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Spatial cognition training rapidly induces cortical plasticity in blind navigation: Transfer of Training Effect & Granger Causal Connectivity analysis

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Abstract

How is the cortical navigation network reorganized by the Likova Cognitive-Kinesthetic Navigation Training? We measured Granger-causal connectivity of the frontal-hippocampal-insular-retrosplenial-V1 network of cortical areas before and after this one-week training in the blind. Primarily top-down influences were seen during two tasks of drawing-from-memory (drawing complex maps and drawing the shortest path between designated map locations), with the dominant role being congruent influences from the egocentric insular to the allocentric spatial retrosplenial cortex and the amodal-spatial sketchpad of V1, with concomitant influences of the frontal cortex on these areas. After training, and during planning-from-memory of the best on-demand path, the hippocampus played a much stronger role, with the V1 sketchpad feeding information forward to the retrosplenial region. The inverse causal influences among these regions generally followed a recursive feedback model of the opposite pattern to a subset of congruent influences. Thus, this navigational network reorganized its pattern of causal influences with task demands and the navigation training, which produced marked enhancement of the navigational skills.

INTRODUCTION

Successful navigation requires spatial cognition abilities, primarily the development of an accurate and flexible *mental, or cognitive, map* of the navigational space and of the route trajectory required to travel to the target location. Importantly, all activities of daily life depend heavily on mechanisms of *spatial cognition* and *visuo-motor* control (e.g., Loomis et al. 2001; Schinazi et al., 2016).

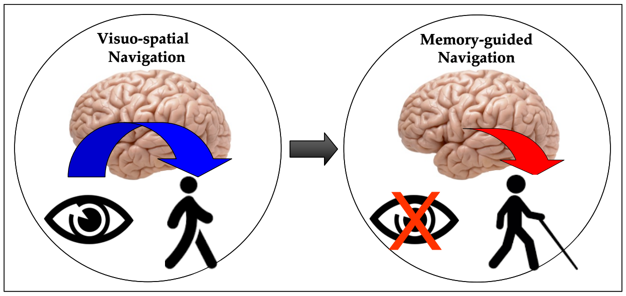


FIG. 1. Illustration of the conceptualization that when the visuospatial coordination is lost or impaired, targeted rehabilitation training for the development of precise and robust **supramodal memory representations**, or **cognitive maps,** is needed for rehabilitation in blind navigation. This conceptualization underlies the Cognitive-Kinesthetic navigation training protocol in this study. (*after Likova, 2014*).

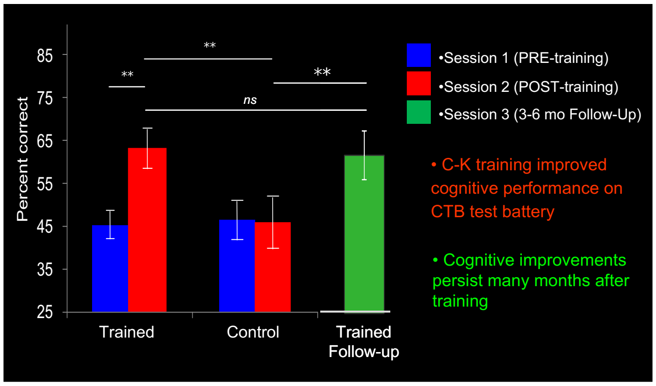
Our philosophy is that when vision with its built-in spatial functionality is greatly impaired or lost, particular reliance must be placed on the development of the *mental* maps, and on the ability to use them effectively for (non-visual) spatiomotor control. Under such circumstances, these spatial *mental/cognitive* maps (or *spatial memory representations)* are supported only by auditory and tactile sensory inputs. The Likova Cognitive-Kinesthetic (C-K) Rehabilitation Training (e.g., Likova, 2012, 2013) utilizes a unique form of blind memory-guided drawing that rapidly and sustainably develops *cognitive mapping* to a high level of proficiency in both the blind and the sighted. To train the spatial cognition abilities and spatial memory underlying successful navigation, in a current clinical trial, we *translated* the power of the Cognitive-Kinesthetic Rehabilitation Training which was initially developed for the manual domain of operation, to the domain of navigation.

Navigation is a complex spatiomotor activity of critical importance in everyone's life but is particularly challenging for visually impaired people.

In terms of navigation, *cognitive maps* are the internal representations of the spatial information necessary for *decision-making* and *operation at any scale* (Tolman, 1948; O'Keefe & Nadel, 1978. Downs, 1981: Thorndyke & Hayes-Roth 1982; Sholl 1987; Lloyd, 1989; Montello 1992; Tversky, 1993; Kitchin 1994; Portugali, 1996; Peuquet, 2002; Epstein & Vass, 2014; Finkelstein et al., 2016).

Guiding philosophy

Thus, the guiding philosophy of the Likova Lab has been that scientific research into *paradigmatically new spatiomotor rehabilitation*, capitalizing on such *spatial memory representations*, is of key importance for improving navigation, quality of life, increasing vocational opportunity, emotional valence, self-esteem and integration into society.



• C-K training improved cognitive performance on CTB test battery

• Cognitive improvements persist many months after training

FIG. 2. **Highly significant and sustainable generalization/ transfer of the C-K training to untrained spatio-cognitive abilities,** assessed through the McCarron-Dial Cognitive Test for the Blind (CTB)**.** Composite scores (in percent correct) on CTB. Note that CTB test battery has a well-established *high (0.93) test-retest reliability* coefficient. ***Trained (left):*** The C-K training improved CTB performance highly significantly (red) relative to pre-training (blue). ***Untrained (center):*** No change without training. ***Trained follow-up (right):*** Long-term persistence of transfer of training effects (green). Error bars are standard error of the mean. * $p < .05$, ** $p < .01$. (Likova & Cacciamani, 2018).
Note: See Fig. 7 for transfer of learning in navigation.

Built on a novel Conceptual Framework (Likova, 2012a,b; 2013), which provides the rationale to use (paradoxically) a form of 'visual' art (drawing) for blindness rehabilitation, the **Cognitive-Kinesthetic (C-K) Training** implements this philosophy. Its high efficacy to rapidly improve spatial memory functions, and cognitive mapping in particular, for *manual* spatiomotor performance in the blind, and to drive brain plasticity in respective cortical networks, has been successfully established. The trainees quickly learn to generate precise and stable *cognitive maps* of *haptically* explored raised-line spatial structures, such as faces and objects, and then use these mental 'maps' to guide the precise motor control for a free-hand memory drawing entirely non-visually (e.g., Likova 2012, 2013, 2018).

The C-K Training overcomes critical barriers to rehabilitation in blindness

What rehabilitation ***barriers*** are overcome by the the Cognitive-Kinesthetic Rehabilitation Training?

i) Neglect of cognitive map enhancement in O&M practice. Although blindness rehabilitation theory has established the importance of supramodal *cognitive maps* (e.g., Casey, 1978; Jacobson, 1998; Golledge et al., 2000; Lahav & Mioduser, 2008; Schinazi, Thrash & Chabat, 2016), in reality, standard Orientation & Mobility (O&M) approaches are largely restricted to specific practical problem solving, rather than focusing on enhancement of deep, *general-purpose cognitive* capabilities that underlie the practical task performance. The Likova C-K approach overcomes this barrier by translating the power of the C-K rehabilitation to enhance *spatial cognitive mapping* to *navigation*, with a focus on navigational decision making, such as route planning, and their execution on both micro- and macro-scales. (While there certainly are highly sophisticated O&M teachers in some locations, the characterization of O&M training as largely practical reflects the experience of the local O&M teachers and rehab institutions we have collaborated with, and of the blind participants recruited over the years. Many such participants were blind O&M trainers themselves, and were keen to invite their blind colleagues to the study.)

The C-K training is specifically designed to not only **enhance cognitive mapping,** but moreover –

to also enhance the ability to use these cognitive/mental maps to **guide precise spatiomotor actions**. Five 2-hour sessions enable even participants totally blind from birth to execute free-hand complex drawing trajectories with as many as 30 segments of varying curvature, length, orientation, etc., dramatically speeding up from minutes to less than 20 seconds post-training, with a parallel increase in accuracy. They report this training highly rewarding, changing their view on life, enhancing their spatial awareness and confidence, and even affecting everyday orientation and navigation performance that were not initially directly targeted. These reports led to the realization that the *non-visual memory-drawing* task can be conceptualized as a form of **'manual navigation'** along the drawing trajectory, enhancing brain mechanisms *shared* with actual navigation, and thus resulted in initiation of *translation* of C-K training to navigation.

ii) Piecemeal approach. Another critical barrier faced by the traditional rehabilitation is the typically *piecemeal approach* of distributed training over many separate daily tasks – an expensive process that usually takes months or years of instruction. What is needed is an integrative rehabilitation training approach to attack ***at one stroke*** in a single, unified paradigm a ***wide-spectrum*** of core components for spatial cognition and spatiomotor control, which has been now achieved by the groundbreaking C-K approach.

Clinical neurology and neuropsychology have long recognized drawing as a powerful *multi-component* tool for the ***diagnosis*** of spatiomotor and memory dysfunctions, such as constructional apraxia, Alzheimer's disease, and other brain pathologies (e.g., Kleist, 1934; De Renzi, 1982; Grossi et al., 1999; Trojano & Conson, 2008; Russell et al., 2010), as drawing has the *unique advantage* of providing an *explicit readout* of ***wide-range*** components of neural functions from a ***single***, unified assay. It is the array of *diverse* functional subsystems involved in drawing that underlies its effectiveness as a *diagnostic* tool in neurology, and now - as a *rehabilitation* tool through our C-K training.

Thus, the C-K training builds on the same unique properties of (memory) drawing used for *diagnostics* in neurology, but importantly - it takes the ***inverse*** approach of using it as an ***active instigator*** of positive change, which operates simultaneously in many neural subsystems and, hence, fulfils the demand for ***wide-spectrum*** rehabilitation through a ***single*** training method. Indeed, our results (e.g., Likova & Cacciamani, 2018; their Fig. 2) have strongly supported this hypothesis (see also Fig. 7). The ~2-hour *standardized* Cognitive Test for the Blind (the McCarron-Dial CTB test battery; recommended by the AFB; see also in Dial et al., 1990, 1991a,b; 1999; McCarron et al., 1991; Hill-Briggs et al., 2007), run **pre-**, **post-** and **3-6 months** after the training, showed that through the *single* but comprehensive task of blind memory-drawing (in its unique form implemented in the C-K training) stably enhances *'at one stroke'* a range of spatial abilities, well beyond the trained drawing task *per se* (Figs. 2). This important finding of **transfer-of-training** effects with **long-term maintenance**, has far-reaching implications for overcoming the task-specific, piecemeal limitations of traditional blindness rehabilitation.

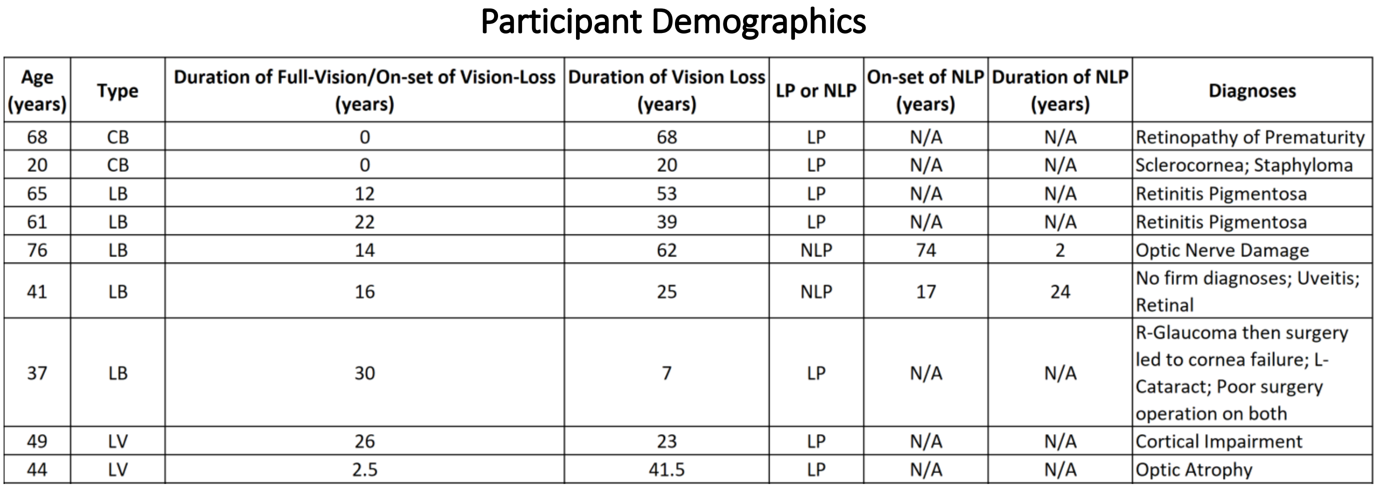
iii) Lack of knowledge of training-driven neuroplasticity mechanisms. Although there are numerous fMRI studies in the blind, and many studies on navigation in particular, typically brain data in the blind are simply compared to those in the sighted on the same experimental task, or a cross-sectional comparison between categories of blindness is done. The few studies implementing a longitudinal training paradigm are focused on a specific sensory substitution device, such as the tongue display unit (TDU) (e.g., Ptito et al., 2012), or sighted adults under temporal blindfolding (Merabet et al., 2008). This dearth of functional MRI or other brain imaging studies of rehabilitation training represents another **barrier** to the progress in the field, although it seems not yet to be widely recognized.

The rapid and highly efficient C-K training made it possible for us to address this gap, and gain knowledge on the cross-modal learning and neuroplasticity mechanisms (Likova 2012a,b; 2013; 2014; 2015; 2017a,b, 2018; Cacciamani & Likova, 2016a,b; 2017) and how they inform training-based effects in navigation in particular.

METHODS

The participants were nine right-handed blind individuals, two congenitally blind (CB), 5 with blindness onset after childhood (LB), and 2 with severe low vision (LV), and relied on either a cane or a dog guide for navigation (see Table 1). All participants gave informed consent for the experimental protocol, as approved by the Smith-Kettlewell Institutional Review Board. Participants were recruited from the local community through flyers, e-mail and online recruitment ads, word-of-mouth, and the SF Light House for the Blind, and were compensated for their time. The LP participants were blindfolded during all aspects of the experiment to eliminate all possible visual input.

As stimuli for the navigational training, we used a custom-designed battery of tactile raised-line maps of up to 20 segments (Fig. 3A). Through the Cognitive-Kinesthetic Training, the participants were trained how effectively to explore the maps to be able to create an as accurate as possible *mental* image of an explored tactile map in their memory. Furthermore, they learn how to make these *memories stable*, how to use them for *making navigational decisions*, and how to then use the mental maps for informing motor control for the *successful execution* of respective navigational plans. First, the navigational motor execution was trained and tested on ***micro-scale*** (through navigational drawing). Second, the transfer of this training was tested on a ***macro-scale*** (through walking in a custom virtual reality, installed in a large empty space; patent pending). The Cognitive-Kinesthetic Training (CKT) takes only five 2-hr sessions on 5 sequential days. Before and after training we run cognitive and navigational tests, and whole-head functional magnetic Resonance Imaging (fMRI).



Participant Demographics

Age (years)	Type	Duration of Full-Vision/On-set of Vision-Loss (years)	Duration of Vision Loss (years)	LP or NLP	On-set of NLP (years)	Duration of NLP (years)	Diagnoses
68	CB	0	68	LP	N/A	N/A	Retinopathy of Prematurity
20	CB	0	20	LP	N/A	N/A	Sclerocornea; Staphyloma
65	LB	12	53	LP	N/A	N/A	Retinitis Pigmentosa
61	LB	22	39	LP	N/A	N/A	Retinitis Pigmentosa
76	LB	14	62	NLP	74	2	Optic Nerve Damage
41	LB	16	25	NLP	17	24	No firm diagnoses; Uveitis; Retinal
37	LB	30	7	LP	N/A	N/A	R-Glaucoma then surgery led to cornea failure; L-Cataract; Poor surgery operation on both
49	LV	26	23	LP	N/A	N/A	Cortical Impairment
44	LV	2.5	41.5	LP	N/A	N/A	Optic Atrophy

FMRI experimental design: Several types of scans were run. In this paper, we discuss three of these conditions, each of them involving a sequence of experimental tasks that were run in Pre- and Post-training fMRI scans by six participants (five LB and one CB). In the first one, participants explored a raised-line tactile map with one hand for 20 s, and after 30 s rest period, had to draw the full map ("*Draw Full Map*", DFM; 30 s) with the other hand (to avoid the use of simple motor memory); this sequence was repeated 3 times in one fMRI scan for each studied map. This task was initially very difficult, as shown in the primitive nature of the Pre-training examples of Fig. 3B. This condition was repeated in the Post-training fMRI session, and an example of the first drawing of the Post session is shown as the fourth panel of Fig. 3B, which can be seen to capture the full structure of the map, though with some local discrepancies of scale. In each fMRI session, the *Exploration* and *Drawing Full Map* from memory scan, was followed by another scan including the tasks of (i) *Planning the Shortest Path (PSP; 10 s)* between two given points on the just learned and drawn full maps, and then (ii) to *Draw this Shortest Path (DSP; 10 s)* that was planned in memory. An example of a given start and endpoints for a path through the map, such as from lower left, LL, to upper right, UR, in the depicted example of Fig. 3A; it required to plan the shortest path between those two endpoints. They then drew the best path that they had planned, which had serious issues in the Pre sessions (in spite of decades of blind tactile experience) but was accurately captured in the Post-training session (Fig. 3C). The C-K training method, which takes only a total of 10 hours (2 hours/day for 5 days), provided notable improvement in the spatial memory capability for complex multi-intersection tactile maps with up to 20 segments or more from brief inspections of only 30 s. To assess the training-driven changes in functional brain organization, we ran functional MRI (fMRI; 3T Siemens Prisma scanner) for a suite of navigation tasks before and after training of blind participants, together with a suite of behavioral measures (not reported here).

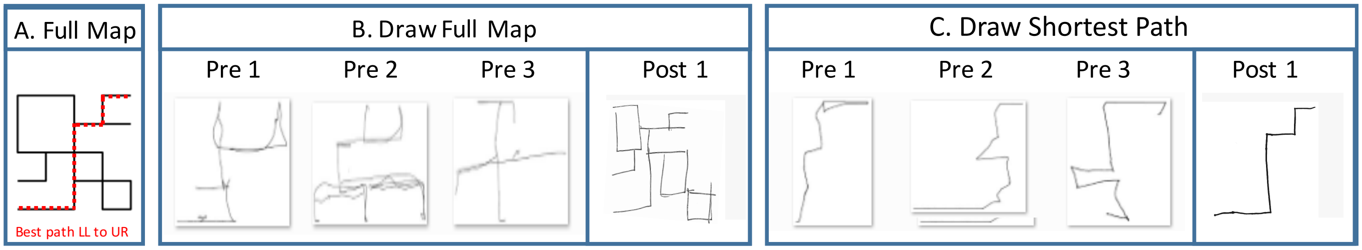


FIG. 3. A. Example of the tactile raised-line maps of up to 20 segments (Fig. 3A). B. Examples of the 3 initial Pre-training drawings of the map, with the first drawing of the Post session shown as the fourth panel. C. Three Pre-training drawings of drawing the shortest path through the map from lower left, LL, to upper right, UR, with the first drawing of the best path in the Post session shown as the fourth panel.

FMRI acquisition. MR data were collected on a 3T Siemens Prisma Fit magnet equipped with a 64-channel head+neck coil. BOLD responses were obtained using an EPI acquisition (TR = 2 s, TE = 30 ms, flip angle = 45, voxel size = 2.5 x 2.5 x 2.5) consisting of 54 axial slices extending across the whole brain. To facilitate segmentation and registration, a whole-brain high-resolution T1-weighted anatomical scan was also obtained for each participant (voxel size = 0.8 x 0.8 x 0.8 mm). White matter segmentation in this T1 scan was conducted using FreeSurfer and gray matter was generated with the mrGray function in the mrVista software package.

FMRI time-course analyses. The data were averaged from the individual participant brains into the Montreal Neurological Institute average of 305 individuals (http://nist.mni.mcgill.ca/?p=957). and analyzed with the Stanford VISTA Lab software. The effective neural activation amplitudes (e.g., Friston et al., 1994) for each task across the repeats of multi-task sequences in the 1.5 hr scan were estimated by the following procedure. A General Linear Model (GLM) consisting of boxcar neural task activations and an auditory stimulus regressor was convolved with an estimated hemodynamic response function (HRF) and fitted to the blood-oxygen-level-dependent (BOLD) responses along with a 4th order polynomial to remove baseline trends. BOLD amplitudes were defined as “task-positive” or “task-negative” according to the sign of the GLM beta fit.

ROI activation analysis. Regions of interest (ROIs) were generated for each of the visualization task-positive and task-negative BOLD activation regions of the navigational network. The navigation neural network involves regions of the hippocampal complex (HCC) (O’Keefe & Nadel 1978; Nadel & Hardt, 2004), the retrosplenial cortex (RSC) (Epstein & Kanwisher, 1998; Epstein et al., 2007) for the allocentric representation of space, and the insula (Chechlacz et al., 2012) for the egocentric representation of the peripersonal location of the body in space. Assessment of the amodal function of spatial visualization of the visually deprived ‘visual’ cortex (Likova, 2012a,b, 2014) in blind navigation is also of importance. The effective neural activation amplitudes for each condition in each defined ROI was estimated by the same GLM procedure applied to the average signal across all voxels within the ROI.

Granger Causality Analysis Procedures. For the waveform Granger causality analyses *for each pair* *of left- and right-hemisphere ROIs from the set of 5 navigational ROIs (45 pairs),* the "full" model containing the prior time points for both ROIs of the pair was compared to a "reduced" model containing only the prior time point of the ROI being modeled. The variance ratio of reduced and full models was tested against a null hypothesis of 1, with p-values determined from the F distribution. To better capture faster interactions, we also ran calculations at 1 s steps on the interpolated time series. The p-values are converted into z-scores based on the standard normal distribution in some analyses for ease of interpretation.

The GC connectivity patterns were quantified in terms of an index of connectivity density, defined as the number of statistically significant connections ($p < 0.05$) relative to the number of ROIs in the task-positive or task-negative networks in each condition.

The fMRI tasks analyzed for the present work were: a) *Draw Full Map*: drawing the explored map from memory (30 s), b) *Plan Shortest Path*: determining solely from that spatial memory the shortest path between two newly-specified locations on the map (10 s), and c) *Draw Shortest Path*: drawing that mentally determined shortest path (10 s).

RESULTS

The current analysis was focused on five cortical regions with known associations with navigational performance in sighted individuals: two lateral anterior regions (encompassing the medial frontal gyrus, MFG, which includes the dorsolateral prefrontal cortex, DLPFC, and the insula), and three medial posterior regions (primary visual cortex, V1, the hippocampus (HC), and the retrosplenial cortex (RSC), which is immediately posterior to the hippocampus).

Before training, there was minimal fMRI activation of the traditionally-visual occipital cortex V1 in the group of blind individuals during the task of *Draw Full Map*. Similarly, the other four navigational brain regions specified above had relatively minimal activation before training with the main activity concentrated in the left-hemisphere hand and motor-control regions. However, following the C-K training, all of the five targeted navigational brain regions showed notable bilateral increases in BOLD activation, manifesting both crossmodal plasticity, in that the traditionally visual cortex had enhanced activation through non-visual stimulation, and supramodal plasticity, in that the same network of navigational areas were enhanced in these blind individuals as activation for navigation in sighted individuals.

Granger Causal Connectivity Reorganization

The main focus of the present paper is the plasticity of the flow of directed causal influences through the navigation network under the present navigational Cognitive-Kinesthetic Training.

Draw Full Map

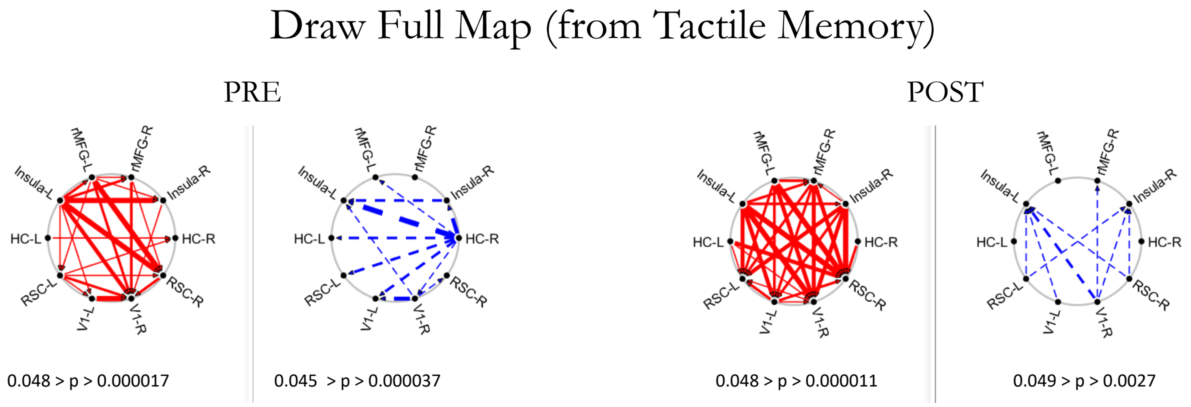
Congruent Granger Causality: *Training-driven network reorganization.* The task used to define the cortical extents of the navigational ROIs was that of drawing a full map (DFM) of the form specified in Methods (Fig. 3). As seen in Fig. 4, the *congruent* Granger causal connections during the *PRE-training* drawing of the full map (red arrows) are strongly *lateralized*, with the main direction of flow being top-down from the left frontal regions (left insula and middle frontal gyrus, MFG) to the right hemisphere regions (retrosplenial cortex/ RSC, V1, MFG, insula) although with a weak input from the right frontal areas also to those posterior regions bilaterally. The hippocampi played little role, although it participated weakly in the left-to-right influences across the hemispheres. Thus, the main targets of the causal influences were the right V1 and RSC, which also received input from the left RSC.

The dramatic effect of the less than one-week training regimen was to *fully symmetrize* these same top-down relationships *Post-training*. All four of the frontal areas of this network now influence all four of its posterior areas, with the hippocampus again playing little role except to break the symmetry with a left hippocampal influence on the right RSC.

Inverse Granger Causality: *Training-driven network reorganization.* The inverse causal connections (blue arrows in Fig. 4) show a very different picture initially, although they undergo a similar *symmetrization* following the training. The

Pre-training connections were strongly right to left, but they emanated from the one area that played a minimum role in the congruent connections. The right hippocampus had a strong inverse influence on the left insula, and weaker on all the left hemisphere ROIs, with no inverse influences coming from the left hippocampus at all.

The *Post-training* pattern of inverse influences follow the congruent influences in becoming strongly symmetrized, with a primarily bottom-up flow to the insula bilaterally to the RSC and V1. It should be specified that a key interpretation of such inverse causality is as representing negative feedback with its signal control functionality when it runs in the opposite direction to a congruent causal connection. These inverse influences thus correspond to feedback connections opposing the primary top-down congruent influences symmetrically from the insula to anterior navigational nodes of RSC and V1.


Draw Full Map (from Tactile Memory)

PRE

POST

FIG. 4. Directed Granger Causal connectivity diagrams for the 10 navigational ROIs for congruent (red arrows) and inverse (blue arrows) Granger-Causal influences between all pairs of ROIs during drawing the full map (DFM). The line thickness codes the significance (p-value) of each connection, with the range of p-values expressed below each diagram.

Plan Shortest Path

Congruent Granger Causality: *Training-driven network reorganization.* Before training, the *congruent* connectivity while *planning the shortest path* through the map (red arrows in Fig. 5) was similar to the pattern for drawing the full map, with top-down influences primarily from the insula bilaterally to the posterior regions of V1 and the RSC, but also bilaterally forward to the MFG. The HC also played a similar role during this planning phase. The Post-training connectivity had a somewhat similar pattern of influences flowing from the insula and HC, though now focused on the RSC more than V1, and with a new lateralized top-down input from the right MFG to the right RSC.

Inverse Granger Causality: *Training-driven network reorganization.* The inverse causal influences (blue arrows in Fig. 5) largely conformed to the *negative feedback model* of running oppositely to the congruent influences, bilaterally from V1 to the insula and the HC for Pre-training and from RSC to the insula and MFG Post-training.

Draw Shortest Path

Congruent Granger Causality: *Training-driven network reorganization.* Having planned the shortest path between the designated point, the final task was to draw this shortest path from memory. *Pre-training*, the causal connectivity network for this task was strongly *lateralized* (red arrows in Fig. 6), consistent with the lateralization of the hand control network for any drawing task. Within the navigation network, the strongest influences ran from the left insula to all the right-hemisphere ROIs except HC, and similarly from the left RSC and HC to the right RSC and V1. The Post-training influences had a similar pattern but with weaker connectivity, presumably because the task of drawing the best path was less demanding after the experience of training for it.

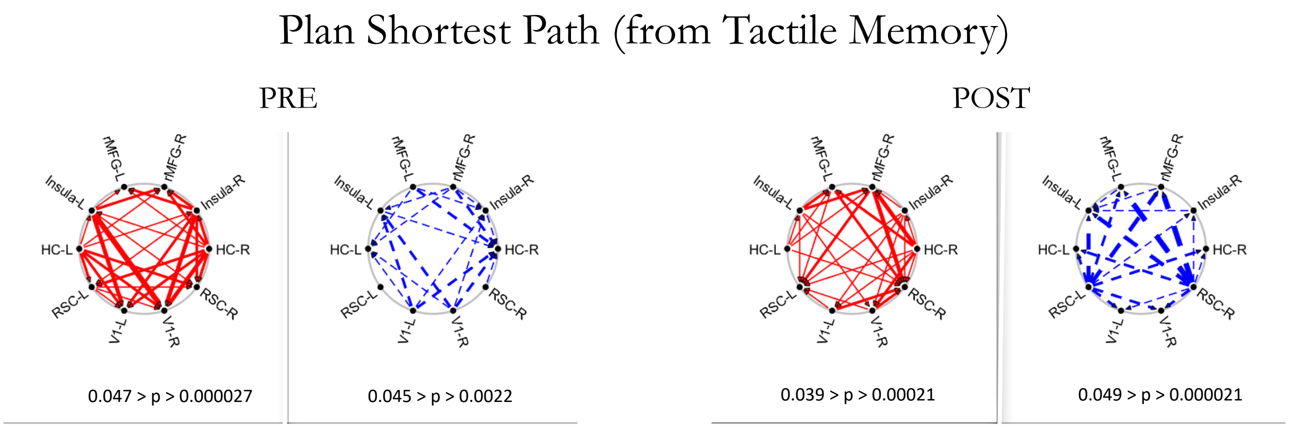


FIG. 5. Granger Causal connectivity for planning (in memory) the shortest path (PSP), in the same format as Fig. 4.

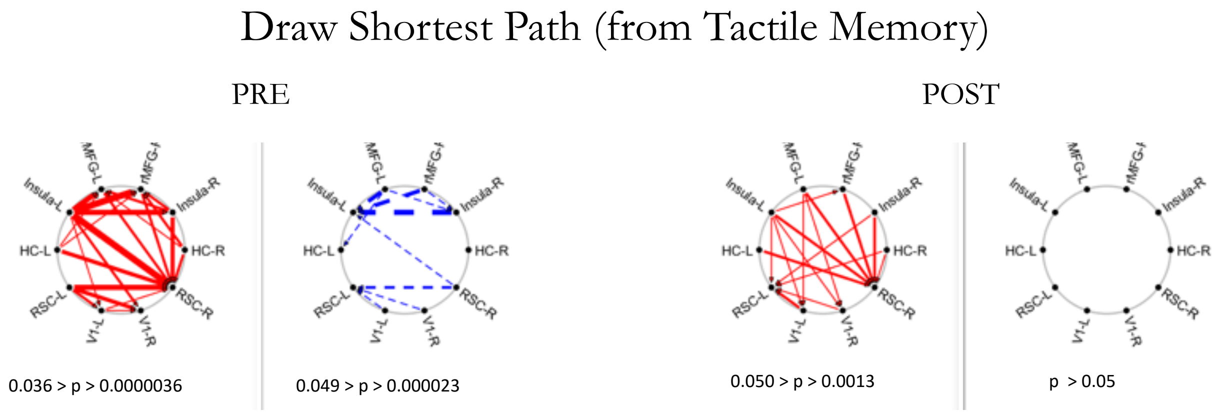
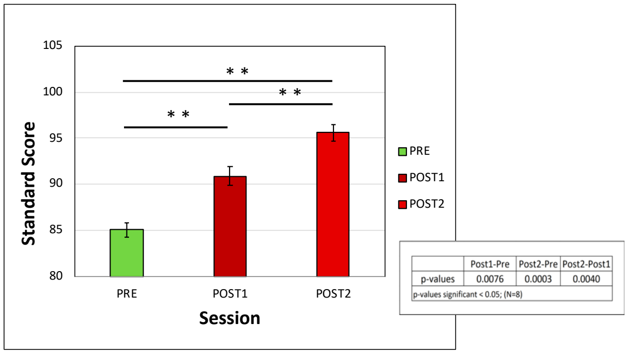


FIG. 6. Granger Causal connectivity for drawing the shortest path guided solely by memory, in the same format as Fig. 4.

Inverse Granger Causality: *Training-driven network reorganization.* The *Pre-training* inverse connectivity for drawing the shortest path (blue arrows in Fig. 6) was again in the opposite (feedback) direction to the congruent influences, but predominantly for the interhemispheric connections for the left and right insula and RSC regions. These dropped out entirely in the Post-training condition, consistent with the reduced strength of the congruent connectivity in this condition.

Transfer of C-K Training Effects to Untrained Abilities: Highly significant and sustainable generalization to spatio-cognitive abilities

Would the translation to navigation of the Likova Cognitive-Kinesthetic training preserve its power of being an ***active instigator*** of core spatio-cognitive improvements? Would it continue to operate simultaneously in many neural subsystems and, hence, fulfil the demand for



	Post1-Pre	Post2-Pre	Post2-Post1
p-values	0.0076	0.0003	0.0040
p-values significant < 0.05; (N=8)			

FIG 7. Highly significant and sustainable generalization/ transfer of the C-K training effects to untrained spatio-cognitive abilities were found in the navigational implementation of the C-K Training as well, further confirming our previous finding in the manual domain application of the training (Fig. 2). Plotted bars are normalized average Standard Scores by testing session (PRE – Green), (POST1 – Dark Red), (POST2 – Red) for 8 subjects, which all completed PRE-POST1-POST2. Normalization was performed by taking the mean of all subjects for each testing session and a final terminal mean across all-participants of the 3 sessions, rescaled to 100 ± SEM.

spectrum rehabilitation through a single training method? The results (Fig. 7) strongly confirmed our previous findings of a highly significant and sustainable transfer of the C-K training effects to untrained spatio-cognitive abilities.

DISCUSSION

In overview, the predominant causal connectivity in this navigational network during ***drawing of the full map*** in the initial session prior to training was that of a primary influence of the left insula on all the right-hemisphere ROIs in the navigational network (except for the right hippocampus). The main result of the C-K training on this connectivity was that it became an almost completely symmetric array of top-down influences bilaterally from the executive control center of the Middle Frontal Gyrus, the insula and the hippocampus to the posterior cortical regions of the retrosplenial cortex and V1. (The main exception to this symmetrization was that the newly-acquired bilateral hippocampal influences went only to the right retrosplenial ROI.) Thus, the result of the C-K training was to convert from the left-dominated influences expected from the local left-hemisphere control of the (right) drawing hand to a more whole-brain pattern typical of full cognitive involvement in the spatial memory retrieval task.

While the top-down influence of the Middle Frontal Gyrus in the map-drawing task is expected in view of encompassing the executive control center, the dominant role of the insula may be moresurprising in view of its association with bodily interoceptive functions. However, the insula has been found to be activated in navigational tasks, along with the traditional navigation regions of the hippocampus and precuneus (including the retrosplenial cortex) by Ghaem et al. (1997). Moreover, the anterior insula, with its unique complement of von Economo neurons associated with long-distance control and mirroring behavior, has also been associated with the representation of the individual spatial viewpoint, as in the tasks involving the alternation between the egocentric and allocentric viewpoints that are necessary for effective map reading and planning (Evrard, Forro & Logothetis, 2012). Such findings were the basis for including the insula in the navigational network, as is amply justified by its predominant role in the top-down causal influences during our navigational drawing task. The pronounced increase in activation of the insula may be related to the subjective experience of ‘travelling’ through the map as it is being drawn.

The inverse causal influences further support the strong symmetrization effect of the C-K training, in that they were almost entirely emanating from the right ROIs toward the left before training (primary from the hippocampus), switching to symmetrical bottom-up influences to the insula after training. Thus, the general direction was opposite to that for the congruent influences, supporting the interpretation that the inverse influences were playing the role of a recursive feedback control function for their neural pathways.

The picture for the *navigational tasks* of *planning-from-memory* and *drawing of the shortest paths* through the maps was interestingly different, though consistent with the above interpretation in relation to the cognitive/motor involvement in the tasks. Thus, *planning the shortest path* is a purely cognitive task with no motor component, and showed largely symmetric influences again from the insula and hippocampus bilaterally for the congruent form of connectivity before training, and to these same areas for the inverse connectivity. It is notable that this pair of regions have indeed been strongly associated with complex spatial representation, navigation and the interplay of egocentric and allocentric perspectives in scene perception.

Following the training, these influences markedly diminished and were replaced by right-hemisphere-biased influences from (for congruent) and to (for inverse) the Middle Frontal Gyrus, focused on the posterior retrosplenial areas. Thus, the training-induced reorganization brought the Middle Frontal Gyrus into its executive control mode, where it had been solely a recipient of navigational information prior to training. The inverse influences were again predominantly in the opposing direction expected for the feedback control function for the congruent influences, though such feedback was missing for the hippocampus bilaterally.

The congruent causal influences returned to the left-lateralized pattern for the *drawing of the shortest paths* (as planned from the memory of the full map), with a very similar picture to the drawing of the full map, except for a stronger left-to-right influence between the retrosplenial areas. Evidently drawing the shortest path was initially just as engaging as drawing the full map, presumably because the participants were still having to reconstruct the full map in their minds as they recalled the requisite path. After training, the connectivity was notably reduced, though maintaining very much the same asymmetric pattern as before the training, suggesting that the participants had become more efficient in recalling the trajectory to be reproduced from their memory of the best path, and could draw it with a reduced cognitive load.

Finally, we asked whether translating the Likova Cognitive-Kinesthetic training to navigation would preserve its power of being an *active instigator* of core spatio-cognitive improvements, based on its philosophy of a method that operates simultaneously in many neural subsystems. The results (Fig. 7) strongly confirmed our previous findings (Fig. 2), as well as our hypothesis of a highly *significant* and *sustainable generalization/ transfer* of training effect of this single training method to a wide-spectrum of (untrained) fundamental spatio-cognitive abilities that are of key importance in everyday tasks.

CONCLUSIONS

These results establish the profound reorganization of neural activation in cortical regions for spatial navigation by the brief period of the Likova C-K training regimen. This shows that it does not take a lifetime of driving a taxicab, for example, to develop this degree of improvement and the access and utilization of spatial memory, which is of supreme importance in the blind as a multipurpose substitute for the many roles of vision in the sighted. By extending our previous findings from the manual to the navigation domain, the present study demonstrates the power of a multidisciplinary approach incorporating art, behavioral and neuroscience methodologies to drive much-needed plasticity in the adult brain.

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AUTHOR CONTRIBUTIONS

LTL conceptualized and supervised all phases and analyses of the study, developed the C-K training method and wrote the paper; ML ran the training and behavioral testing; ZZ ran the fMRI & GC analyses; CWT contributed to the supervision of the brain imaging methods and collaborated in writing the paper.

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