובראשונה. מצאתי כי התגובות לגירוי פאסיבי של מגע לא הוגבלו לקורטקס הסומטוסנסורי, אלא חשפו תבנית מורכבת גם בקורטקס הראייתי. מגע פאסיבי עורר תגובה חיובית ספציפית בחלקים הקשורים לזיהוי כלים באזור הנקרא lateral occipital (LO), ובמקביל הוביל לסיגנל BOLD שלילי כמעט בכל שאר הקורטקס הראייתי. האקטיבציה של LO על ידי מגע פאסיבי הייתה סלקטיביות לגירוי של היד והכתף. אנליזה של קישוריות פונקציונאלית במהלך מנוחה (resting state) חשפה כי בעוד אזורים שונים המתמחים בעיבוד מידע הקשור לאובייקטים מראים קישוריות רבה ביניהם, רק tactile-LO מראה קישוריות נרחבת לאזורים בקורטקס הפריאטלי ומעבר לכך, אזור זה היווה את החוליה המקשרת היחידה אל הקורטקס הסומטוסנסורי הראשוני. על בסיס תוצאות אלו אני מציעה כי LO משמש כנקודת חיבור מרכזית המקשרת בין אזורים ראיתיים בעלי סלקטיביות לכלים ואובייקטים, ובין המידע הסומטוסנסורי הנובע מגירוי של היד. קישוריות זו קיימת גם במהלך מנוחה, ככל הנראה בשל התפקיד האבולוציוני החשוב של מגע בזיהוי ותפעול אובייקטים. הממצאים הללו מעלים את אפשרות קיומו של עקרון כללי יותר, על פיו גיוס או השתקה של הקורטקס הראייתי על ידי קלטים סנסורים אחרים יהיו תלויים במידת הרלוונטיות של המידע לתפקיד הפונקציונאלי או לחישוב המתבצע באזורים אלו, וזאת גם כאשר הקלטים מתקבלים באופן פאסיבי, ללא מטרה קוגניטיבית ספציפית. זוהי תפיסה חדשה המרחיבה את גבולות התיאוריה הנוכחית, מכלילה אותה לסט רחב יותר של תנאים ומציעה פרדיקציות לבחינתה גם באזורי מוח אחרים. בנוסף על כך, עבודה זו מציעה גם כי גיוס תלוי-מטלה שכזה יהיה מתווך על ידי תבנית מובחנת של קישוריות בין כל אזור מוחי מסוים ושאר המוח.

לסיכום, המסקנות העולות מתזה זו מציעות כי הן תגובות BOLD חיוביות והן שליליות כוללות מאפיינים טופוגרפיים כך שעבור אזור קורטיקלי חושי מסוים (הסומטוסנסורי או ראייתי) כל אחד מאיברי הגוף מעורר רק את תתי האזורים הרלוונטיים, ובמקביל מוריד את רמת הפעילות באזורים הלא רלוונטיים הסמוכים. על כן, האיזון בין הסיגנלים החיוביים לשליליים ומידת הרלוונטיות שלהם לתפקיד הפונקציונאלי בכל נקודה בזמן עשויים להיות הכרחיים להבנתם של מגוון תפקודים מוחיים החל מתהליכי עיבוד חושי בסיסיים, דרך פונקציות קוגניטיביות גבוהות וכלה בתהליכי אינטגרציה רב-חושיים.