Published in final edited form as:

Neurobiol Learn Mem. 2017 May ; 141: 101–107. doi:10.1016/j.nlm.2017.03.013.

Memory-guided drawing training increases Granger causal influences from the perirhinal cortex to V1 in the blind

Laura Cacciamani^{a,1} and Lora T. Likova^a

^aThe Smith-Kettlewell Eye Research Institute, 2318 Fillmore St., San Francisco, CA, 94114 USA

Abstract

The perirhinal cortex (PRC) is a medial temporal lobe structure that has been implicated in not only visual memory in the sighted, but also tactile memory in the blind (Cacciamani & Likova, 2016). It has been proposed that, in the blind, the PRC may contribute to modulation of tactile memory responses that emerge in low-level “visual” area V1 as a result of training-induced cortical reorganization (Likova, 2012; 2015). While some studies in the sighted have indicated that the PRC is indeed structurally and functionally connected to the visual cortex (Clavagnier et al., 2004; Peterson et al., 2012), the PRC’s direct modulation of V1 is unknown—particularly in those who lack the visual input that typically stimulates this region. In the present study, we tested Likova’s PRC modulation hypothesis; specifically, we used fMRI to assess the PRC’s Granger causal influence on V1 activation in the blind during a tactile memory task. To do so, we trained congenital and acquired blind participants on a unique memory-guided drawing technique previously shown to result in V1 reorganization towards tactile memory representations (Likova, 2012). The tasks (20s each) included: tactile exploration of raised line drawings of faces and objects, tactile memory retrieval via drawing, and a scribble motor/memory control. FMRI before and after a week of the Cognitive-Kinesthetic training on these tasks revealed a significant increase in PRC-to-V1 Granger causality from pre- to post-training during the memory drawing task, but not during the motor/memory control. This increase in causal connectivity indicates that the training strengthened the top-down modulation of visual cortex from the PRC. This is the first study to demonstrate enhanced directed functional connectivity from the PRC to the visual cortex in the blind, implicating the PRC as a potential source of the reorganization towards tactile representations that occurs in V1 in the blind brain (Likova, 2012).

Keywords

blindness; Granger causality; perirhinal cortex; visual cortex; tactile memory; drawing training

Corresponding Author: Laura Cacciamani, The Smith-Kettlewell Eye Research Institute, 2318 Fillmore St., San Francisco, CA 95115, Lcacciamani@gmail.com.

¹Present address/affiliation: California Polytechnic State University, Department of Psychology and Child Development, 1 Grand Ave., San Luis Obispo, CA, 93407

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Authors Contributions

LC and LTL both contributed to the idea, subject recruitment, data analysis, and writing of the manuscript. LTL had developed the experimental design and the Cognitive-Kinesthetic Drawing Training and conducted the drawing training of each blind participant.

1. Introduction

Acquiring and accessing previously formed memories of objects that we encounter is crucial to interacting with our surroundings. In sighted adults, this process of memory encoding and retrieval is seamless and automatic; we can quickly visually assess all aspects of an object in parallel. In those who are blind, however, forming and accessing memory representations must be accomplished through other sensory modalities, such as the tactile modality, which makes this seemingly simple act much more difficult. A key structure that has been shown to be involved in object memory is the perirhinal cortex (PRC) of the medial temporal lobe (MTL). The majority of research on the PRC has demonstrated its role in visual object recognition (Brown and Aggelton, 2001; Suzuki et al., 1993; Mumby and Pinel, 1994), although it has also been implicated in perceptual processes (Murray and Bussey, 1999; Bussey et al., 2002; Murray et al., 2007; Baxter, 2009; Peterson et al., 2012).

Importantly, recent research has shown that the PRC is also involved in tactile object memory in those who are blind (Cacciamani & Likova, 2016). In this previous study, as well as in the current study, the experimental paradigm was a replication of that in Likova (2012). Blind participants underwent a unique tactile memory training, known as Likova's Cognitive-Kinesthetic method (Likova, 2010; 2012; 2013), wherein over the course of 5 days, they learned how to draw guided solely by memory. The experiment consisted of 3 tasks (see Figure 1a). Participants first perceptually explored and memorized raised line drawing stimuli with their left hand (Perceptual Exploration, or PE, condition). They then were taught how to use that memory representation to draw the stimulus from memory with their right hand (Memory Drawing, or MD, condition). The last task was a motor and memory control task, where participants drew random scribbles with their right hand (Scribble, or S, condition). Importantly, using different hands for exploring and drawing required participants to rely on their memory representation rather than motor movements. Over 5 days, participants were trained on these tasks, such that by the end of training, they were successfully able to draw each stimulus. Before and after training, functional magnetic resonance imaging (fMRI) scans were conducted in order to assess the effect of training on representations in the PRC. Cacciamani and Likova's (2016) results showed that the PRC signaled the object memories of each stimulus created during the training, thereby indicating that the PRC represents tactile memory in the blind as it does visual memory in the sighted.

In addition to the PRC, dramatic neural changes have also been observed in primary visual area V1 as a result of the Cognitive-Kinesthetic training. Specifically, Likova (2012, 2013, 2014) found that blood oxygen level dependent (BOLD) waveforms in V1 went from being erratic, immature, and weak before training to well fit to the BOLD predictor for the MD task after training. This prominent shift indicates that, after only 5 days of this well-targeted training, "visual" areas of the brain as low as V1 can reorganize to represent tactile memory information in those who are blind. These important findings implicated V1 as a site suitable for the neural implementation of the theoretical working memory "visuo-spatial sketchpad" and allowed for its re-conceptualization into a "supramodal spatial sketchpad" (Likova, 2012; 2013).

The training-induced cortical reorganization observed in both the PRC and V1 separately is suggestive of a possible interaction between these two seemingly disparate brain areas. Indeed, Likova (2012, 2015) proposed that the PRC may be a source of the reorganization that has been observed in visual area V1 during a memory task. The present experiment tests Likova's proposal.

This PRC-to-V1 feedback hypothesis is also consistent with previous research in the sighted that has shown that the PRC is both structurally and functionally connected to the visual cortex. In rats, visual area 17—the equivalent to human V1—has been shown to receive direct structural projections from the PRC (Miller & Vogt, 1984). Clavagnier et al. (2004) also found direct connections from the PRC to V1 using a retrograde tracer injection technique in sighted monkeys. Uncovering the existence of these structural connections laid the foundation for further research on the functional influences that the PRC can exert on the visual cortex. Given the PRC's well-known role in primarily declarative memory processes, its ability to modulate activation at low-level "visual" areas is a new concept that has recently challenged the traditional "memory-only" view. The first evidence of the PRC's ability to modulate visual cortex activation was observed by Peterson and colleagues (2012; based on proposal by Barense et al., 2012). In Peterson et al.'s study, sighted participants made familiar/novel judgments to silhouettes presented in the periphery while activation in both the PRC and the visual cortex was assessed via fMRI. Their results demonstrated that the PRC signaled the familiarity of both the whole object depicted by the silhouette and the familiarity of the object's individual parts—a finding that extended previous work showing that the PRC only responds to whole object familiarity (e.g., Barense, Henson, & Graham, 2011). Of even greater interest to the present study, Peterson et al. also found that the visual cortex mimicked the PRC's pattern of activation and signaled the familiarity of not only the parts, but also the whole object. Given that the receptive field size of V1-V2 neurons (1–2° of visual angle) are not large enough to encompass the whole silhouetted object (4°), this object-level response in low-level visual cortex must have originated from a higher level such as the PRC (Peterson et al., 2012). This prior study therefore suggested that the PRC modulates functional responses at low-level visual regions (Barense et al., 2012; Peterson & Cacciamani, 2013)—a finding consistent with a feedforward-feedback view of PRC-to-V1 connectivity. These studies, however, did not examine any causal influences and was restricted to the sighted population.

In the present study, we searched for direct evidence of modulation of area V1 specifically by the PRC during a tactile memory task in the blind. To do so, we used Likova's Cognitive-Kinesthetic Drawing Training method in order to generate training-induced changes in PRC-to-V1 causal connectivity during memory-guided drawing. As in previous studies using Likova's experimental paradigm (e.g., Likova, 2012; 2013; 2014; Cacciamani & Likova, 2016), fMRI was conducted before and after 5 days of training. To interrogate causal relationships between the PRC and V1, a Granger causality analysis was employed on the pre- and post-training BOLD data and compared between them. Granger causality (Granger, 1969) is a method of assessing directed functional connectivity based on the principle of temporal precedence and predictability. Specifically, it can be conceptualized as follows: activity in brain area X (the "seed" region) is said to "Granger cause" (or G-cause) activity in brain area Y if the past activation in X is a better predictor of future activation in Y than

the past Y activation alone. This analysis technique has been applied to both bivariate and multivariate BOLD data (Roebroek et al., 2005; Deshpande et al., 2008; Seth, 2010) and has been shown to be robust to changes in hemodynamic properties (Seth, Chorley, & Barnett, 2013). We employed this analysis in order to go above and beyond any implied or correlative interactions between the PRC and the visual cortex that have been previously found in the sighted (Peterson et al., 2012) or suggested in the blind (Likova, 2012) and search for a more direct top-down relationship—specifically in a blind population where connections between and reorganization of these “visual” areas is pertinent. Doing so can provide insight into the mechanisms of cortical plasticity and top-down interactions in the blind brain, thereby answering previously posed questions as to the origin of V1 reorganization (Likova, 2012; 2015) and laying the foundation necessary for future rehabilitative initiatives.

If the PRC indeed modulates tactile memory-related activation in V1 in the blind, then we expected to observe a significant increase in the top-down PRC-to-V1 Granger causal influence from before to after training. We specifically expected to see this effect during memory-guided drawing (the MD task) when cortical reorganization in both the PRC and V1 has been observed previously (Likova, 2012; 2013; 2014; 2015; Cacciamani & Likova, 2016). We also investigated the bottom-up Granger causality from V1 to PRC, although our previous findings did not lead us to expect any training effects in this direction.

2. Methods

2.1. Participants

The participants were 8 congenital and acquired blind volunteers (4 females, 4 males; ages 31–76) whose demographics are summarized in Table 1. The experimental protocol was approved by the Smith-Kettlewell Institutional Review Board; prior to participating, all volunteers provided their informed consent. Participants were compensated for their time and were right-handed.

Our participants did vary somewhat with respect to their age of blindness onset and their degree of remaining vision. The current visual status of all participants was assessed using the Berkeley Rudimentary Vision Test (Bailey et al., 2012). In this brief test, cards with black and white tumbling E's, gratings, and field projections were shown to each participant. No participants reported perceiving any of the information on these cards with either eye. Light perception was also assessed via a flashlight shown at different angles. Five participants had some light perception (LP) in segments of the visual field in one or in both eyes; these participants were blindfolded during all aspects of the experiment in order to eliminate any residual visual input. The remaining three participants had no light perception (NLP), and two of these NLP participants (#1 and #2) were totally blind from birth.

2.2. Design

The present study used the same experimental design as Likova, 2012 (see Figure 1). Specifically, the Cognitive-Kinesthetic drawing training was employed as an effective instrument that has previously allowed us to achieve remarkable behavioral and neural

changes within only 5 daily sessions at 2 hours per day. Before and after this training, fMRI scans were conducted during which participants performed three tasks in a blocked paradigm: during Perceptual Exploration (PE), participants tactually explored and encoded into memory a raised line drawing stimulus using their left (non-dominant) hand; during Memory Drawing (MD), participants relied their tactile memory to draw the stimulus using their right (dominant) hand; and during Scribble (S), participants drew random, unstructured scribbles with their right hand as a motor and memory control (the randomness of these scribble drawings was confirmed by visually assessing the recorded scribbles). Each task lasted 20 s, and participants were instructed to respectively explore/draw or scribble for the entire 20 s such that equal time was spent on each task. The tasks were separated by a 20-s rest interval (RI) during which participants were instructed to clear their mind of any shapes or images. An auditory cue indicated the start of each task. This three-task sequence (RI, PE, RI, MD, RI, S, RI) was presented twice for each of the 6 line drawing stimuli (3 faces and 3 objects), for a total of 12 cycles of the sequence. Prior to beginning, participants were informed as to the nature of the experiment and briefly familiarized with the tasks and equipment.

As a result of the complex and interactive procedures of the Cognitive-Kinesthetic training, each participant learned how to efficiently and accurately perform the tasks. As training progressed, the 20-s time limit became achievable for each task and each stimulus. Participants' ability to accurately draw the stimuli solely guided by memory within this short time limit marked the behavioral success of the Cognitive-Kinesthetic training. A key idea behind this approach is that "drawing has the unique advantage of providing an explicit readout of the memory content recalled during task [MD] performance, as it objectively 'externalizes' the specific memory representation guiding the motor output in each trial" (Likova, 2012).

2.3. Equipment

A custom MRI-compatible stimulus presentation and drawing system was used while participants were performing the tasks in the scanner (see Figure 1c). This unique system consisted of a plexiglass table extending across the participant's lap, topped with a dual-slot height-adjustable surface. In the left slot was the line drawing stimulus to be explored during the PE task, and in the right slot was an MRI-compatible electronic drawing tablet to be used during the MD and S tasks. Between scans, the participant was instructed to remove the top-most line drawing stimulus (which was just explored and drawn) from the left slot and place it by their side, exposing the next stimulus in the prescribed sequence. Participants held a plastic stylus in their right hand to draw and scribble, and the movement of the stylus across the drawing tablet was recorded and presented in real-time to the experimenters. The auditory cues were presented through Resonance Technologies headphones (Resonance Technologies, Salem, MA). Our custom MRI-compatible drawing system allowed the participant to draw comfortably on the plastic table across their torso/lap without moving their head. Additionally, during scanning, the participant's head was stabilized in the head coil with comfortable but firm padding around all sides to further reduce movement.

2.4. Data Acquisition and Pre-processing

FMRI data were collected on a Siemens Trio 3T magnet equipped with a 12-channel head coil. BOLD responses were obtained using an EPI acquisition (TR = 2 s, TE = 28 ms, flip angle = 80°, voxel size = 3.0 × 3.0 × 3.5 mm) consisting of 35 axial slices extending across the whole brain. Pre-processing was conducted using FSL (Analysis Group, FMRIB, Oxford, UK) and included slice-time correction and two-phase motion correction, consisting of both within-scan and between-scan 6-parameter rigid-body corrections. To facilitate segmentation and registration, a whole-brain high-resolution T1-weighted anatomical scan was also obtained for each participant (voxel size = 0.8 × 0.8 × 0.8 mm). White matter segmentation in this T1 scan was conducted using FreeSurfer (Martinos Center for Biomedical Imaging, Massachusetts General Hospital) and Gray matter was generated with the mrGray function in the mrVista software package (Stanford Vision and Imaging Science and Technology).

2.5. Granger Causality Analysis Procedures

The PRC was used as the seed region of interest (ROI) for the top-down Granger causality analysis, as assessing the connections from this region to the visual cortex was the central purpose of this study. The left and right PRC ROIs were defined anatomically in each subject based on previously determined guidelines (Insausti et al., 1998; Kivisaari et al., 2013). Given that there are often substantial individual differences in MTL anatomy, care was taken to define the PRC ROI as consistently as possible between participants. Specifically, the PRC was defined from anterior to posterior as beginning 2 mm anterior to the appearance of the limen insulae gray and ending 4 mm posterior to the apex of the intralimbic sulcus. From medial to lateral, the PRC extended from the shoulder of the medial bank of the collateral sulcus to the shoulder of the lateral bank of the collateral sulcus. Using these anatomical landmarks, ROIs for the left and right PRC were hand-drawn in each individual brain in FSL.

To assess bottom-up influences from V1 to the PRC, separate Granger causality analyses were conducted using left and right V1 as the seed ROIs. As in previous work (e.g., Likova, 2012), these V1 ROIs were defined anatomically in each subject using the Brodmann area maps generated automatically during cortical reconstruction in FreeSurfer (version 5.0). The Granger causality analysis was conducted analogously for each directional influence—top-down (PRC-seed to V1) and bottom-up (V1-seed to PRC). For each of these analyses, Granger causality maps were generated from the seed ROI to every voxel in the brain (x2y) for each of three tasks (PE, MD, S) during the fMRI scan cycle. First, 40-second temporal segments of BOLD data were extracted starting at the onset of each task and proceeding through the end of the 20-second rest interval following the task (in order to account for any task-related functional connectivity effects that may persist into this interval due to the slow hemodynamics of the BOLD signal). With a 2-second repetition time, there were 20 BOLD volumes in these segments. The average time course of all voxels that were members of the seed ROI was computed. Multiple linear regressions were performed, fitting the 2nd–20th volumes of each voxel in the brain as a function of the 1st–19th volumes of themselves and as a function of the seed ROI, plus a constant term (x2y). This “full” model containing the prior time points both of the voxel itself and of the seed ROI was compared to a “reduced”

model containing just the prior time point of the voxel itself in order to assess the contributions of the seed ROI to the activation of each voxel in the brain. Regression coefficients between the ROI and these individual voxels were converted to z-scores by dividing by the estimated standard error of the coefficient. Z-scores sufficiently different from zero were interpreted to imply a causal linkage, with the sign of the z-score indicating whether the causality was excitatory or inhibitory.

To assess top-down influences using the PRC as the seed, Granger z-scores were extracted from all voxels within the V1 ROI and averaged across that ROI within each hemisphere. Similarly, for the bottom-up analysis using V1 as the seed, z-scores were extracted from all voxels in the PRC ROI and averaged across that ROI within each hemisphere.

In order to create an average Granger causality map representing all blind participants, each participant's results were normalized to a standard brain in Freesurfer (fsaverage), after which they were averaged across participants.

3. Results

The results of the PRC-to-V1 (and vice versa) Granger causality analysis are depicted in Figure 2. In short, we did observe strong training-induced increases in top-down Granger causality across all 8 blind participants. Specifically, our averaged data show that with the left PRC as the seed ROI, a significant pre- to post-training increase in Granger causal influence from the PRC was evident in the left V1 during the memory-guided drawing task [$t(7) = 2.24, p = .038$; see Figure 2a]. Likewise, with the right PRC seed, the same increase in PRC-to-V1 Granger causality was observed again during the MD task in the ipsilateral (right) hemisphere [$t(7) = 2.55, p = .019$] and marginally in the contralateral (left) hemisphere [$t(7) = 1.60, p = .08$]. Although our main statistics of interest are these pre- to post-training changes in Granger causality, it is also insightful to examine each session individually. At pre-training, no PRC-to-V1 Granger causality values during the MD task were significantly greater than 0 ($p > .50$), whereas after training, PRC-to-V1 Granger causal influences from bilateral PRC to bilateral V1 were significantly greater than 0 [L PRC to L V1: $t(7) = 3.66, p < .01$; L PRC to R V1: $t(7) = 2.80, p < .05$; R PRC to L V1: $t(7) = 3.50, p < .01$; R PRC to R V1: $t(7) = 3.52, p < .01$]. These data are shown in Figure 2a.

These important results demonstrate that, as predicted, the top-down directed functional connectivity from bilateral PRC to the visual cortex during a tactile memory task was enhanced as a result of the training.

As expected, no significant changes in PRC-to-V1 Granger causality from pre- to post-training were observed during the PE or S tasks ($p > .15$). This lack of significance is further addressed in Section 4.

We also conducted an analysis investigating changes in Granger causal influences from V1 to the PRC (i.e., bottom-up influences), and the results are shown in Figure 2b. Unlike the results reported above in the top-down direction, V1-to-PRC Granger causal influences were unaffected by the training. During the MD task (where we observed our top-down effects), there were no significant differences from pre- to post-training in either the left or right PRC

using either left or right V1 as the seed ROI ($p s > .12$). In examining each session individually, no V1-to-PRC Granger causality values were significantly greater than 0 for any task, session, or hemisphere ($p s > .10$).

Together, these findings suggest that the Cognitive-Kinesthetic training mainly targeted and enhanced top-down, rather than bottom-up, directed functional connectivity between the PRC and V1.

In addition to these specific PRC-V1 analyses, we also visualized Granger causal influences from each seed ROI (PRC and V1) to the rest of the cortex (see Figure 3 for medial views of these influences). As can be seen, the training caused increases in Granger causal influences from the PRC to not only V1, but also other cortical areas including extrastriate “visual” areas as well as the medial parietal lobe bilaterally (Figure 3a). In contrast, directed connectivity from V1 to the PRC was unaffected by the training (Figure 3b), consistent with the bottom-up results observed above. As the focus of the present study is on the interactions between the PRC and V1 specifically, we do not further examine these widespread Granger influences; future research could elucidate the influences between the PRC and other cortical areas.

We also conducted follow-up analyses to assess the effects of various demographic factors that we have collected (see Table 1) on the training-induced changes in Granger causality between the PRC and V1. These analyses first revealed that neither participants’ current age nor the number of years in their current visual status were significantly correlated with PRC-to-V1 Granger causal influences ($p s > .15$). Additionally, there was no significant effect of Braille fluency on Granger causality ($p s > .12$). Lastly, there was no significant difference in PRC-to-V1 connectivity between participants who were congenitally blind (never had full vision) vs. acquired blind (born with full vision).

4. Discussion

This study is the first to provide evidence that within only 5 days, directed top-down functional connectivity from the PRC (a “memory” area) to the visual cortex (a “visual” area) in those who are blind can be enhanced. Specifically, an increase in PRC-to-V1 Granger causality after the Cognitive-Kinesthetic training was observed during a tactile memory task that involved retrieving stored object representations and drawing them from memory. Previous research has found that the V1 and PRC (separately) reorganize to represent tactile memory information in the blind as a result of this unique memory-guided drawing training (Likova, 2012; 2013; 2015; Cacciamani & Likova, 2016). Now, we are able to conclude that these areas are functionally connected in a top-down fashion. In particular, our results support the previously proposed hypothesis (Likova, 2012) that the reorganization that occurs in V1 might be originating from higher level such as the PRC where both the memory and perception of an object is represented.

That such striking changes in functional activation and connectivity can be observed within such a short amount of time sheds light on the robustness of Likova’s Cognitive-Kinesthetic training, as well as the plasticity of the adult human brain. This cortical plasticity may be of

even more importance in those who are blind, as the “visual” areas of the brain must reorganize to represent non-visual tasks and information. It makes sense, then, that the connectivity to these visual regions would also shift such that tactile information is represented. These changes that occur in the blind brain may help them compensate for their vision loss by enhancing the responsiveness of and cortical connections devoted to the other senses (in our case, the sense of touch) and/or engaging supramodal mechanisms. Uncovering this important finding—that functional connectivity subserving tactile memory can be enhanced within only 5 days of fun and engaging training—can pave the way for future applied research on blindness rehabilitation.

The current findings add new dimensions to the scope of previous studies and models in the sighted suggesting that the PRC modulates responses in low-level visual regions (Peterson et al., 2012; Barense et al., 2012). These previous studies, however, did not investigate directed, or causal, functional relationships and did not assess either memory tasks or a blind population. Here, for the first time, we have provided evidence of top-down directed functional connectivity from the PRC to a “visual” area as low as V1. These important findings support recent research indicating that the PRC is not only involved in memory, but also perception (Murray and Bussey, 1999; Bussey et al., 2002; Murray et al., 2007; Baxter, 2009; Peterson et al., 2012), consistent with a dynamical feedforward-feedback view of object processing (Likova & Tyler, 2008; Peterson & Cacciamani, 2016). In the present study, as well as in recent work (Cacciamani & Likova, 2016), we have added to this important research by showing that the PRC’s representations and connections are not only perceptual-mnemonic, but also supramodal.

The data we present in this article are averaged across all 8 of our blind participants. We note that there were individual differences in the magnitude of the pre- to post-training change in Granger causality across participants; however, this was expected, as our blind participants did differ along many factors, including their degree of residual vision (NLP or LP), current age, age of blindness onset, and diagnosis (see Table 1). However, follow-up analyses revealed that none of these factors were correlated with the increase in PRC-to-V1 Granger causality that we observed; thus, any individual differences in our neural change of interest cannot be attributed to these factors, and instead, is likely attributable to differences in higher-order cognitive factors. Regardless of the origin of the individual differences, that we were able to observe significant changes in Granger causality on data that were averaged across 8 blind participants (see Figures 2 and 3) despite these differences speaks to the robustness of our effect.

The analysis we used in this study, Granger causality, assesses directed functional influences based on the notion of temporal precedence and prediction—that is, whether the past activation in one region (the seed ROI) can predict future activation in another region. This type of analysis has been applied to BOLD fMRI data previously (Roebroeck et al., 2005; Deshpande et al., 2008; Seth, 2010) and has been shown to be robust to hemodynamic invariance (Seth et al., 2013). However, it does have limitations. Specifically, we acknowledge that, based on the temporal precedence concept, Granger causality does not directly measure causal relationships *per se*. What it does provide, however, is *directionality* of functional influences, which has not previously been evaluated between the PRC and the

visual cortex in either the sighted or the blind. Moreover, our primary measure of interest was the pre- to post-training *change* in connectivity between these two regions, which did not require us to interpret or make assumptions regarding raw Granger causality values. Therefore, we strongly believe that the contributions of this Granger causality analysis to our understanding of PRC-to-V1 training-induced changes greatly outweigh its potential limitations.

One question that arises with our findings is why we only observed enhanced top-down Granger causality during the tactile memory-drawing task (MD), and not during the perceptual exploration task (PE). Indeed, previous research has shown that the PRC is involved in both the perceptual and mnemonic representation of objects in the visual modality in the sighted (Murray and Bussey, 1999; Bussey et al., 2002; Murray et al., 2007; Baxter, 2009; Peterson et al., 2012), as well as in the tactile modality in the blind (Cacciamani & Likova, 2016). Additionally, research in the sighted has found evidence of top-down modulation of the visual cortex during a *perceptual* task (Peterson et al., 2012; Barense et al., 2012). So, in the present study, one might have expected to observe enhanced PRC-to-V1 connectivity during both the tactile memory and perceptual exploration tasks. However, prior research in the blind has shown that at the level of V1, the training-induced reorganization that occurs is only evident during the tactile memory task, which is consistent with the proposal of V1 as the implementation of a supramodal spatial memory buffer or ‘sketchpad’ on which stored memory representations are projected (Likova, 2012; 2013; 2015). If the PRC is modulating the reorganization of this V1 tactile memory sketchpad, then it makes sense for the top-down influence from the PRC to only be observed during the tactile memory task. This is not to say that the functional connectivity from the PRC to the visual cortex is always restricted to the memory domain—only that the task used in the current study may have specifically targeted these functional connections.

Our training effects on Granger causality values were only observed in the top-down direction (PRC to V1), not in the bottom-up direction (V1 to PRC). Our predictions were centered on these top-down effects, as our previous work (Likova, 2012; 2015) allowed us to hypothesize that a high-level area such as the PRC modulates the V1 reorganization that occurs in the blind. We did not have any specific hypotheses regarding the bottom-up functional connectivity. Even though we did not find any effects of training on these bottom-up influences, we do not refute the existence of feedforward connections from V1 to the PRC.

The current study assessed, for the first time, training-induced changes in Granger causality between two specific areas—the PRC and V1. It is likely that there are other functional connections involved in and enhanced by the Cognitive-Kinesthetic training; indeed, it has been shown before that this training affects a distributed whole-brain network (Likova, 2013; 2014). However, analysis of the whole network is beyond the scope of the present study. Our goal was to test the specific hypothesis proposed by Likova (2012) that the PRC—which has both a mnemonic function and a direct anatomical connection to V1 (Clavagnier et al., 2004)—modulates tactile memory responses in V1 as a result of the training, and that is what we have shown. Future studies should investigate the potential broader network effects of the Cognitive-Kinesthetic training.

Acknowledgments

This work was supported by the National Eye Institute at the National Institute of Health (R01EY024056), awarded to Lora Likova. Laura Cacciamani was supported by a Rachel C. Atkinson Postdoctoral Fellowship while working on this study. The authors would like to thank Spero Nicholas for helping with data collection and analysis, and Kristyo Mineff for assisting with the drawing training.

References

- Bailey IL, Jackson AJ, Minto H, Greer RB, Chu MA. The Berkeley rudimentary vision test. *Optometry & Vision Science*. 2012; 89(9):1257–1264. [PubMed: 22842307]
- Barense MD, Henson RN, Graham KS. Perception and conception: temporal lobe activity during complex discriminations of familiar and novel faces and objects. *Journal of Cognitive Neuroscience*. 2011; 23(10):3052–3067. [PubMed: 21391761]
- Barense MD, Ngo JK, Hung LH, Peterson MA. Interactions of memory and perception in amnesia: The figure–ground perspective. *Cerebral Cortex*. 2012; 22(11):2680–269. [PubMed: 22172579]
- Baxter MG. Involvement of medial temporal lobe structures in memory and perception. *Neuron*. 2009; 61(5):667–677. [PubMed: 19285463]
- Brown MW, Aggleton JP. Recognition memory: what are the roles of the perirhinal cortex and hippocampus? *Nature Reviews Neuroscience*. 2001; 2(1):51–61. [PubMed: 11253359]
- Bussey TJ, Saksida LM, Murray EA. Perirhinal cortex resolves feature ambiguity in complex visual discriminations. *European Journal of Neuroscience*. 2002; 15(2):365–374. [PubMed: 11849302]
- Cacciamani L, Likova LT. Tactile object familiarity in the blind brain reveals the supramodal perceptual-mnemonic nature of the perirhinal cortex. *Frontiers in Human Neuroscience*. 2016; 10(92):1–11. [PubMed: 26858619]
- Clavagnier S, Falchier A, Kennedy H. Long-distance feedback projections to area V1: implications for multisensory integration, spatial awareness, and visual consciousness. *Cognitive, Affective, & Behavioral Neuroscience*. 2004; 4(2):117–126.
- Deshpande G, Hu X, Stilla R, Sathian K. Effective connectivity during haptic perception: a study using Granger causality analysis of functional magnetic resonance imaging data. *Neuroimage*. 2008; 40(4):1807–1814. [PubMed: 18329290]
- Henson RNA, Cansino S, Herron JE, Robb WGK, Rugg MD. A familiarity signal in human anterior medial temporal cortex? *Hippocampus*. 2003; 13(2):301–304. [PubMed: 12699337]
- Kivisaari, SL., Probst, A., Taylor, KI. fMRI. Springer; Berlin Heidelberg: 2013. The Perirhinal, Entorhinal, and Parahippocampal Cortices and Hippocampus: An Overview of Functional Anatomy and Protocol for Their Segmentation in MR Images; p. 239–267.
- Likova LT, Tyler CW. Occipital network for figure/ground organization. *Experimental Brain Research*. 2008; 189:257–267. [PubMed: 18604528]
- Likova, LT. IS&T/SPIE Electronic Imaging. International Society for Optics and Photonics; 2010. Drawing in the blind and the sighted as a probe of cortical reorganization; p. 752708–752720.
- Likova LT. Drawing enhances cross-modal memory plasticity in the human brain: a case study in a totally blind adult. *Frontiers in Human Neuroscience*. 2012; 6
- Likova LT. A cross-modal perspective on the relationships between imagery and working memory. *Frontiers in Psychology*. 2013; 3:561. [PubMed: 23346061]
- Likova LT. Learning-Based Cross-Modal Plasticity in the Human Brain: Insights from Visual Deprivation fMRI. *Advanced Brain Neuroimaging Topics in Health and Disease-Methods and Applications*. 2014:327–358.
- Likova, LT. IS&T/SPIE Electronic Imaging. International Society for Optics and Photonics; 2015. Temporal evolution of brain reorganization under cross-modal training: insights into the functional architecture of encoding and retrieval networks; p. 939417–939432.
- Miller MW, Vogt BA. Direct connections of rat visual cortex with sensory, motor, and association cortices. *Journal of Comparative Neurology*. 1984; 226(2):184–202. [PubMed: 6736299]

- Murray EA, Bussey TJ, Saksida LM. Visual Perception and Memory: A New View of Medial Temporal Lobe Function in Primates and Rodents*. *Annu Rev Neurosci.* 2007; 30:99–122. [PubMed: 17417938]
- Murray EA, Bussey TJ. Perceptual–mnemonic functions of the perirhinal cortex. *Trends in cognitive sciences.* 1999; 3(4):142–151. [PubMed: 10322468]
- Peterson, MA., Cacciamani, L. Shape perception in human and computer vision. Springer; London: 2013. Toward a dynamical view of object perception; p. 443-457.
- Peterson MA, Cacciamani L, Barense MD, Scalf PE. The perirhinal cortex modulates V2 activity in response to the agreement between part familiarity and configuration familiarity. *Hippocampus.* 2012; 22(10):1965–1977. [PubMed: 22987675]
- Roebroeck A, Formisano E, Goebel R. Mapping directed influence over the brain using Granger causality and fMRI. *Neuroimage.* 2005; 25(1):230–242. [PubMed: 15734358]
- Seth AK. A MATLAB toolbox for Granger causal connectivity analysis. *Journal of neuroscience methods.* 2010; 186(2):262–273. [PubMed: 19961876]
- Seth AK, Chorley P, Barnett LC. Granger causality analysis of fMRI BOLD signals is invariant to hemodynamic convolution but not downsampling. *Neuroimage.* 2013; 65:540–555. [PubMed: 23036449]

Highlights

- The proposal that the perirhinal cortex (PRC) modulates V1 in the blind was tested.
- FMRI scans were conducted before and after Cognitive-Kinesthetic drawing training.
- The training led to enhanced top-down Granger causal influences from the PRC to V1.
- Results suggest that the PRC is a potential source of V1 reorganization in the blind.

Figure 1. Experimental set-up

(A) Experimental design on which participants were trained. (B) Raised-line drawing stimuli. (C) Custom MRI-compatible equipment used in the scanner. PE = perceptual exploration; MD = memory drawing; S = scribble.

a. Top-down influences **b. Bottom-up influences**

Figure 2. Granger causal influences between the PRC and V1 during the memory-guided drawing task. (a) Top-down influences from the PRC to V1, and (b) bottom-up influences from V1 to the PRC

Italicized Granger values indicate non-significance ($p > .05$); bolded Granger values indicate a significant influence ($p < .05$). The thickness of the lines reflects the strength of the connection. On the bar graphs, error bars represent standard error of the mean. PRC = perirhinal cortex. * $p < .05$; + $p < .10$

a. From the PRC **b. From V1**

Figure 3. Granger causal influences between each seed region and the rest of the cortex during the memory-guided drawing task. (a) Granger values from the PRC and (b) from V1

PRC = perirhinal cortex; LH = left hemisphere; RH = right hemisphere

Table 1

Participant demographics

Part #	Gender	Age	Current visual status	Age of onset of current visual status	Visual status at birth	Did participant ever have full vision?	Could participant ever use vision to see shapes/objects?	Diagnosis	Braille fluency
1	M	68	NLP	15	LP	No	No	Retinopathy of prematurity	High
2	F	66	LP	<1	LP	No	No	Retinopathy of prematurity	High
3	F	57	LP	30	Tunnel vision	No	Yes	Retinitis pigmentosa	High
4	M	76	LP	16	Full vision	Yes	Yes	Optic neuropathy	Moderate
5	F	31	NLP	28	LP	No	Yes	Optic nerve hypoplasia	High
6	F	66	NLP	16	Full vision	Yes	Yes	Glaucoma	Moderate
7	M	70	LP	60	Full vision	Yes	Yes	Optic neuropathy	None
8	M	56	LP	47	Full vision	Yes	Yes	Glaucoma	None

Note: Part = participant; NLP = no light perception; LP = light perception