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Learning-Based Cross-Modal Plasticity in the Human Brain: Insights from Visual Deprivation fMRI

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Additional information is available at the end of the chapter

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1. Introduction

Neuroimaging, and functional Magnetic Resonance Imaging (fMRI) in particular, has brought dramatic changes in all fields of brain studies, one notable field under intensive development being that of brain plasticity. To overcome the artificiality of typical experimental paradigms, this chapter presents a set of interrelated investigations focused on the reorganization of working memory and sensorimotor mechanisms as a result of training in a complex 'real-life' paradigm. The novel paradigm that I have introduced is based on drawing – from artistic to technical – because it is a 'real-life' task that uniquely incorporates diverse aspects of perceptual, cognitive and motor processing. In this way, drawing activates the full '*perception-cognition-action loop*'. (I have introduced this expanded terminology, going beyond the usual '*perception-action loop*', to emphasize the key role of the cognitive linkages between the perception input processing and the action components.) It is important to recognize that drawing engages a wide range of spatial manipulation abilities (e.g., spatio-constructional, coordinate transformations, geometric understanding and visualization), together with engaging precise mental representations, conceptual knowledge, motor planning and motor control mechanisms, working and long-term memory, attention, as well as, empathy, emotions and forms of embodied cognition (Grossi and Trojano, 1999, for review; Trojano et al., 2009; Likova, 2012a; 2013). Furthermore, the development of the Cognitive-Kinesthetic Drawing Method (Likova, 2010a; 2012a,b; 2013) – a novel method to train drawing even without vision – makes it possible to use drawing to study cross-modal reorganization in visual areas activated by non-visual tasks.

A further advanced aspect of the studies is that populations with different degrees of development of the visual system were investigated. These populations ranged from sighted (under

blindfolded conditions), through late-onset blind with past visual experience, to congenitally blind who have never experienced any visual stimulation.

A problem specific to brain plasticity studies in the blind is that usually they do not include direct causal manipulation, such as training, but simply make a cross-sectional comparison of activation in the blind to that in the sighted. In contrast, the studies in this chapter have taken a *training-based* approach by capitalizing on my Cognitive-Kinesthetic Method, coupled with a novel *memory paradigm* based on drawing. This training approach allows us to go beyond a mere task/activation correlation to *causal* inferences, and also, enables us to investigate the temporal *evolution* of plastic changes *within the same* brain. Such pre/post-training brain changes were assessed by fMRI, with the respective behavioral changes assessed by comparisons of the drawing performance. Furthermore, comparative analyses between the subject populations allowed us to evaluate novel hypotheses on cross-modal brain plasticity, and suggested a reconceptualization of basic principles of the functional architecture of the brain.

1.1. The novel approach of drawing training

Can we harness the power of drawing to drive brain plasticity and enhance learning and memory?

Conceptual Framework

1. *Space transcends any specific sensory modality.* As emphasized by the phenomenon of drawing by the blind (e.g., Kennedy, 1993, 2000, 2003, 2006; Ponchilla, 2008; Likova, 2010 a,b; 2012a,b; 2013), space and spatial structure are not represented solely by vision. The visual system may be the modality best suited to process spatial information, but it is not the only one. When deprived of visual input, the brain is capable of employing the 'free' visual resources in the most relevant way. (As there is an ambiguity in the use of the term 'spatial', particularly in the working memory and imagery literature, we note that when used in this paper, 'spatial' refers to the perception of any spatial structure – 2D or 3D, static or dynamic – *independently* of the sensory modality exploring it. For example, a face can be recognized by exploring its spatial structure with the hands, or a geometric function can be represented by audio-graphics, etc.) My view is that *drawing* deals with spatial structures in this general sense, and consequently it has the advantage that it can readily be 'translated' from a visual into a tactile form.
2. *Closing the perception-cognition-action loop is a powerful amplifier for learning.* Drawing is just such a task, fully involving the whole 'loop', while precisely orchestrating multiple brain mechanisms, and leading to my hypothesis that it has the power to enhance learning.
3. *Training in highly engaging unfamiliar tasks with fun and inspiring outcomes* is a fruitful paradigm for driving brain reorganization and assessing its temporal evolution. *Drawing* is ideally suited for this role, particularly when studied under the unusual circumstances of visual deprivation.
4. *Tasks that demand detailed re-expression of memory representations* force the development of precise and robust memory. *Drawing-from-memory* requires just such explicit *re-expres-*

sion through the motor loop, and hence, it demands the development of ‘high-resolution’ internal representations to be communicated back through the drawing act.

5. *Direct memory ‘readout’ would greatly benefit memory-studying paradigms.* Drawing from memory provides such direct memory ‘readout’ in the form of the drawn image, as it ensures an explicit expression of the remembered information by externalization of the mental representation that guides the drawing hand.

Drawing as a Novel Paradigm for Training and Studying Memory

Since drawing uniquely incorporates all the principles of my conceptual framework (outlined above), I have hypothesized that drawing – under memory guidance, in particular – is a powerful paradigm for the training of memory. It forces the learners beyond passive exploration of the stimuli, to development of detailed and stable *memory* representations (*Drawing/Memory Hypothesis*). A further conceptualization was that drawing can become an effective tool for studying *learning-based cross-modal* brain reorganization, as this novel paradigm can be adapted from the visual to the tactile modality. This led me to the development of the Cognitive-Kinesthetic Method for non-visual drawing, which enabled a series of studies on the *training* and *studying* of cross-modal memory (e.g., Likova, 2010b; 2012a,b; 2013).

The Need for the Cognitive-Kinesthetic Training Method

The visual appreciation of line drawings (e.g., Fig. 1) seems such an effortless process that we may not be aware of the invisible work of powerful high-level cognitive mechanisms that provide the artist with the ability to transform a 3D object into its 2D projection by abstracting just the right contours into a line drawing. Moreover, we may not appreciate how our brains make the ‘inverse transformation’ to the immediate understanding of what such 2D drawings represent.



Figure 1. Matisse: Lithographes No. 54: ‘Marie’ (left), No. 35: ‘Ma Maîtresse’ (center), No. 45: ‘Les Colombes Amoureuses’ (right), from the illustrations for Ronsard’s ‘*Florilège des Amours*’ (1948).

It came as a surprise, therefore, to find out that, when exposed for the first time to 2D raised-line drawings, many blind participants have tremendous difficulty with tactile recognition and comprehension of the depicted 3D objects, i.e., as would be manifested in an infantile stage

of development of the respective mechanisms. This ‘negative’ finding, however, resulted into a positive outcome, as it brought the realization that drawing has the potential to enable for the first time investigations of the *full* temporal evolution of learning *in adults*, thus revealing the developmental process of key cognitive components.

The inherently visual nature of drawing, however, is an obvious barrier for the direct implementation of the drawing-based paradigm for research or rehabilitation of people with blindness or profound visual impairment. To overcome this barrier, I developed a novel method for training freehand drawing without any vision, guided solely by *non-visually acquired* memory: the Cognitive-Kinesthetic Drawing Training Method (C-K method). This unique method has already shown that it can enhance detailed working memory, and in particular, the generation and maintenance of robust spatial-memory representations (Likova, 2012a,b; 2013). Such spatial representations are crucial for replacing the ‘eye-hand’ coordination (that is lost under blindness) by *non-visual* ‘memory-hand’ coordination (Fig. 2). Moreover, the effectiveness of the C-K training method led to further conceptual advances; in particular, the realization that the single-but multicomponent drawing task-has the potential to fulfill the demand for an effective tool to wide-spectrum blindness rehabilitation.

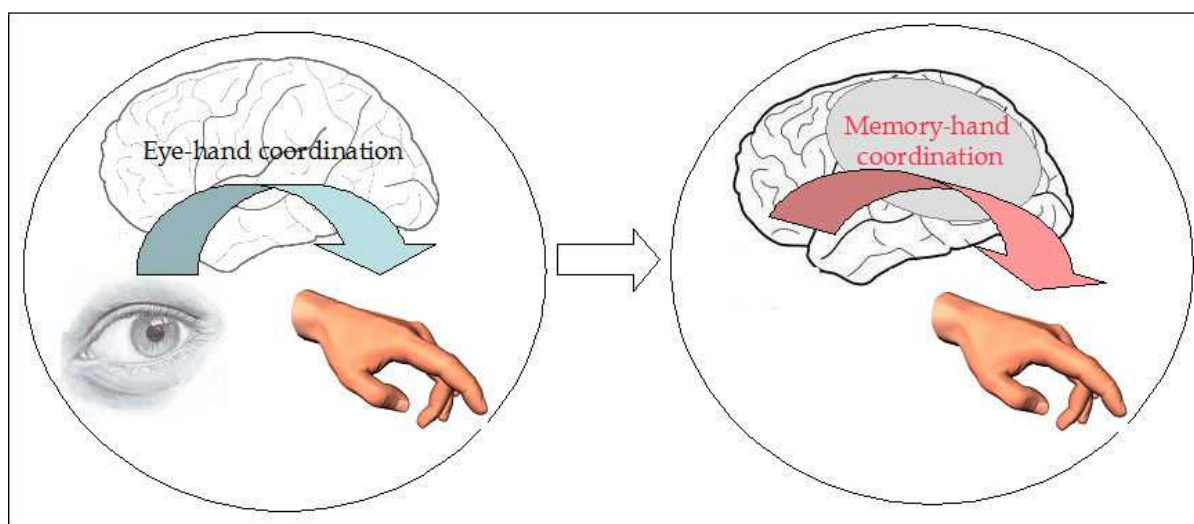


Figure 2. Illustration of the novel conceptualization that the ‘eye-hand’ coordination lost under blindness has to be replaced by *non-visual* ‘memory-hand’ coordination, which requires the development of capability for precise (nonvisual) memory representations in order to guide spatiomotor coordination without vision. This conceptualization underlies the Cognitive-Kinesthetic Drawing Training Method and its rehabilitation potential.

The Cognitive-Kinesthetic training has proved to be highly effective even in the training of people who are totally blind. In only a week of 1-1.5 hour/day training sessions, the blind participants learn to draw complex structures, such as faces and objects (see Fig. 3 B).

To provide for pre/post training comparisons of brain activation, an innovative fMRI platform was developed, including an MRI-compatible multisensory drawing tablet, with a stylus incorporating a fiber-optic motion-capture system to record the drawing movements to ~1 mm accuracy. The C-K Method, with the technological advances of the innovative experimental

platform, allowed us to run the first neuroimaging studies on *learning* to draw and on *cross-modal memory reorganization* within the same brains.

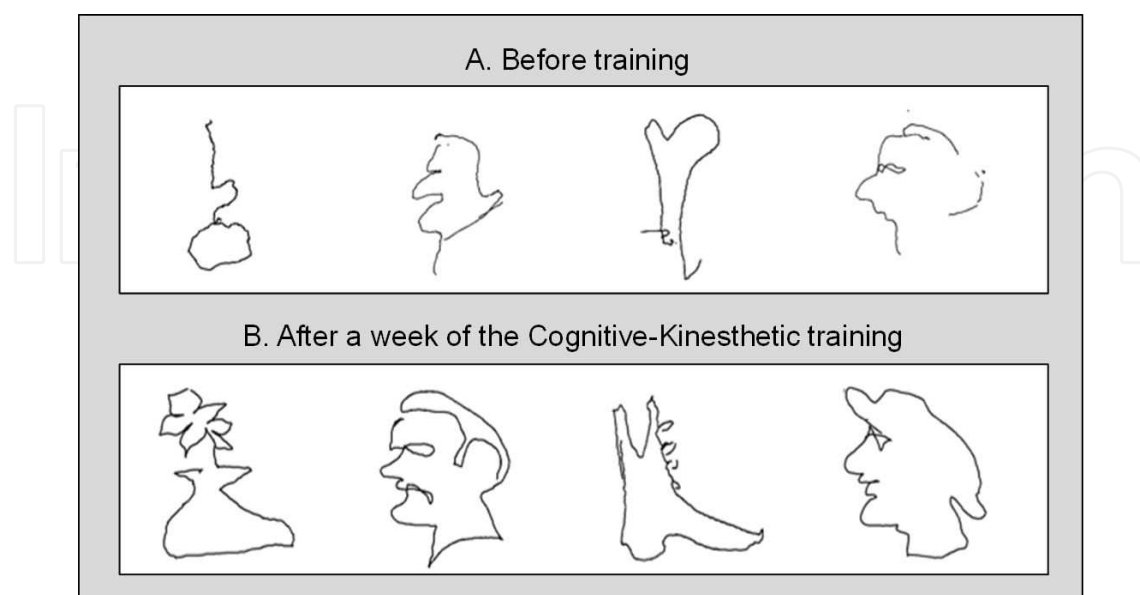


Figure 3. Examples of drawings from totally blind participants recorded by our motion-capture system in the fMRI scanner. **A.** Top row: Blind subjects' drawings before the training. **B.** Bottom row: The same faces and objects drawn by the same subjects after a week of the Cognitive-Kinesthetic training.

1.2. The working memory 'Sketchpad' puzzle

More than a century ago, Helmholtz (1871) had pointed out that artists possess not only advanced observational capabilities, but also an enhanced *memory* of the observed images. While the first part of this statement is often cited in vision science, the memory-related aspect has been widely neglected. Our recent results, however, come fully in support of Helmholtz' observation, and are consistent with the *Drawing/Memory Hypothesis* proposed above.

Freehandmemory-guided drawing, in particular, challenges the brain to provide encoding, retrieval and effective 'projection' of memory representations back onto an internal high-resolution '*projection screen*', so as to guide the spatial trajectory of the drawing-hand with the requisite precision. Drawing thus closes the full processing loop from perception through memory to precisely controlled motor action (Likova, 2012a).

The classic working memory model (Baddeley and Hitch, 1974; Baddeley, 1986, 2000, 2003) provides a framework for understanding the memory processes specific to the drawing task (Likova, 2012a, 2013). In this model, working memory (WM) is the "ability to retain information for several seconds to guide goal-directed behaviors" (Baddeley and Hitch, 1974). This influential model has provided major insights for the study of memory, and in turn, has been updated based on neuroimaging data. Recently, for example, it has been suggested that WM processes are not restricted to short-term memory but reflect activation of long-term memory

representation as well (e.g., Ranganath, 2009; Buchsbaum and D'Esposito, 2009; Ishai, 2009). Our treatment of WM is consistent with this recently expanded interpretation.

The Baddeley model consists of four major components, the one of interest here being the visuo-spatial 'sketchpad', which conveys the idea that memory is 'drawing' or generating a mental sketch of the memorized object – an internal representation that can be further spatially manipulated. Therefore, the 'sketchpad' concept provides much of the functionality of the internal 'projection screen' that introspectively seems to be needed for drawing.

However, where in the brain the WM 'sketchpad' might be implemented? The neural substrate required to serve such 'sketchpad' function has to provide a large, high-resolution topographic 'screen' or a 'map'. Although the full neural implementation of the sketchpad concept is still a puzzle, these requirements point out to the primary visual cortex, area V1, as the best candidate. A few theoretical and neurophysiological studies in non-human primates (e.g., Mumford, 1992; Super et al., 2001a,b; Lee and Mumford, 2003; Super, 2003) had already suggested that V1 may provide the high-resolution visuo-spatial 'sketchpad' function, but there has been little supporting evidence in human. Traditionally, all regions of the early visual cortex have been considered predominantly bottom-up, purely sensory regions, specifically devoted to the visual modality. However, it is now known that this is not the case, as many of these regions are also subject to *top-down visual* processes such as visual imagery (Ishai and Sagi, 1995; Kastner et al. 1998; Ishai et al., 2000; Kosslyn et al., 1996, 1997, 1999; Kosslyn and Thompson 2003; Kreiman et al., 2000; Lambert et al., 2004; Mechelli et al., 2004; O'Craven and Kanwisher, 2000; Ganis et al., 2004; 2005; Amedi et al., 2005; Slotnick et al. 2005), or even short-term visual memory (e.g., William et al., 2008; Harrison and Tong, 2009). Beyond visual top-down effects, different regions of the visual cortex have also been activated cross-modally in some auditory and tactile *sensation* tasks (e.g., Sadato et al., 1996; Cohen et al., 1997; Zangaladze et al., 1999; Pascual-Leone and Hamilton, 2001; Block, N., 2003). Moreover, two recent studies have found primary visual cortex activation during verbal and episodic memory tasks (Amedi et al., 2003; Raz et al., 2005).

No previous investigation has been done, however, on the *cross-modal* involvement of these regions in *tactile memory*.

1.3. Can blind drawing help in solving the puzzle? If there is a working memory sketchpad, may it be amodal?

Recently, I hypothesized that the early visual areas, and V1, in particular, can support *modality-independent* (i.e., *amodal*) 'sketchpad' in human (Likova, 2010b; 2012a; 2013). This hypothesis, is of importance for models of memory and functional brain architecture, and was investigated under the novel, drawing-based paradigm. To critically test this amodal sketchpad hypothesis, the studies in this chapter focus on groups of participants with different forms of total visual deprivation (of ocular origin) – congenitally blind, late-onset blind and blindfolded. Their brain reorganization is studied by fMRI run before and after the C-K training. To our knowledge, there are no previous studies on the *learning* to draw in the blind and on the *corresponding dynamic phases* of adult brain reorganization.

The data showed strong, well-structured V1 activation in drawing guided by *tactilely-acquired memory*. These results are consistent with V1 implementing the WM sketchpad concept, however, as no vision was involved, they support a reconceptualization of the sketchpad from being 'visuo-spatial' to being '*amodal-spatial*'.

2. General methods

2.1. Innovative experimental platform

As there are no preceding neuroimaging studies of such training, we had to develop a unique experimental platform integrating a number of innovations, such as (i) the *Cognitive-Kinesthetic Method*, (ii) a *multisensory MRI-Compatible Drawing Tablet* (for both tactile and visual drawing), incorporating a motion-capture stylus, (iii) a *Method for Estimating Topographic Maps in the Blind*, and (iv) the first implementation of *Probabilistic Visual Topographic Maps* in blind individuals.

2.2. Experimental design

A battery of raised-line models of faces and objects was developed as the drawing targets, and a three-task block fMRI paradigm, with task duration being 20 s, interleaved with a 20 s null intervals (Fig. 4 A) was implemented. The tasks were as follows: *Explore/Memorize*, *E/M*—perceptual exploration and memorization of the raised-line model to be drawn; *Memory-Draw*, *MD*—a memory-guided non-visual drawing task; and *Scribble*, *S*—a motor-control and 'negative' memory-control task. Importantly, as opposed to the traditional null intervals, the subjects not only rested motionless during these intervals (*NullInterval*, *NI*) but were instructed (and practiced) to clear any memory or image structures from awareness ('mind blank'). The start of each task or null interval was prompted by an auditory cue. The whole three-task sequence with interleaved null intervals (*NI*, *E/M*, *NI*, *MD*, *NI*, *S*, *NI*) was repeated 12 times in each 1-hour fMRI session, using a new drawing model for each repeat.

In *Explore/Memorize*, using the left hand only, the subjects had to explore tactually a raised-line drawing model on the left slot of the drawing tablet continuously for 20 s, and to develop a full memory representation of the image in preparation for the *MemoryDraw* task. Then the model was removed and the subjects rested motionless for 20 s with no image in mind (*NullInterval*). In the following *MemoryDraw* phase, the fiber-optic stylus was used to draw the image (from tactile memory) on the right slot of the tablet using the right hand only. In the control task *Scribble*, the subjects moved the stylus with the right hand in a random trajectory matching the extent and rate of the drawing movements but with 'mind-blank'.

This design ensures that the drawing was performed exclusively by the right hand while keeping the left hand motionless during *MemoryDraw*; moreover, because the virtual stylus was used to draw on the plastic surface of the tablet slot, there was no tactually perceivable trace and no possibility for tactile tracing with the left hand during drawing in the scanner. The lack of left hand movement during drawing was also confirmed by the lack of BOLD

activation in the left hand motor area. These restrictions thus enforce the encoding of robust *memory* representations as the only option left to guide the drawing trajectory.

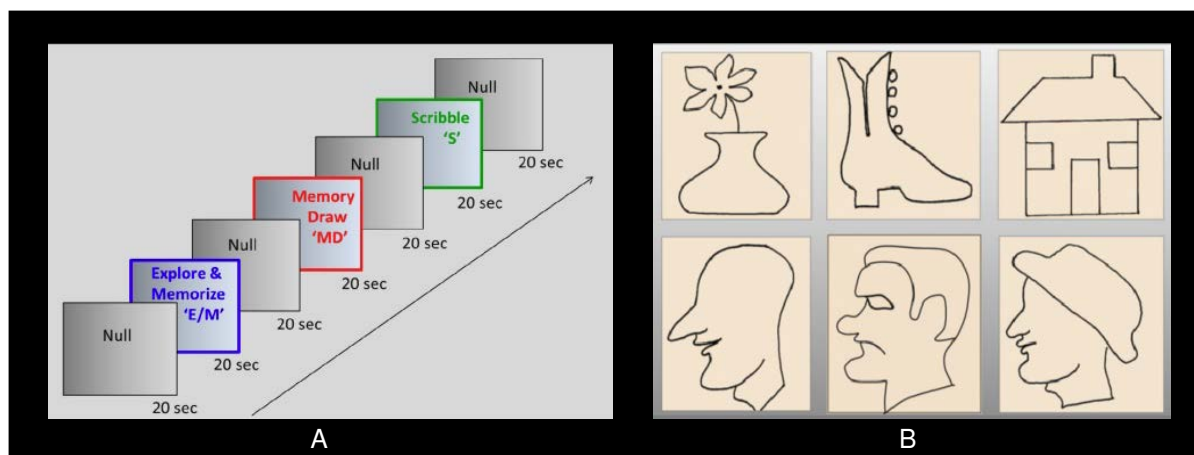


Figure 4. Experimental design.(A) Drawing was investigated in a three-phase paradigm consisting of a (tactile) memory-guided drawing task, abbreviated as “MemoryDraw” (MD), plus two control tasks: motor and “negative” memory control “Scribble” (S), and a task of perceptual exploration and memorization of the model to be drawn “Explore/ Memorize” (E/M). Each task duration was 20 s, with 20 s null intervals interposed between tasks. The whole 140 s trial sequence was repeated 12 times in each of the 1-hour pre-and post-training fMRI sessions using a new image for each repeat. (B) Raised-line drawings of realistic faces and objects were presented as templates to be explored by the subject using left hand in the E/M phase. Two repetitions of each stimulus were run. The quality of the reproductions was assessed by a masked rating procedure, based on recognition and similarity to the raised-line models. Examples of drawing reproductions are shown in Figs. 3 and 6 B.

2.3. Tactile stimulus presentation and hand-movement control

A custom-built, multisensory MRI-compatible drawing system. To run drawing studies within the scanner is not a conventional protocol, so a lot of technological challenges had to be overcome. Therefore, we have developed a special-purpose drawing system (Fig. 5) that (i) is MRI-compatible, (ii) is ergonomically adaptable to the small space available inside the scanner bore, (iii) importantly, has a multisensory design that allows fMRI investigations of *tactually*-guided drawing by making it possible for multiple tactile models to be presented sequentially in the scanner without the need of any operator assistance, (iv) captures the hand/ stylus movement and records the drawing trajectory with high precision, and (v) when appropriate, such as in *visual* drawing, can provide real-time visual feedback of the drawn trajectory. This system incorporates a dual-slot drawing tablet that is height/distance adjustable for the subject’s arm length and a specially-adapted version of a fiber-optic motion-capture system for on-line recording of the drawing movements. Also, it allows relevant behavioral events to be recorded and correlated the brain activation for full off-line analysis.

Auditory cue presentation. The auditory stimuli were presented through Resonance Technologies Serene Sound earphones (Resonance Technologies, Salem, MA). To reduce scanner noise, this equipment employs external ear protectors with perforated earplugs that conduct the auditory cues directly into the auditory passage while blocking much of the scanner noise.



Figure 5. A subject on the scanner bed operating our novel multimodal MRI-compatible drawing device. The plexiglass gantry supports a drawing tablet while a fiber-optic drawing stylus captures and records the drawing movements with high precision. This motion-capture information synchronized with the fMRI signal allows the effect of behavioral events during drawing to be correlated with brain activation.

2.4. Computerized Recognizability Index (CR Index)

The Cognitive-Kinesthetic training results in dramatic drawing improvements (e.g., Fig. 3 B, bottom row; Fig. 7 B) in all forms of visual deprivation. To be able to quantify that improvement we developed the CR Index, which is based on an optimized spatial-correlation fit across the full spectrum of affine transformations (translation, rotation, scaling and shear). It is applied to each recorded drawing with respect to the set of raised-line model images to be drawn, cumulating the proportion of the image that contains matching contours (with sparse-matrix correction for incomplete drawings). The total CR Index of the drawings can then be compared before and after training, to quantify the improvement in the quality of the drawing skill that has been achieved. The CR Index was validated by a masked rating procedure for the quality of the drawing reproductions based on perceptual similarity to the raised-line models.

2.5. MRI data collection, analysis, and visualization

FMRI acquisition

MR data were collected on a Siemens Trio 3T scanner equipped with 8-channel EXCITE capability, a visual stimulus presentation system and response buttons. A high-resolution anatomical (T1-weighted) volume scan of the entire brain was obtained for each observer ($0.8 \times 0.8 \times 0.8$ mm voxels). The fMRI blood-oxygenation-level-dependent (BOLD) responses were collected with EPI acquisition from the whole head coil. There were 34 axial slices at 2 s TR, with TE of 28 ms and flip angle of 80° , providing $3.0 \times 3.0 \times 3.5$ mm voxels throughout the brain. The functional activations were processed for slice-time correction and motion correction. An anatomical segmentation algorithm (mrGray, part of the VISTA software package

specified below) was applied to the T1 scan, ensuring localization of the signal within the cortical gray matter close to the activated neurons.

FMRI time course analyses

The analysis software was Stanford Vision and Imaging Science and Technology (VISTA, Stanford University) software. The data were analyzed to estimate the effective neural activation amplitudes (e.g., Friston et al., 1994) for each task across the 12 repeats of the 3-task sequence in the one-hour scan by the following procedure. A General Linear Model (GLM) consisting of a (3+1)-parameter boxcar neural activation model convolved with an estimated hemodynamic response function (HRF) was fitted to the BOLD responses for each 3-task sequence, combined with a 1-parameter boxcar model of the 8 auditory cue presentations and an additive 4th-order polynomial to capture low-frequency drift in the BOLD signal. (The HRF was determined once per session by optimizing it to a subset of gray matter voxels identified as those whose average modulation (as a result of the task alternation sequence across the E/M, MD and S tasks) exceeded the statistical level of $z=3$ in each voxel ($p < 0.001$).) Thus, the parameters of the activation model consisted of the boxcar activation amplitudes for the three task periods, relative to the remainder of the 140 s scan duration.

Voxel-wise parametric maps

For each task, statistical parametric maps were generated, based on the estimated activation amplitudes from the above GLM in each voxel. As is standard for GLM, the boxcar neural activation model for each 20 s task period was contrasted with the entire remainder of the 140 s scan duration. All three task-models were optimized jointly to the detrended BOLD waveform. These maps could be viewed in the 3D volume or projected onto 3D views of the inflated cortex or on flatmaps of cortical regions of particular interest.

ROI activation analysis

The effective neural activation amplitudes (bar graphs) for each condition in each region of interest (ROI) were estimated by the same GLM procedure but now applied to the average signal across all voxels within the ROI. This procedure also provided high-quality time courses for evaluation of the response dynamics and its comparison across tasks and stages of training.

The confidence intervals and error bars were defined by the amplitude variability of the 12 repeats of the 3-task sequence in each one-hour scan. The dashed lines represent the 99% “zero” confidence interval within which the activation amplitudes are not significantly different from zero (at $p < 0.05$, corrected for multiple applications within each figure). The error bars are “difference” confidence intervals designed to illustrate the t-test for the significance of differences between any two activation levels.

In the text, the significance of all ROI-comparisons are specified by the t-test using a statistical criterion threshold of $p < 0.05$ corrected for multiple comparisons.

Retinotopic maps and motion localizer in the sighted

There is a topographic ‘projection’ or ‘mapping’ of the visual input information to the retinal surface, and from the retinal surface to corresponding points on the surface of the visual cortex

of the brain, thus forming what are known as retinotopic cortical maps. The boundaries of the retinotopic projection areas in the occipital cortex V1, V2d, V2v, V3d and V3v were established as described in Sereno et al. (1995); Tootell et al. (1996) and Engel, Glover and Wandell (1997).

Retinotopic projection areas V3A, V3B, hV4 and V7 were specified in accordance with Tyler et al. (2005) and Schira et al (2010). The hMT+motion complex was identified using the standard stimuli of an expanding and contracting motion vector field of low-contrast random dots, alternating with a field of static dots as previously implemented in Likova and Tyler, 2007.

Topographic maps in the blind

On the one hand, no informed analysis of the visual cortex could be done without knowledge of its retinotopic and functional organization; on the other hand, no retinotopic mapping is possible in the blind, so it is a challenge to localize any specific visual area. To resolve this issue and determine the borders of different 'visual' areas in the blind participants, we combined three different approaches. First, we used an innovative 14-step procedure (Likova, 2010a) to warp the brains of sighted and blind subjects to the same MNI brain coordinates. Second, for the primary visual cortex in particular, the location of the V1 ROI was confirmed by its intersection with its anatomical marker (i.e., the calcarine sulcus). Additionally, we also compared the result with Freesurfer probability maps, such as that of V1, which aligned sufficiently accurately (within 87% overlap of the voxels) with those from the other methods.

3. Where may the amodal 'sketchpad' for spatial memory be implemented?

Blindfolded studies and reconceptualization of the WM sketchpad

3.1. Beyond the traditional view of modality-specific cortices specialized for sensory processing

According to the traditional view of brain architecture, the so-called 'sensory' cortical areas are modality-specific and specialized for sensory processing only. Although this view is still prevalent in textbooks, increasing evidence suggests that the function of these areas is not restricted to sensory processing, but (as discussed in the Introduction) is also subject to a number of top-down processes such as modality-specific imagery; furthermore, many of these 'sensory' areas are activated in cross-modal tasks. A body of experimental data shows that in blind individuals, brain areas commonly associated with the processing of visual information can be recruited in tasks such as Braille reading, naming, tactile object perception or tactile motion (e.g., Sadato et al., 1996; Uhl et al., 1991, 1993; Cohen et al., 1997; DeVolder et al., 1997; Buechel et al., 1998; Hamilton et al., 2000; Burton et al., 2002, 2003, 2004; Gizewski et al., 2003; Theoret et al., 2004; Merabet et al., 2005; Merabet, 2008; Pascual-Leone et al., 2005; Amedi et al., 2003, 2004, 2008; Goyal et al., 2006; Borowsky et al., 2007; Ptito et al., 2008; Deibert et al., 1999; Pietrini et al., 2004; Hagen et al., 2002; Matteau et al., 2010) and during drawing in blind individuals (Amedi et al., 2008; Likova, 2010a,b; 2012a,b). Transcranial magnetic stimulation (TMS) of the visual cortex has been found to disrupt Braille reading or verb-generation in the blind (Cohen et al., 1997; Hamilton & Pascual-Leone, 1998; Amedi et al., 2004).

This section probes deeper levels of cross-modal interactions that are of importance for advanced models of functional architecture of the brain.

3.2. Subjects and methods

A group of six subjects with normal vision were blindfolded throughout the experimental procedures. The subjects ranged in age from 25 to 59 and were 4 females and 2 males, right-handed with no formal training in visual art and with no cognitive disorders. All subjects gave informed consent for the experimental protocol approved by the local research ethics committee. Each subject underwent the Cognitive-Kinesthetic training in blindfolded drawing (1 to 1.5 hour/day for a week). The general methods were as described in the General Methods section above (Section 2).

3.3. Results

Functional MRI, run before and after blindfolded Cognitive-Kinesthetic training, revealed strong activation in the primary visual cortex (area V1) for the tactile memory-guided drawing task (*MemoryDraw*, Fig. 6 A), while, in contrast, no significant V1 activation was recorded for the non-memory drawing task (*Scribble*, Fig. 6 B).

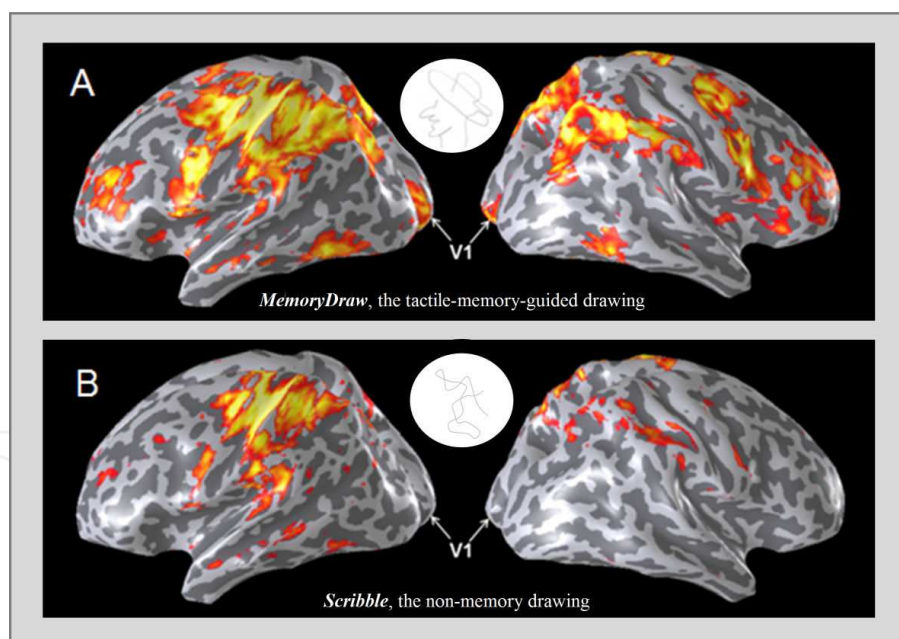


Figure 6. Comparison of the activation networks in two types of drawing: (A) *MemoryDraw* (tactile-memory-guided drawing): Detailed recall from memory of the specific raised-line model explored 20 s earlier (during the *Explore/Memorize* phase) is critical for the successful guidance of the precise movements of the drawing hand. **(B) *Scribble*** (non-memory, 'mindless' drawing) was used as a motor control and 'negative' memory control condition. Note the dramatic difference between these two types of drawing activity **(A vs B)**: The memory-guided drawing (A) activates an expanded bilateral network; remarkably, there is a well-localized activation in the primary visual cortex, V1. In contrast, the non-memory drawing (B) predominantly activates the left hemisphere within the right hand region; most importantly, it does not activate the visual cortex at all.

Remarkably, without any visual involvement at any stage of the image exploration, learning or drawing processes, the Cognitive-Kinesthetic training enabled the blindfolded participants to memorize and draw well complex images in only 20 s, guided solely by memory acquired during haptic exploration! Note how well coordinated and recognizable these drawings are (see Fig. 7 B).

3.3.1. Retinotopic maps for memory-guided drawing in the blindfolded

The best way to look in detail at the puzzling activation in the visual cortex is to present the data in a flatmap format with the retinotopic maps delineated (Fig. 7 A).

MemoryDraw in the blindfolded produced an unexpected, unique occipital response. Despite the lack of any visual (or even tactile) stimulation during drawing, there was extensive activation of the primary retinotopic area, V1, while the rest of the visual hierarchy showed a pronounced suppression of the BOLD response relative to the baseline level.

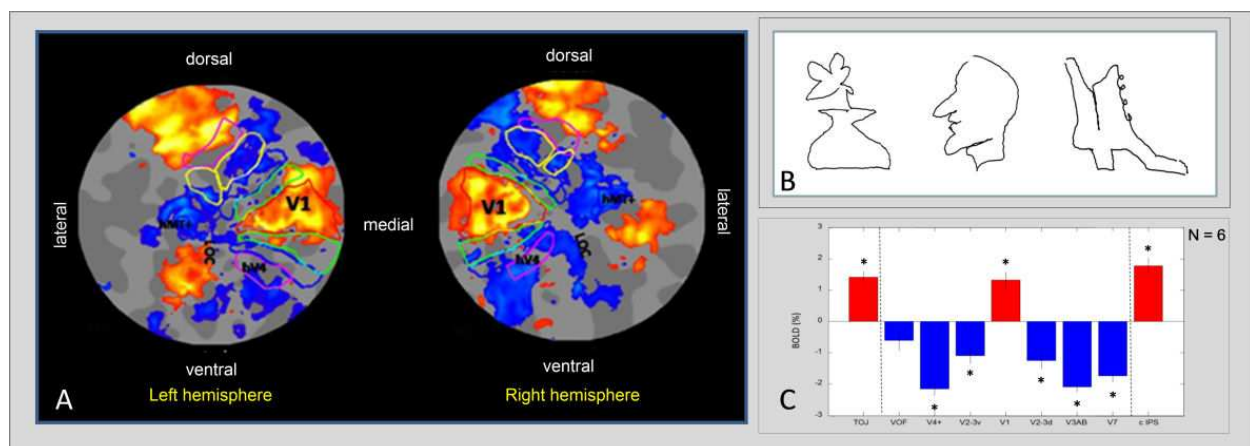


Figure 7. A. Flat maps for *MemoryDraw*, centered on the occipital pole. ROIs for the retinotopic hierarchy are indicated by colored outlines. The post-training *MemoryDraw* map shows a unique 'triad' of three activation regions (orange-yellow coloration). Note in particular that the (non-visually-stimulated) primary visual cortex, V1, forms an isolated 'island' of activation surrounded by a 'sea' of suppression in the adjacent retinotopic areas. The other two activated regions seen on the flat map are the caudal intraparietal sulcus (cIPS) dorsally and an additional locus at the temporo-occipital border (LOtv). **B.** Post-training examples of blindfolded drawings demonstrating the level of detail the participants became able to complete in 20 s in the MRI scanner. Note that no vision was involved at any stage of the learning or drawing process! Recorded by the virtual stylus in the scanner are drawings of a vase with a flower, a face profile and a boot, each of which is easy to recognize (the corresponding raised-line models are the 1st and the 2nd on the top row, and the 1st on the bottom row in Fig. 4 B). **C.** Average response amplitude with standard errors for blindfolded memory-guided drawing in a group of 6 subjects, showing positive signal in the triad of areas – primary visual area V1, cIPS and LOtv; these three 'islands' of positive activation are separated by strong deactivation throughout both the ventral and the dorsal extrastriate areas. Error bars represent 1 standard error of the means. Asterisks indicate activations significant at $p < 0.01$. [After Likova, 2013]

The other two activated regions seen on the flat map are the caudal intraparietal sulcus (cIPS) and an additional locus at the temporo-occipital border in LOtv. The latter site, although in close proximity and often partially overlapping with the ventro-anterior visual LOC, is shifted anteriorly towards the temporal lobe. These two non-occipital loci have been previously

reported to be involved in tactile perception (Prather & Sathian, 2002; Amedi et al., 2001, 2002; James et al., 2002; Stoesz et al., 2003; Pietrini et al., 2004; Reed et al., 2004; Merabet et al., 2005; Van Boven et al., 2005; Weisser et al., 2005; Zhang et al., 2005).

3.4. Discussion

3.4.1. Reconceptualization of the memory sketchpad

Tactile memory processing in the primary visual cortex?

Employing a pioneering memory paradigm based on non-visual drawing demonstrated that V1 can be strongly activated in a non-visual working memory task in the blindfolded. The V1 activation we have found is remarkable in many respects: i) the retinotopic analysis shows that it is rather well localized within V1, ceasing rapidly at a specific eccentricity; ii) surprisingly, this eccentricity is about 10 deg (in terms of retinotopic mapping), which corresponds approximately to the physical angular projection of the raised-line models at the subject's face; and iii) most remarkably – there is a massive *deactivation* surrounding V1, thus effectively 'cutting-off' any signal propagation from or through the extrastriate cortex. These results have major implications as discussed below.

To our knowledge, this study is the first evidence of involvement of the primary visual cortex in a *tactile-memory* task. We also know no other neuroimaging study either on *learning to draw*, or on the effect of *training* on *tactile-memory* under visual deprivation. Note, that in *MemoryDraw*, the tactile model under the fingers of the left hand is memorized and then removed, so the drawing movements of the right hand are guided solely by that tactilely-acquired memory with no concurrent tactile input from the drawn template.

Amodal spatial memory vs visual imagery interpretations: Distinct activity patterns

To put the present results in a neurobiological perspective, we need a relevant concept about memory encoding and retrieval for the kinds of detailed spatial images used in the drawing task. The visuo-spatial sketchpad component of the classic WM model (Baddeley and Hitch, 1974; Baddeley, 1986, 2000, 2003) conveys the idea that working memory incorporates a detailed mental sketch of the retrieved object that can be further spatially manipulated (Fig. 8). This model provided us with a basis to generating specific hypothesis about the activation components in the drawing task.

There is a current tendency to attribute any new result that does not fit into the classical feedforward model of brain architecture, to a narrow number of top-down processes and – most recently – to visual imagery. However, the pattern of strong V1 activation surrounded by deactivation in the higher extrastriate areas (Fig. 7 A, B) that we found, is distinct, essentially *the inverse* of the known visual imagery pattern. In direct contrast to our results, the known neural substrate for visual imagery has been found to exhibit a gradient of activation *decreasing* from the higher visual areas downwards to V1, where the activation is much weaker or even lacking entirely. Although a weak level of V1 activation has sometimes been reported during imagery (Kosslyn et al., 1993; Le Bihan et al., 1993; Sabbah et al., 1995; Chen et al., 1998; Thompson et al., 2001; Ishai, Haxby, and Ungerleider, 2002; Lambert, Sampaio, Scheiber,

and Mauss, 2002; Ganis et al., 2004), a larger number of other studies did not find any V1 activation at all (Goldenberg et al., 1991; Charlot et al., 1992; D'Esposito et al., 1997; Mazard et al., 2004; Mellet et al., 1995, 1998a, 1998b; Ishai, et al., 2000; Knauff et al., 2000; Trojano et al., 2000; Wheeler et al., 2000; Formisano et al., 2002; Sack et al., 2002; Kaas et al., 2010). This decreasing gradient of activation implies that the imagery signal propagates from higher cortical regions in a top-down manner through the visual hierarchy towards V1.

In summary, while substantial imagery activation in the higher occipital areas has been consistently found across studies, this has not been the case with V1; furthermore, imagery does not produce any significant negative signal in the occipital cortex (Ganis et al., 2004; also see that paper for an overview of the imagery areas throughout the brain).

Our approach allows for testing between the following hypotheses: **Hypothesis I:** If the memory-based activation was due to the visual imagery mechanism, the predicted response-profile in the visual cortex would have had the top-down 'imagery signature' of activation significantly *decreasing* from the higher extrastriate areas toward V1 (as reviewed above). **Hypothesis II:** If V1 was employed as an (amodal) WM sketchpad independently from the visual imagery process, it would be activated by a separate pathway *external* to the visual hierarchy, together with activation of WM-related sites beyond the occipital lobe.

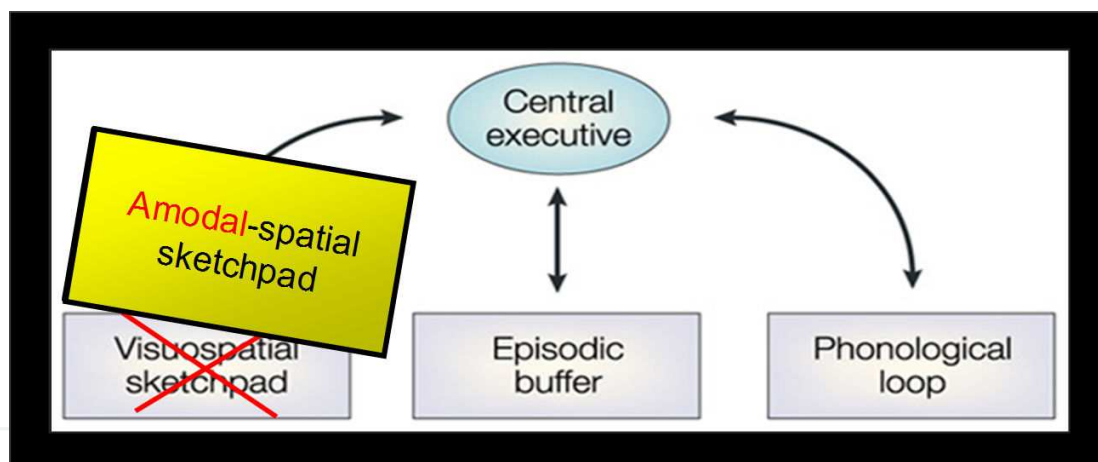


Figure 8. Our proposal for a re-conceptualization of the visuo-spatial sketchpad as an amodal-spatial sketchpad. Modified schematic of the main modules of Baddeley's classic model of working memory including the visuo-spatial sketchpad [after Baddeley, 2003], where the added "Amodal Spatial Sketchpad" block depicts my re-conceptualization of the visuo-spatial sketchpad as being accessible to any sensory modality. [From Likova, 2012a]

The imagery hypothesis is not supported by the data because we find the pattern of response for the *MemoryDraw* task to be just the *opposite* to the top-down response observed in imagery, i.e., our data show strong activation in the iconic visual area V1, but *no* activation in the higher extrastriate areas. Moreover, these extrastriate areas were massively *deactivated*. This deactivation is remarkable, as it means that it is implausible the signal in V1 to be 'delivered' top-down through the visual hierarchy (because this hierarchy is suppressed, i.e., V1 is 'cut-off' from the higher cortical regions that could generate and propagate imagery signals). Thus, this unique activation/deactivation pattern is incompatible with the main principle of visual imagery as a

top-down process propagating downward through the visual pathway to V1. Instead, this pattern seems to be consistent with my Hypothesis II, that V1 is operating as a working memory component, such as the hypothetical spatial memory buffer/sketchpad of the composite working memory model, however in an amodal form.

Re-conceptualization of the visuo-spatial sketchpad as an amodal-spatial sketchpad

The overall pattern of our results suggests that, even under complete visual deprivation, the high-resolution, topographically organized early visual cortex can operate as the conscious 'projection screen' for working memory, even when evoked by non-visual tasks. The spatiotopic organization and inherently parallel processing of the largest cortical map, V1, and most importantly, the small receptive fields providing the high-spatial resolution of the V1 map (e.g., Hubel & Wiesel, 1968; van Essen & Maunsell, 1980; van Essen et al., 1984; Mumford, 1992), makes it a very attractive candidate for precise spatial and spatial-memory processing, in particular, once it is freed up from visual processing, as in blindfolding or blindness (see sections 4 & 5). The data described in this chapter provide a direct evidence supporting such an implementation of a spatial sketchpad in human V1. Most notably, our results make another step forward implying for a first time a *generalization* of the 'visuo-spatial' sketchpad concept beyond the visual modality, into a modality-independent or *amodal* spatial sketchpad.

It is important to note, however, that such an interpretation does not mean that V1 is employed for long-term storage of the memory trace, but merely for its operational activation in working memory to meet the task demands. Moreover, in contrast to the usual format of a baseline condition, we instructed and practiced the subjects to eliminate any rehearsal of either the just-explored templates or of any other memory images for the full 20 s duration of each null interval, which was also too long to account for the known retention time of any visual or iconic image of the memory trace, which is of the order of a second or less (Sperling, 1963; Di Lollo, 1980; Loftus et al., 1992). Since the drawings were not experienced as spatial images during the null interval, they were evidently held in some other, non-conscious storage location until it was needed for the subsequent drawing task.

3.4.2. Why is V1 surrounded by extrastriate deactivation?

The current analysis was not designed to directly answer the question of the role of the extrastriate suppression (Fig. 7 A, C), but it allows several general considerations to be drawn. For instance, our results demonstrate a unique activation/deactivation pattern in the occipital cortex produced without either visual or tactile sensory stimulation. This fact eliminates potential sensory mechanisms, such as a direct drive of the primary visual cortex through direct connections from the primary somatosensory cortex.

Why is this suppression needed? One possible explanation is the existence of a mechanism homologous to what we have found previously in a figure/ground paradigm: a topographically precise, suppressive top-down feedback to the ground projection in V1 (Likova and Tyler, 2008). We suggested that such suppression of the less relevant information (that of the ground) makes strong computational sense. Such an interpretation is also consistent with theoretical

predictions in Tsotsos et al. (1995). It seems logical that a similar principle of active suppression of task-irrelevant regions (i.e., of the extrastriate visual pathways) may operate in our non-visual memory task but on a much larger scale, i.e., on a cross-modal instead of intramodal scale. This principle allows task-irrelevant or conflicting pathways to be excluded or 'cut-off' from functional involvement. Thus, the extrastriate suppression surrounding V1 prevents any potential propagation of the entirely non-visual V1 signal through the visual hierarchy pathway, which would be an inappropriate pathway in this case.

4. How does a learning-based reorganization develop? *Insights from a congenitally blind case*

4.1. Introduction

A congenitally blind novice with no experience with drawing or writing provides an ideal paradigm for investigating the earliest stages of V1 reorganization, and also provides for a critical probe of our amodal sketchpad idea, because congenital blindness eliminates the possibility of any visual mechanisms influencing the neural processing. Specifically, it abolishes not only the bottom-up visual input but also any potential top-down visual processing, such as visual imagery (since congenital blindness eliminates any visual experience on which to base such processing). We were lucky to find such an absolute novice. This individual was well-adapted to operating in the spatial world, including longstanding familiarity with complex tactile manipulations and Braille reading, but had no drawing, writing or even pen-holding experience. Functional MRI was run before and after a week of Cognitive-Kinesthetic training in order to test our hypothesis that V1 uses an amodal spatial representation in its operation as the putative memory buffer, and to investigate the temporal evolution of brain reorganization as a function of learning to draw.

4.2. Methods

The methods were as described in the General Methods section above (Section 2).

4.2.1. Subject and training

The congenitally blind subject was a 61-year-old right-handed female, totally blind with no light perception, who lost her vision shortly after birth as a result of rubella (German measles) in her expectant mother, severely and permanently damaging the fetal optic nerves, and also degrading her hearing to some degree. She had not been previously studied by fMRI or behavioral methods of any kind. She is a sophisticated intellect and a fluent Braille reader, with a graduate education and lifetime employment including the professional use of a computer keyboard, and was highly motivated to participate in the study. Nevertheless, despite her Braille fluency, the subject had no experience with writing or drawing, so her training to draw had to start with the basics, such as the proper holding of the pen and key spatial concepts of the representation of 3D structure on a 2D plane. She had relied heavily on active tactile

exploration for her whole life, so it was quite surprising that she did not have clear idea of elementary geometric concepts such as a straight line vs a curve, right angles, etc.; she also was unable to reproduce any simple geometric figure or object by drawing. These issues were manifested at all levels of the experimental process – the tactile recognition and memorization phase, the memory recall in drawing, the understanding of spatial relationships, and even the kinesthetic feedback and self-evaluation of her own performance. For example, she could think she had just drawn a straight line when she had actually drawn an almost-closed curve, and so on.

It became clear, however, that these ‘negatives’ could be turned into significant ‘positives’ that would allow better tracking of the full evolution of the process of learning to draw. Another advantage was the fact that this subject was an intelligent adult, able both to readily follow instructions and to express back her introspections.

The novel Cognitive-Kinesthetic technique allowed our subject to learn to draw freehand, i.e., without using any tactile feedback from the non-drawing (left) hand. As specified in 3.4.1., by eliminating the tactile feedback during drawing, this approach enforces the use of memory representations for guiding the drawing trajectory.

The training procedure was able to inspire and motivate this blind subject to acquire the exciting drawing skill. After only a week, she significantly advanced relative to her starting level, although her capability was still not satisfactory to her. Two months later she came back for two ‘refresher’ training sessions which she felt brought her up to an adequate skill level. To study the dynamics of the learning process, we ran fMRI before training, as well as after a prolonged consolidation period.

4.3. Results

4.3.1. Comparative pre/post-training analysis: Training-induced memory specialization in V1

The focus of the analysis presented here is the occipital region along the calcarine sulcus corresponding to the location of the primary visual cortex, area V1. Comparison of the voxelwise parametric maps in the primary visual cortex during the *MemoryDraw* task reveals dramatic enhancement of the activation (orange coloration) in V1 (green outline) from negligible patchy activation before training (Fig. 9 A) to a massive task-specific activation after training (Fig. 9 B). Remarkably, the extension of post-training activation in V1 approximately corresponds to the spatial extent of that in the blindfolded (normally-sighted) subjects in Section 3.

Lack of task-specificity before training, but development of MemoryDraw dominance after training

Bar-graphs for the estimated activation in V1 in each hemisphere *before* training (Fig. 9 C) indicate a lack of task specificity, i.e., similar activation levels for the *MemoryDraw* (MD, red) and both control tasks (*Explore/Memorize*, E/M and *Scribble*, S) in the left hemisphere, with negligible responses to E/M and MD in the right hemisphere.

In contrast, *after* training (Fig. 9 D), the MD response (red bars) dominates in both left and right V1. As indicated by the confidence intervals, the following relationships are statistically significant post-training ($p < 0.01$): MD > E/M and MD > S in both hemispheres, and E/M > S in the left hemisphere. Thus, after training, MD is the task that most powerfully activates V1 bilaterally, showing highly significant % BOLD responses at a low noise level; the E/M task gives much weaker, left-dominant responses; while the motor-control scribbling task, S (which lacks any memory component), is suppressed even in the left hemisphere.

Pre/post comparison of the pattern of response in V1 across tasks shows significant reorganization of this response pattern as a result of training

Pre/post comparison of the pattern of V1 response across three tasks after training (Fig. 9 D) to that before training (Fig. 9 C) shows the following statistically significant ($p < 0.01$) relationships: $E/M_{\text{post}} \equiv E/M_{\text{pre}}$, $DM_{\text{post}} > DM_{\text{pre}}$ and $S_{\text{post}} < S_{\text{pre}}$ in both the left and the right hemispheres. This analysis implies a significant reorganization in the V1 response pattern as a result of training. Importantly, the V1 response in the memory-guided drawing task (MD) was substantially increased, while the response of the non-memory motor-control task (S) became insignificant. Note that, in contrast, no such increase was present in the area of the left motor cortex (controlling the drawing right hand), which even showed a reduction in response after training, as may be expected when a motor task becomes familiar (e.g., Jenkins et al., 1994). The E/M condition, which used the left hand (controlled by contralateral right motor cortex), developed the expected suppression in the ipsilateral (unused) cortex after training, manifesting the known cross-hemispheric competition in motor cortices (e.g., Nowak et al., 2009).

Bar-graphs in Fig. 9 show the estimated average activation in each hemisphere (left – LH, right – RH) for E/M (blue), MD (red), non-memory drawing S (green). The dashed lines indicate 99% confidence interval for the significance of the activation relative to zero. Error bars represent the 99% confidence intervals for assessing significant differences between pairs of activation levels. Pairs of activations are significantly different if they exceed the 99% confidence intervals for both activations. Time-courses show the average time courses of BOLD activity (black lines) for the sequence of three task intervals (white bars). The four dark-grey bars indicate the 20 s rest intervals separating E/M, MD and S tasks.

Top row (A, B) in Fig. 9: No significant V1 activation *before* training (in A), but massive, spatiotopic recruitment of V1 in the *MemoryDraw* (MD) task after the Cognitive-Kinesthetic training (in B). Second row (C, D): Pre/post training comparison of response amplitudes across all three tasks reveals the development of a clear functional specialization for the MD task *after* training (in D). Third row (E, F): Response waveform analysis reveals how the immature and non-specific transient ‘bursts’ before the training (in E) are transformed into a well-developed response waveforms for the memory-drawing MD post-training (in F), but any significant response is lacking for the non-memory drawing S. Bottom row (G, H): In contrast to V1, the left motor area M1 produced well-formed responses for the two right-hand tasks (MD and S) both before (in G), and after training (in H) (but did not respond, and became significant suppressed for the left-hand task E/M).

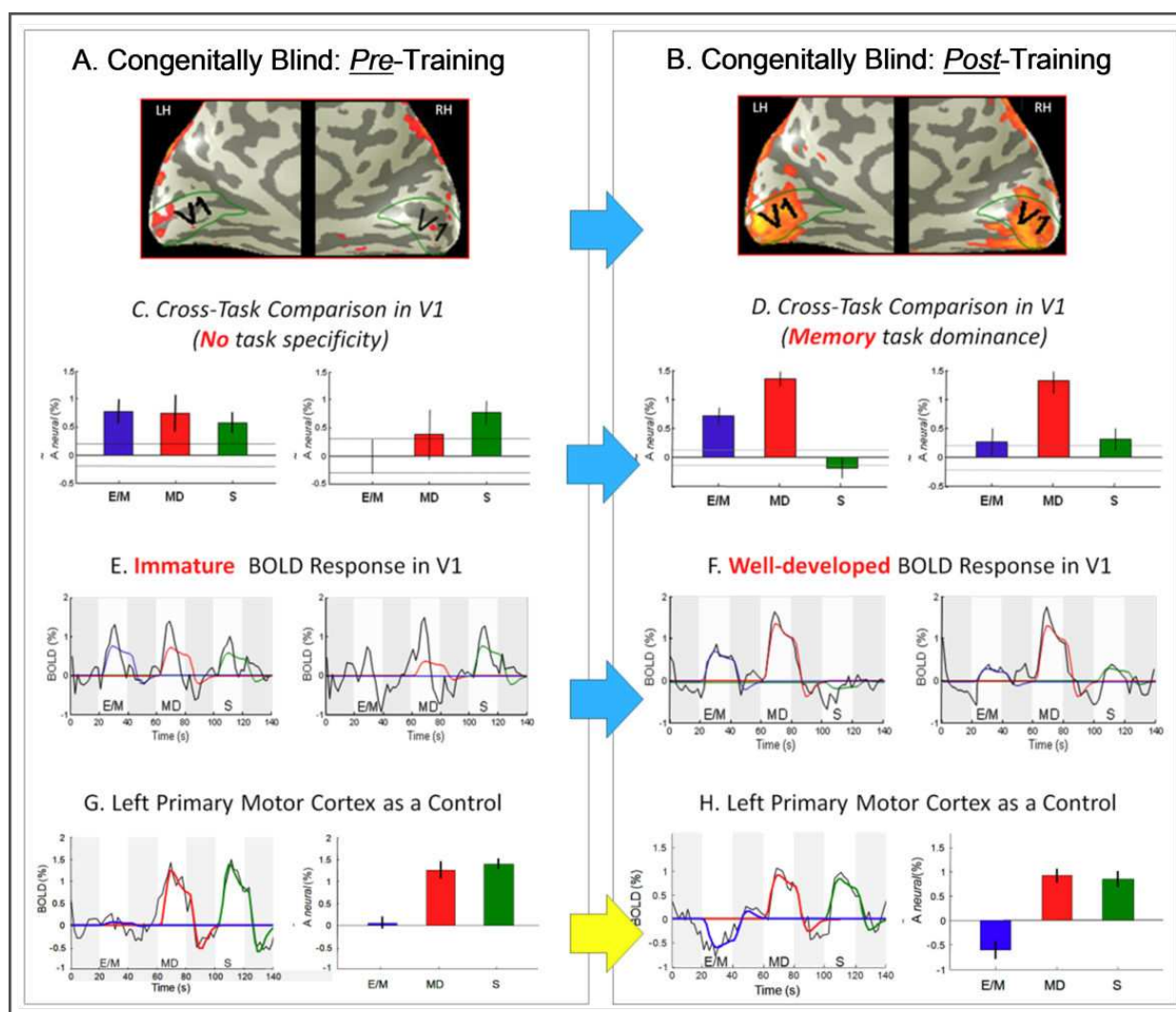


Figure 9. The first three rows present a comparative pre/post-training analysis of the primary visual cortex V1 (green outline in A and B), revealing its dramatic training-based functional reorganization, specific to the memory task MD. The fourth row is a control to show that—as opposed to the dramatic pre/post reorganization in V1—nonvisual areas, such as the area of the left primary motor cortex that controls the right (drawing) hand, does not significantly change their response characteristics.

4.3.2. Dramatic reorganization of the time course of the BOLD response in V1

Immature pre-training BOLD response waveforms in V1 (Fig. 9 E)

The advantage of training a total novice was also manifested by allowing us to capture the very early stages of functional reorganization as expressed in the changes of the time course of the BOLD responses. As seen in Fig. 9 E the average time courses for the sequence of the three task intervals (white bars) have substantial deviations of the waveforms (black lines) of the model prediction fits (color curves). The model takes into account both the task duration and the estimated HRF (see General Methods). The pre-training response waveforms are rudimentary, poorly-developed and noisy, with a prominent transient nature and early offsets

long before the end of the 20 s task periods, in spite of the continuous hand movements during the full task period (these continuous hand movements are evident from both the motion-capture records and also from the fully-fledged time course in the motor hand area, Fig. 9 G). Such early offset in V1 implies that the neural response was essentially a brief transient pulse that was immediately withdrawn, suggesting an unsuccessful attempt to activate this area. The subject self-report and drawing performance were consistent with such undeveloped utilization.

After training, the undeveloped pre-training waveforms undergo a total transformation into well-developed BOLD response waveforms (Fig. 9 F)

Notably, as a result of training, the temporal waveform of the V1 response regularized to become a good match to the linear model prediction (colored curves in Fig. 9 F), with maximum strength for the *MemoryDraw* task bilaterally. We no longer see the transient early-offset signals. Importantly, however, *Scribble*, which has no memory involvement, is lacking any significant V1 response.

4.4. Discussion

4.4.1. Support of the amodal spatial 'sketchpad' and its implementation in the primary visual cortex

This study is the first to investigate the temporal evolution of functional reorganization of V1 as a result of a non-visual memory training task. Working with an adult who was an absolute novice has the advantage that such a subject can provide full introspection and produce complex behavioral measures (as opposed to working with difficult-to-communicate-with infants). This investigation thus opens a window on research in the developmental evolution of both neural and behavioral changes, capitalizing on the effectiveness of the Cognitive-Kinesthetic training to speed up the process.

Except for her blindness and reduced hearing, this congenitally blind subject was in a very good physical and mental health, with robust BOLD responses in right-hand motor cortex, M1 (Fig. 9 G, H), so there were no reasons to expect abnormal BOLD responses in V1. Thus, a primary explanation of her V1 response patterns of undifferentiated, transient activation across all the tasks (Fig. 9 C, E) implies the lack of memory-specific role for V1 at that early stage. In particular, the poor response pattern may mean that, despite her lifetime of tactile experience including the professional use of a computer keyboard, the primary visual cortex was not able to serve as an effective 'amodal memory sketchpad' before training. The immature, early-offset waveforms suggest a rudimentary and unsuccessful attempt to activate V1, showing that, remarkably, the six decades of reliance on tactile perception in everyday tasks was evidently insufficient for the development of V1 functionality as demanded by the challenging memory-drawing task.

The rapid, learning-based recruitment of V1 in the *MemoryDraw* task after blind training (Fig. 9D, F), supports our reconceptualization of the memory 'sketchpad' as an amodal-spatial sketchpad, implemented in the primary visual cortex. Importantly, several parallel measures, such as subject's self-reports on the quality of the memory recall and the objective memory

readout (the drawings recorded by our motion-capture system) with the concurrently recorded fMRI activation, all converged in supporting this hypothesis. Importantly, the use of the training paradigm itself provides *causal* inferences about the cross-modal changes in V1.

4.4.2. General considerations

Although a mature adult, this congenitally blind individual showed rapid functional reorganization of her brain in the process of learning to draw. It seems particularly surprising to find such reorganization in the primary visual cortex, whose main role is considered to be the early processing modality-specific information from visual input. The implication is that, although this cortical region had never been visually stimulated during the six decades of this blind subject's life, it still retained sufficient plasticity to be accessible for use when the need arose. Thus, the drawing task was sufficiently demanding to activate functional reorganization that was not instigated by any other task during her life (despite the intensive use of other forms of detailed spatial information such as Braille characters for reading). Further studies are needed to investigate the specific cross-modal mechanisms mediating the V1 reorganization; in general, there is a wide range of theoretical possibilities, such as unmasking of pre-existing connections, synaptic weight changes, or a combination of a number of different mechanisms (e.g., Florence and Kaas, 1995; Jones, 2000; Raineteau and Schwab, 2001; Merabet, 2008; Van Brussel et al., 2011; Likova, 2012a).

Furthermore, the post-training *MemoryDraw* BOLD response map extended to an eccentricity of ~10 deg, which is in accordance with that in the blindfolded subjects. Such multidimensional consistency between the congenitally blind and the blindfolded responses is likely not to be accidental but to reflect common mechanisms operating under both short- and long-term visual deprivation. To further explore this finding, a comparative analysis of groups of congenitally and late blind individuals is described in the next section.

5. Is there a universal 'language' of modality-independent space?

5.1. Introduction

The eccentricity overlap of the post-training MD activation in V1 for the congenitally blind (Fig. 9 B) and the blindfolded (Fig. 7 A) appears even more remarkable knowing that what they had in common was that they all explored and memorized the same battery of tactile images, with all images being of the same overall size. Therefore, the consistent extent of V1 activation raises a number of fundamental questions, as it is suggestive of i) preservation of a form of topographic organization in V1 despite complete visual deprivation, and ii) utilization of this topography by cross-modal memory.

Does such a topographic operation of the amodal memory sketchpad reflect a universal (i.e., modality-independent) 'language' of spatial representation? This section does not aim to provide complete answers but to raise questions and show their legitimacy based on our results in two additional groups of totally blind people.

5.2. Subjects and methods

A group of 6 congenitally blind and 7 late-onset blind individuals were studied before and after Cognitive-Kinesthetic training. All methods were as described in the General Methods section, with delineation of the normal retinotopic and functional organization in the whole-brain averaging by means of the novel method we have developed. The late-onset blind group had blindness onsets ranging from 3 to 39 years of age. Only patients with total ocular but not cerebral blindness, were included. (Human vision is well-established to be close to adult level by the age of 3, so the primary requirements for visually processing would have been well developed before the onset of blindness in this late-onset group.)

5.3. Results and discussion

Consistent with the findings from sections 3 and 4, *MemoryDraw* strongly activated V1 along the calcarine in both blind groups, and remarkably, the activation did not fill in the whole of V1 but extended only about half way posteriorly, covering what in the sighted would be approximately the central 10 deg retinotopic representation. The dashed white lines in Fig. 10 A, B show the 10 deg eccentricity contour, on the basis of our approach to enabling retinotopic mapping in the blind (see General Methods). Both the late-onset blind (Fig. 10A) who had full visual experience during early development, and the congenitally blind (Fig. 10B) who did not, show activation extending from the foveal representation all along to the 10 deg eccentricity contour but not beyond it (to an accuracy of $\pm 10\%$ of its cortical extent).

The fact that eccentricity-robust activation was systematically obtained in V1 as a result of training in *all* visually-deprived populations is indicative of topographically organized *non-visual* processing in this earliest visual area. This paradoxical result raises an array of questions. Does retinotopy develop by a nature or nurture mechanism, or by an interplay between the two? How would a topographic organization develop in the congenitally blind despite the absence of visual experience to drive it? Is its development determined entirely genetically and independently from visual stimulation in congenital blindness? How is an already developed retinotopy preserved after the total loss of visual input, as in the case of the late-onset blind subjects? How is a still functioning retinotopy, such as in the blindfolded, rapidly recruited by cross-modal memory? What is the frame of reference for such topographic metrics?

The current studies leave open questions for future research, although a basis for some answers is already emerging. Interestingly, a recent 7-T high-resolution structural MRI study in congenitally blind individuals has established the presence of another organizational landmark of V1 – the stria of Gennari – in this population (Trampel et al., 2011). This finding indicates that neither the development nor the preservation of this V1 landmark depends on the presence of visual input. Moreover, Cang et al. (2008) demonstrated for the first time that the development of the topographic axes of V1 are genetically controlled. The same group has also shown, however, strong experience-based V1 plasticity in non-human experiments (reviewed in Espinosa and Stryker, 2012). Thus, the plasticity mechanisms in V1 appear to be a complex interplay between genetic and environmental factors, which

further tune-up and refine the rough genetically-determined layout (for a recent review see Maya-Vetencourt and Origlia, 2012).

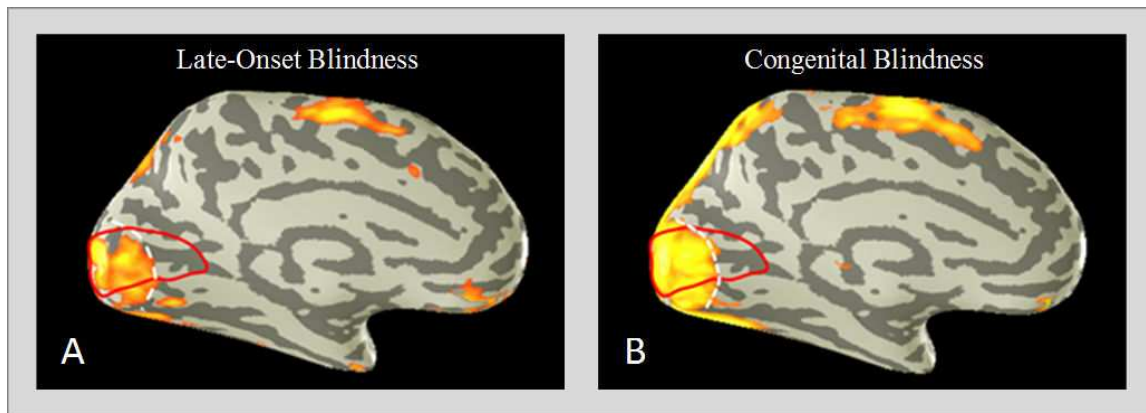


Figure 10. Group data in the blind.(A) The post-training group activation in V1 for the *MemoryDraw* task in the late-onset blind group expanded to approximately 10 deg eccentricity (dashed white line), similarly to the results in previous sections. (B) Remarkably, even the group data of congenitally blind individuals with no visual experience throughout their life manifested similar eccentricity (dashed white line).

6. Concluding comments

Detailed discussions are included in each of the experimental sections. Here, to sum up, the analyses of the fMRI data from our novel drawing-based memory paradigm and the Cognitive-Kinesthetic training led us to discover a unique pattern of V1 response, cut-off from propagation throughout the visual hierarchy by surrounding deactivation. Consideration of these results, in turn, excludes the most expected hypotheses and suggests a novel straightforward interpretation: That V1 in human implements the visuo-spatial working memory sketchpad concept but does so in an *amodal* form that transcends the sensory-modality specialization of the visual hierarchy. Based on this reasoning, we generated the prediction that, under the same memory paradigm, V1 will be activated even in the congenitally blind, who had never had any visual stimulation. This prediction was tested in a subsequent experiment, which replicated the freehand memory-drawing paradigm in a congenitally-blind novice. The data from this unique case study confirmed our initial interpretations of i) an amodal working memory role of V1, and ii) a spatiotopic character of the amodal memory representation. Furthermore, they also revealed for the first time the temporal evolution of the BOLD response during this learning-based cross-modal reorganization in the primary visual cortex. The larger-scale study in groups of both congenitally and late-onset totally blind participants provided further strong evidence of these discoveries, and also contributed to the formulation of new research questions. The strong training effect implies *causal* or functionally relevant reorganization of the (non-visual) processing in area V1. It is also particularly noteworthy that the effectiveness of the Cognitive-Kinesthetic training was felt as transformative by the blind individuals in opening a new domain of experience.

Our findings of unusual immature BOLD waveforms in V1 before training might be taken as a warning for neuroimaging studies on plasticity, indicating that finding some unspecified activation is not sufficient as an indicator of functional employment. Additional criteria considering the time-course characteristics of the response have to be analyzed as well. The training-based evolution of cortical response to becoming task-specific and develop fully-fledged BOLD waveforms, eliminates epiphenomenon-based explanations for the initially immature waveforms, such as explanations related to excess of excitability or a generic lack of synaptic pruning.

Generalization beyond the WM sketchpad: V1 as a generic 'projection screen' of an amodal nature?

The present results are consistent with our *Hypothesis II* (see 3.4.1), namely that V1 was operating as the neural substrate for the putative working-memory sketchpad in the *MemoryDraw* task, and not as a visual imagery component. Note however, that our current findings have further significance beyond this specific memory/imagery dichotomy. In a more general sense, these results provide a strong demonstration of massive employment of V1 in a *higher-order cognitive* task that involves *no* visual (or even tactile) *sensory* stimulation. Therefore, in principle, these results do not exclude a broader, *overarching hypothesis* that V1 may play the role of a *generic 'projection screen'* of an *amodal* nature, which could be utilized by each of the two main cognitive constructs discussed above, as well as by other forms of cognitive functions requiring such a high-resolution 'projection screen'. Moreover, it may be utilized in either a cross-modal or intramodal manner, depending on the specific *task needs*.

The research reviewed in this Chapter exemplifies how an innovative learning method, the Cognitive-Kinesthetic method, integrated with a complex memory paradigm employing art, can further empower functional neuroimaging to shed light on long-standing puzzles concerning memory and cross-modal plasticity, and lead to re-conceptualization of organizational principles of the brain.

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References

- [1] Amedi A., Malach, R., and Pascual-Leone, A. (2005) Negative BOLD Differentiates Visual Imagery and Perception. *Neuron*, 48, 859–872.
- [2] 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. *Nature Neuroscience* 7:1266–1270.
- [3] Amedi, A., Jacobson G., Hendler T., Malach R., Zohary E. (2002) Convergence of visual and tactile shape processing in the human lateral occipital complex. *Cereb Cortex* 12:1202–1212.
- [4] Amedi, A., Malach R., Hendler T., Peled S., Zohary E. (2001) Visuo-haptic object-related activation in the ventral visual pathway. *Nat Neurosci* 4, 324–330.
- [5] Amedi, A., Merabet, L.B., Camprodon, J., Bermpohl, F., Fox, S., Ronen, I., Kim, D.S., and Pascual-Leone, A. (2008) Neural and behavioral correlates of drawing in an early blind painter: a case study. *Brain Res.* 25, 252–62.
- [6] 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. *Nature Neuroscience* 6, 758–766.
- [7] Baddeley, A.D. (1986) *Working Memory*. Oxford University Press: New York.
- [8] Baddeley, A.D. (2000) The episodic buffer: a new component of working memory? *Trends Cognit Sci* 4, 417–23.
- [9] Baddeley, A.D. (2003) Working memory: looking back and looking forward. *Nature Reviews Neuroscience* 4, 829–839.
- [10] Baddeley, A.D., and Hitch, G.J. (1974). Working memory. In G Bower (Ed.), *The Psychology of Learning and Motivation*, Vol. 8, pp. 47–90. San Diego, CA: Academic Press.
- [11] Block, N. (2003) Tactile sensation via spatial perception. *Trends Cogn. Sci.* 7, 285–286.
- [12] Borowsky, R., Esopenko, C., Cummine, J., and Sarty, G.E. (2007) Neural representations of visual words and objects: a functional MRI study on the modularity of reading and object processing. *Brain Topogr.* 20:89–96.
- [13] Buchsbaum, B.R. and D’Esposito, M. (2009) Is there anything special about working memory? in *Neuroimaging of Human Memory*, eds Rosler, F. Ranganath, C., Roder, B. and Kluwe R. Oxford University Press: Oxford, 255–265.
- [14] Buechel, C., Price, C., Frackowiak, R.S., and Friston, K. (1998) Different activation patterns in the visual cortex of late and congenitally blind subjects. *Brain* 121, 409–419.

- [15] Burton, H. (2003) Visual cortex activity in early and late blind people. *J Neurosci*, 23, 4005–4011.
- [16] Burton, H., Sincler, R.J., MacLaren, D.C. (2004) Cortical activity to vibrotactile stimulation: an fMRI study in blind and sighted individuals. *Hum Brain Mapp* 23:210–228.
- [17] Burton, H., Snyder, A.Z., Conturo, T.E., Akbudak, E., Ollinger, J.M., and Raichle M.E. (2002) Adaptive changes in early and late blind: a fMRI study of Braille reading. *J Neurophysiol* 87, 589–607.
- [18] Cang, J., Niell, C.M., Liu, X., Pfeifferberger, C., Feldheim, D.A. and Stryker M.P. (2008) Selective disruption of one Cartesian axis of cortical maps and receptive fields by deficiency in ephrin-As and structured activity. *Neuron* 57, 511–23.
- [19] Charlot, V., Tzourio, N., Zilbovicius, M., Mazoyer, B., and Denis, M. (1992). Different mental imagery abilities result in different regional cerebral blood flow activation patterns during cognitive tests. *Neuropsychologia* 30, 565–580.
- [20] Chen, W., Kato, T., Zhu, X.-H., Ogawa, S., Tank, D. W., and Ugurbil, K. (1998). Human primary visual cortex and lateral geniculate nucleus activation during visual imagery. *NeuroReport*, 9, 3669–3674.
- [21] Cohen, L.G., Celnik, P., Pascual-Leone, A., Corwell, B., Falz, L., and Dambrosia, J. (1997) Functional relevance of cross-modal plasticity in blind humans. *Nature* 389, 180e–183.
- [22] D’Esposito, M., Detre, J.A., Aguirre, G.K., Stallcup, M., Alsop, D.C., Tippet, L.J. and Farah, M.J. (1997) A functional MRI study of mental image generation. *Neuropsychologia* 35, 725–730.
- [23] Deibert, E., Kraut M., Kremen S., Hart J.Jr. (1999) Neural pathways in tactile object recognition. *Neurology*. 52:1413–1417.
- [24] DeVolder, A.G., Bol, A., Blin, J., Robert, A., Arno, P., and Grandin, C. (1997) Brain energy metabolism in early blind subjects: neural activity in the visual cortex. *Brain Res* 750, 235–244.
- [25] Di Lollo, V. (1980) Temporal integration in visual memory. *J Exp Psychol Gen.*, 109,75-97.
- [26] 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.
- [27] Espinosa, J.S. and Stryker, M.P. (2012) Development and plasticity of the primary visual cortex. *Neuron*, 75, 230-49
- [28] Florence, S.L., and Kaas, J.H. (1995) Large-scale reorganization at multiple levels of the somatosensory pathway follows therapeutic amputation of the hand in monkeys. 15, 8083-95.

- [29] Formisano, E., Linden, D.J., Di Salle, F., Trojano, L., Esposito, F., Sack, A.T., Grossi, D., Zanella, F.E. and Goebel, R. (2002). Tracking the mind's image in the brain: I. Time-resolved fMRI during visuospatial mental imagery. *Neuron*, 35, 185–194.
- [30] Friston, K.J., Jezzard, P., and Turner, R. (1994) Analysis of functional MRI time-series. *Hum. Brain Map.* 1:153–171.
- [31] Ganis, G., Thompson, W.L., and Kosslyn, S.M. (2004). Brain areas underlying visual mental imagery and visual perception: An fMRI study. *Cognitive Brain Research*, 20, 226–241.
- [32] Gizewski, E.R., Gasser, T., de Greiff, A., Boehm, A., and Forsting, M. (2003) Cross-modal plasticity for sensory and motor activation patterns in blind subjects. *Neuroimage* 19, 968–75.
- [33] Goyal, M.S., Hansen, P.J., and Blakemore, C.B. (2006) Tactile perception recruits functionally related visual areas in the late-blind. *Neuroreport* 17, 1381–4.
- [34] Grossi D and Trojano L. (1999) Constructional apraxia. In Denes G., and Pizzamiglio L. (Eds), *Handbook of Clinical and Experimental Neuropsychology*. Hove: Psychology Press.
- [35] Hagen, M.C., Franzen, O., McGlone, F., Essick, G., Dancer, C., Pardo, J.V. (2002) Tactile motion activates the human middle temporal /V5(MT/V5) complex. *Eur J Neurosci.* 16, 957–964.
- [36] Hamilton, R.H, Keenan, J.P., Catala, M., and Pascual-Leone, A. (2000) Alexia for Braille following bilateral occipital stroke in an early blind woman. *NeuroReport* 11, 237–240.
- [37] Hamilton, R.H., Pascual-Leone, A., (1998) Cortical plasticity associated with Braille learning. *Trends Cogn Sci*, Elsevier, 2, 168–174.
- [38] Harrison, S.A., Tong, F. (2009) Decoding reveals the content of visual working memory in early visual cortex. *Nature* 458, 632–5.
- [39] Helmholtz, H. von (1871) *Popular Lectures on Scientific Subjects*. Longmans: London.
- [40] Hubel D.H., Wiesel T.N. (1968) Receptive fields and functional architecture of monkey striate cortex. *J Physiol.* 195, 215–43.
- [41] Ishai, A. (2009) Retrieving pictures from long-term memory. In *Neuroimaging of Human Memory*. Rosler, F., Ranganath, C., Roder, B., Kluwe, R., (Eds.) Oxford Univ. Press: New York.
- [42] Ishai, A., and Sagi, D. (1995) Common mechanisms of visual imagery and perception. *Science* 268, 1772–1774.

- [43] Ishai, A., Haxby, J.V., and Ungerleider, L.G. (2002) Visual imagery of famous faces: effects of memory and attention revealed by fMRI. *Neuroimage* 17, 1729–1741.
- [44] Ishai, A., Ungerleider, L.G., and Haxby, J.V. (2000) Distributed neural systems for the generation of visual images. *Neuron* 28, 979–990.
- [45] 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.
- [46] Jenkins, I. H., Brooks, D. J., Nixon, P. D., Frackowiak, R.S.J., Passingham, R. E. (1994) Motor sequence learning: a study with positron emission tomography. *J. Neurosci.* 14, 3775–3790.
- [47] Jones, E.G. (2000) Plasticity and neuroplasticity. *J. Hist. Neurosci.*, 9, 37–39.
- [48] Kaas, A., Weigelt, S., Roebroek, A., Kohler, A. and Muckli, L. (2010) Imagery of a moving object: the role of occipital cortex and human MT/V5+. *NeuroImage*, 49, 794–804.
- [49] Kastner, S., De Weerd, P., Desimone, R., Ungerleider, L.G. (1998) Mechanisms of directed attention in the human extrastriate cortex as revealed by functional MRI. *Science* 282: 108–111.
- [50] Kennedy, J. M. (1993) *Drawing and the Blind*. New Haven, CT: Yale University Press.
- [51] Kennedy, J.M. (2000) Recognizing outline pictures via touch: Alignment theory. In M.A. Heller (Ed.) *Touch, Representation and Blindness*. Oxford University Press: Oxford (pp. 67–98).
- [52] Kennedy, J.M., and Igor, J. (2003) Haptics and projection: Drawings by Tracy, a blind adult. *Perception* 32, 1059–1071.
- [53] Kennedy, J.M., and Juricevic, I. (2006) Foreshortening, convergence and drawings from a blind adult. *Perception* 35, 847–851.
- [54] Knauff, M., Kassubek, J., Mulack, T. and Greenlee, M.W. (2000) Cortical activation evoked by visual mental imagery as measured by fMRI. *NeuroReport*, 11, 3957–3962.
- [55] Kosslyn, S. M., Alpert, N. M., Thompson, W. L., Maljkovic, V., Weise, S. B., Chabris, C. F., et al. (1993). Visual mental-imagery activates topographically organized visual cortex – pet investigations. *J. Cogn. Neurosci.* 5, 263–287
- [56] Kosslyn, S. M., Thompson, W. L., Kim, I. J., Rauch, S. L., and Alpert, N. M. (1996). Individual differences in cerebral blood flow in area 17 predict the time to evaluate visualized letters. *J Cognit Neurosci*, 8, 78–82.
- [57] Kosslyn, S.M., Pascual-Leone, A., Felician, O., Camposano, S., Keenan, J.P., Thompson, W.L., Ganis, G., Sukel, K.E., and Alpert, N.M. (1999) The role of area 17 in visual imagery: convergent evidence from PET and rTMS. *Science* 284, 167–170.

- [58] Kosslyn, S.M., Thompson, W.L. (2003) When is early visual cortex activated during visual mental imagery? *Psychol Bull* 129: 723–746.
- [59] Kosslyn, S.M., Thompson, W.L., and Alpert, N.M. (1997). Neural systems shared by visual imagery and visual perception: A positron emission tomography study. *NeuroImage*, 6, 320–334.
- [60] Kreiman, G., Koch, C., and Fried, I. (2000) Imagery neurons in the human brain. *Nature* 408, 357–361.
- [61] Lambert S, Sampaio E, Scheiber C, Mauss Y. (2002) Neural substrates of animal mental imagery: calcarine sulcus and dorsal pathway involvement--an fMRI study. *Brain Res.* 924(2):176–83.
- [62] Lambert, S., Sampaio, E., Mauss, Y., and Scheiber, C. (2004) Blindness and brain plasticity: contribution of mental imagery? An fMRI study. *Brain Res. Cogn. Brain Res.* 20, 1–11.
- [63] Le Bihan, D., Turner, R., Zeffiro, T.A., Cuénod, C.A., Jezzard, P. and Bonnerot, V. (1993). Activation of human primary visual cortex during visual recall: A magnetic resonance imaging study. *Proc Natl Acad Sci, USA*, 90, 11802–11805.
- [64] Lee, T.S., and Mumford, D. (2003) Hierarchical Bayesian inference in the visual cortex. *J Opt Soci Amer, A* 20: 1434–1448.
- [65] Likova L.T. (2012a) Drawing enhances cross-modal memory plasticity in the human brain: A case study in a totally blind adult. *Frontiers in Human Neuroscience*.6:44. doi: 10.3389/fnhum.00044.
- [66] Likova L.T. (2012b) The spatiotopic ‘visual’ cortex of the blind. *Proc. SPIE 8291, Human Vision and Electronic Imaging XVII*, 8291–10L doi:10.1117/12.912257.
- [67] Likova L.T. (2013) A cross-modal perspective on the relationships between imagery and working memory. *Front. Psychology*, 3:561. doi: 10.3389/fpsyg.00561.
- [68] Likova, L.T. (2010a) Drawing in the blind and the sighted as a probe of cortical reorganization. *Human Vision and Electronic Imaging XV*. Edited by Rogowitz, Bernice E.; Pappas, Thrasyvoulos N. *Proceedings of the SPIE*, Volume 7527, 8–14.
- [69] Likova, L.T. (2010b) The primary visual cortex as a modality-independent ‘screen’ for working memory. *J Vision*, 10(7): 776,
- [70] Likova, L.T. and Tyler C.W. (2007). Stereomotion processing in the human occipital cortex. *NeuroImage* 38:293–304.
- [71] Likova, L.T., Tyler, C.W. (2008) Occipital network for figure/ground organization. *Experimental Brain Research*, 189, 258–67.

- [72] Loftus, E.F., Levidow, B. and Duensing, S. (1992) Who remembers best? Individual differences in memory for events that occurred in a science museum. *Applied Cogn, Psychol*, 6, 93-107.
- [73] Loomis, K.M., and Klatzky R. (2008) Functional equivalence of spatial representations from vision, touch, and hearing: Relevance for sensory substitutions. In M.A. Heller (Ed.) *Touch, Representation and Blindness* (pp. 67-98), Oxford University Press: New York.
- [74] Matteau, I., Kupers, R., Ricciardi, E., Pietrini, P., 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, 264-70.
- [75] Maya-Vetencourt, J.F. and Origlia, N. (2012) Visual cortex plasticity: a complex interplay of genetic and environmental influences. *Neural Plast*, 2012:631965.
- [76] Mechelli, A., Price, C.J., Friston, K.J., and Ishai, A. (2004) Where bottom-up meets top-down: neuronal interactions during perception and imagery. *Cereb. Cortex* 14, 1256–1265.
- [77] Mazard, A., Tzourio-Mazoyer, N., Crivello, F., Mazoyer, B., and Mellet, E. (2004). A PET meta-analysis of object and spatial mental imagery. *Eur. J. Cogn. Psychol.* 16, 673–695.
- [78] Mellet, E., Petit, L., Mazoyer, B., Denis, M., and Tzourio, N. (1998a). Reopening the mental imagery debate: Lessons from functional anatomy. *Neuroimage* 8, 129–139.
- [79] Mellet, E., Tzourio, N., Denis, M., and Mazoyer, B. (1995). A positron emission tomography study of visual and mental spatial exploration. *J. Cogn. Neurosci.* 7, 433–445.
- [80] Mellet, E., Tzourio, N., Denis, M., and Mazoyer, B. (1998b). Cortical anatomy of mental imagery of concrete nouns based on their dictionary definition. *Neuroreport* 9, 803–808.
- [81] Merabet, L. (2008) The plastic brain in blind individuals: The cause of disability and the opportunity for rehabilitation. In, *Blindness and Brain Plasticity in Navigation and Object Perception*. Lawrence Erlbaum Associates, London.
- [82] Merabet, L., Rizzo, J., Amedi, A., Somers, D., and Pascual-Leone, A. (2005) What blindness can tell us about seeing again: Merging neuroplasticity and neuroprostheses. *Nature Rev. Neurosci* 6:71–77.
- [83] Mumford, D. (1992) On the computational architecture of the neocortex II *Biol. Cybern.* 66, 241–251.

- [84] Nowak DA, Grefkes C, Ameli M, Fink GR (2009) Interhemispheric competition after stroke: brain stimulation to enhance recovery of function of the affected hand. *Neurorehabil Neural Repair*. 23:641-56.
- [85] O'Craven, K.M., and Kanwisher, N. (2000) Mental imagery of faces and places activates corresponding stimulus-specific brain regions. *J Cogn Neurosci* 12, 1013–1023.
- [86] Pascual-Leone, A., Amedi, A., Fregni, F., Merabet, L. (2005) The plastic human brain. *Annual Review of Neuroscience*, 28: 377-401.
- [87] Pascual-Leone, A., Hamilton, R., (2001) The metamodal organization of the brain. *Prog. Brain Res*. 134, 427-445.
- [88] Perkel, D.J., Bullier, J., Kennedy, H. (1986) Topography of the afferent connectivity of area 17 in the macaque monkey: a double-labelling study. *J Comp Neurol* 253, 374–402.
- [89] Piercy, M., Hecaen H., and Ajuriaguerra, J. (1960) Constructional apraxia associated with unilateral cerebral lesion—Left and right-sided cases compared. *Brain* 83, 225–242.
- [90] Pietrini, P., Furey, M.L., Ricciardi, E., Gobbini, M.I., Wu, W.H., Cohen, L., Guazzelli, M., Haxby, J.V. (2004) Beyond sensory images: Object-based representation in the human ventral pathway. *Proc Natl Acad Sci USA* 101, 5658–5663.
- [91] Ponchilla, P. E. (2008) Non-visual sports and arts: Fertile substrates for the growth of knowledge about brain plasticity in people who are blind or have low vision. In *Blindness and Brain Plasticity in Navigation and Object Perception*. Lawrence Erlbaum Associates: London.
- [92] Prather, S.C., Sathian, K. (2002) Mental rotation of tactile stimuli. *Brain Res Cogn Brain Res* 14: 91–98.
- [93] Ptito, M., Fumal A., de Noordhout A.M., Schoenen J., Gjedde A., and Kupers R. (2008) TMS of the occipital cortex induces tactile sensations in the fingers of blind Braille readers. *Exp Brain Res*, 184, 193-200.
- [94] Raineteau, O., and Schwab, M.E., (2001) Plasticity of motor systems after incomplete spinal cord injury. *Nat Rev Neurosci*. 2, 263-73.
- [95] Ranganath, H., (2009) Interrelationships between working memory and long-term memory. In *Neuroimaging of Human Memory*. Rosler, F., Ranganath, C., Roder, B., Kluwe, R. (Eds.) Oxford Univ. Press: Oxford.
- [96] Raz, N., Amedi, A., and Zohary, E. (2005). V1 activation in congenitally blind V1 activation in congenitally blind humans is associated with episodic retrieval. *Cereb. Cortex* 15, 1459–1468.
- [97] Reed, C.L., Shoham, S., Halgren, E. (2004) Neural substrates of tactile object recognition: an fMRI study. *Hum Brain Mapp* 21:236–246.

- [98] Sabbah, P., Simond, G., Levrier, O., Habib, M., Trabaud, V., Habib, M., Murayama, N., Raybaud, C., Mazoyer, B., Briant, J.F., and Salamon, G. (1995). Functional magnetic resonance imaging at 1.5 T during sensorimotor and cognitive task. *European Neurology*, 35, 131–136.
- [99] Sack, A. T., Sperling, J. M., Prvulovic, D., Formisano, E., Goebel, R., Di Salle, F., Dierks, T., and Linden, D.E. (2002). Tracking the mind's image in the brain: II. Transcranial magnetic stimulation reveals parietal asymmetry in visuospatial imagery. *Neuron*, 35, 195–204.
- [100] Sadato, N., Pascual-Leone, A., Grafman, J., Ibanez, V., Deiber, M.P., Dold, G., Hallett, M. (1996) Activation of the primary visual cortex by Braille reading in blind subjects. *Nature* 380, 526–528.
- [101] Schira, M.M., Breakspear, M., Spehar, B., Tyler, C.W., (2010) Modeling magnification and anisotropy in the primate foveal confluence. *PLoS, Computational Biology*, 6(1):e1000651.
- [102] 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* 26, 889–893.
- [103] Slotnick, S.D., Thompson, W.L., Kosslyn, S.M. (2005) Visual mental imagery induces retinotopically organized activation of early visual areas. *Cereb Cortex* 15, 1570–1583.
- [104] Sperling G (1963) A model for visual memory tasks. *Human Factors*, 5, 19-31.
- [105] Stoesz, M.R., Zhang, M., Weisser, V.D., Prather, S.C., Mao, H., Sathian, K. (2003) Neural networks active during tactile form perception: common and differential activity during macrospatial and microspatial tasks. *Int J Psychophysiol* 50, 41–49.
- [106] Super, H. (2003). Working memory in the primary visual cortex. *Arch. Neurol.* 60, 809–812.
- [107] Super, H., Spekreijse, H., and Lamme, V. A. F. (2001a). A neural correlate of working memory in the monkey primary visual cortex. *Science* 293, 120–124.
- [108] Super, H., Spekreijse, H., and Lamme, V. A. F. (2001b). Two distinct models of sensory processing observed in monkey primary visual cortex (V1). *Nat. Neurosci.* 4, 304–310.
- [109] Theoret, H., Merabet, L., Pascual-Leone A. (2004) Behavioral and neuroplastic changes in the blind: Evidence for functionally relevant cross-modal interactions. *J Physiol, Paris* 98, 221–233.
- [110] Thompson, W. L., Kosslyn, S. M., Sukel, K. E., and Alpert, N. M. (2001) Mental imagery of high- and low-resolution gratings activates Area 17. *NeuroImage*, 14, 454–464.

- [111] Tootell, R.B., Dale, A.M., Sereno, M.I., and Malach, R. (1996) New images from human visual cortex. *Trends Neurosci*, 95, 818–824.
- [112] Tootell, R.B., Reppas, J.B., Kwong, K.K., Malach, R., Born, R.T., Brady, T.J., Rosen, B.R., Belliveau, J.W. (1995) Functional analysis of human MT and related visual cortical areas using magnetic resonance imaging. *J Neurosci* 15: 3215–3230.
- [113] Trampel, R., Derek, V. M., Ott, R.T. (2011). Do the congenitally blind have a Stria of Gennari? First Intracortical Insights in Vivo. *Cereb Cortex*, 21, 2075-2081.
- [114] Trojano L., Grossi D, Flash T. (2009) Cognitive neuroscience of drawing: Contributions of neuropsychological, experimental and neurofunctional studies. *Cortex*, 45, 269-277.
- [115] Trojano, L., Grossi, D., Linden, D.E., Formisano, E., Hacker, H., Zanella, F.E., Goebel, R. and Di Salle, F. (2000) Matching two imagined clocks: the functional anatomy of spatial analysis in the absence of visual stimulation. *Cereb Cortex*, 10, 473– 481.
- [116] Tsotsos, J.K., Culhane, S.M., Kei Wai, W.Y., Lai, Y., Davis, N., NuXo, F. (1995) Modeling visual attention via selective tuning. *Artif Intell*, 78:507–545.
- [117] Tyler, C.W., Likova. L.T., Kontsevich, L.L., Schira, M.M., Wade, A.R. (2005) Enhanced concept of occipital retinotopy. *Current Medical Imaging Reviews* 1, 319-329.
- [118] Uhl, F., Franzen, P., Lindinger, G., Lang, W., Deecke, L. (1991) On the functionality of the visually deprived occipital cortex in early blind persons. *Neurosci Lett* 124, 256–9.
- [119] Uhl, F., Franzen, P., Podreka, I., Steiner, M., Deecke, L. (1993) Increased regional cerebral blood flow in inferior occipital cortex and cerebellum of early blind humans. *Neurosci Lett* 150, 162–4.
- [120] Van Boven, R.W., Ingeholm, J.E., Beauchamp, M.S., Bickle, P.C., Ungerleider, L.G. (2005) Tactile form and location processing in the human brain. *Proc Natl Acad Sci USA* 102, 12601–12605.
- [121] Van Brussel, L., Gerits, A., Arckens, L. (2011) Evidence for cross-modal plasticity in adult mouse visual cortex following monocular enucleation. *Cereb. Cortex* 21, 2133-2146.
- [122] Van Essen DC, Maunsell JH (1980) Two-dimensional maps of the cerebral cortex. *J Comp Neurol*. 191, 255-81.
- [123] Van Essen DC, Newsome WT, Maunsell JH (1984) The visual field representation in striate cortex of the macaque monkey: asymmetries, anisotropies, and individual variability. *Vision Res*. 24, 429-48.
- [124] Weisser, V., Stilla, R., Peltier, S., Hu, X., Sathian, K. (2005) Short-term visual deprivation alters neural processing of tactile form. *Exp Brain Res* 166:572–582.

- [125] Wheeler, M.E., Petersen, S.E., and Buckner, R.L. (2000). Memory's echo: Vivid remembering reactivates sensory-specific cortex. *Proc Natl Acad Sci, USA*, 97, 11125–11129.
- [126] Williams, M., Baker, C. I., Op de Beeck, H. P., Shim, W. M. Dang, S., Triantafyllou, C., and Kanwisher, N. (2008) Feedback of visual object information to foveal retinotopic cortex. *Nature Neuroscience*. 11, 1439-45.
- [127] Zangaladze, A., Epstein, C.M., Grafton, S.T., Sathian, K (1999). Involvement of visual cortex in tactile discrimination of orientation. *Nature* 401, 587-590.
- [128] Zhang, M., Mariola, E., Stilla, R., Stoesz, M., Mao, H., Hu, X., Sathian, K. (2005) Tactile Discrimination of grating orientation: fMRI activation patterns. *Hum Brain Mapp* 25, 370–377.

