PROTOCOL TITLE: Spatial Cognitive Training in Visual Impairment

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Relevance: This study is consonant with the mission of the CVNR, directed by the PI, and will take advantage of the resources of the Center and its primary University affiliate for recruitment of blind participants through the CVNR Registry, the Atlanta VA Eye and Low Vision Clinics and the Emory Eye Center, behavioral testing and training in CVNR space, expertise in use of tele-rehabilitative technology, and acquisition and analysis of neuroimaging data using state-of-the-art resources at Emory University. Vision loss is a highly significant problem in the veteran population, and the long-term goal of this research is the application of current neuroscientific insights to design novel rehabilitative approaches for visual rehabilitation of veterans with vision loss. The present project is intended as a proof of concept for the utility of spatial cognitive training for low vision and blindness rehabilitation. The advantage of the spatial imagery task for training is that it can be used in the laboratory or home to train path integration skills in a safe environment. Providing the training over a telehealth interface enhances its potential for practical applicability. If successful, the training approach used here will be further built upon in future research, by extending path integration training from the spatial imagery context into real-world contexts to enhance cognitive map formation. Such training will then be developed into a rehabilitative program that can be used to complement currently used O&M training.

Background and Significance

Vision loss is a huge problem worldwide: the WHO estimates about 285 million people globally have vision loss, of whom about 39 million are blind (Pascolini & Mariotti, 2012), i.e. have visual acuity of 20/400 or worse, as defined in the International Classification of Diseases, 10th Revision (ICD-10). Corresponding estimates in the US are over 3.6 million with visual impairment of whom 1 million are legally blind, i.e. with visual acuity of 20/200 or worse (National Eye Institute, 2012). Vision loss is of profound significance to the veteran population, leading causes being macular degeneration, glaucoma and diabetic retinopathy. An estimated 1 million veterans are visually impaired, including about 131,581 veterans in the US who are legally blind. Thus, it has been – and continues to be – vital that the VA invest in low vision and blindness rehabilitation. The VA has led the way in seeking to establish an evidence base for low vision rehabilitation: a multicenter, randomized clinical trial concluded that an outpatient low vision VA rehabilitation program for patients with macular disease was beneficial for a number of visual function outcomes (Stelmack et al., 2008). However, more targeted research is needed across the range of rehabilitative interventions for low vision and blindness.

Conventional programs for rehabilitation of Veterans who are legally blind utilize a set of training courses (e.g., home and daily living skills). Among these is “Orientation and Mobility” (O&M) training. The VA was largely responsible for the development and spread of O&M training (Welsh, 2005), which evolved in clinical settings based on years of trial and error experience (Guth et al., 2010; Wiener & Sifferman, 2010). O&M instructors tailor instruction to meet individual needs, typically using widely divergent approaches toward accomplishing similar objectives (e.g., Wiener, 2004 vs. Altman & Cutter, 2004). A Cochrane review concluded that there is little evidence to indicate what specific O&M training procedures are best (Virgili and Rubin, 2010).

Spatial cognition is critically important for navigating our environment. Cognitive psychology and cognitive neuroscience approaches have produced substantial gains in our understanding of spatial cognition (e.g. Derdikman and Moser, 2010; Landau and Lakusta, 2009; Sack, 2010), and have also begun to yield some insight into the nature of spatial cognition in the visually impaired (Long and Giudice, 2010). It is important to note that there is wide variability in spatial cognitive abilities in the normal population. Some individuals excel at spatial tasks and others perform poorly; those with poor spatial skills tend to rely on non-spatial strategies such as object (iconic) imagery or verbalizing (Kozhevnikov et al., 2005; Blazhenkova and Kozhevnikov, 2009). The sighted can compensate for poor spatial skills, e.g. using signs and visible landmarks, which is facilitated by parallel processing in vision. When sighted people lose their spatial cognitive abilities as a result of stroke, dementia, traumatic brain injury (TBI), etc., their ability to function in the community, home and workplace is severely limited.

People with severe visual loss, especially in the peripheral visual field, are also at a profound disadvantage and have difficulty in compensating for poor spatial skills. For instance, loss of vision results in inability to gauge distance (Geruschat & Smith, 2010). In a mobility context, distance affords anticipation: the ability to preview the travel path ahead and quickly orient to its spatial structure – e.g., a sighted person can quickly and without much attention, acquire critical spatial information, finding entrances and exits, offices, restrooms, etc., when walking into a building (Geruschat & Smith, 2010). People who are blind tend to rely on egocentric reference frames (i.e. orienting with respect to oneself) but have difficulty maintaining orientation in allocentric coordinates (i.e using external frames of reference); thus, O&M instructors incorporate training to aid orienting in space, including teaching exploratory strategies and using small-scale tactile maps to provide a sense of specific spatial layouts before navigating them (Long and Giudice, 2010). While such training can improve spatial cognitive function, there is a consensus that more research is needed to optimize spatial cognitive training to enhance the function of visually impaired individuals (Guth et al., 2010; Long and Giudice, 2010).

In previous work from our laboratory, we showed that acquired blindness is associated with impairment on a spatial imagery task (Occelli et al., 2014). Performance on this task correlated positively with scores on a validated index of real-world spatial navigational abilities, the Santa Barbara Sense of Direction Scale (SBSoDS)(Hegarty et al., 2002). Thus, spatial cognitive abilities represent a potentially important target for rehabilitation of individuals with vision loss, and the spatial imagery task offers a useful tool to both index and provide a training ground for spatial ability that can generalize to the real world. Studies in the normally sighted indicate that spatial training can indeed improve spatial skills but that individual differences are important to consider during training (Hegarty et al., 2008; Keehner et al., 2006; Fields and Shelton, 2006). Furthermore, the effects of such training can generalize to untrained spatial, but not verbal tasks (Wright et al., 2008), and spatial abilities are correlated across various tasks (Hegarty and Waller, 2004; Picard and Pry, 2009). However, there are no parallel published reports, to our knowledge, on the efficacy of such spatial cognitive training for low vision or blindness rehabilitation. Spatial cognition was highlighted as one of the areas of key strategic importance for research into low vision and blindness rehabilitation (National Eye Institute, 2012) – the panel responsible was co-chaired by the consultant of the present proposal, Dr. Sathian.

We hypothesize that evidence-based spatial cognitive training would inform the development of more effective training interventions for rehabilitation of veterans with low vision and blindness, that would complement and enhance existing O&M training programs. The training methods employed in this proposed study differ from those currently used in O&M training, in that they focus specifically on the ability to perform mental path integrations while imagining movement along a pathway of selected points in a grid pattern, with the help of audio-haptic cues. Path integration is important for formation of cognitive maps, which in turn are critical for effective spatial navigation. Training will be performed in the Veterans' homes using iPads and live video connections via the internet. We will also assess how the training translates to the physical world. As such, the results will lead to potentially more effective methods that can be used to complement existing O&M training approaches.

Preliminary Studies

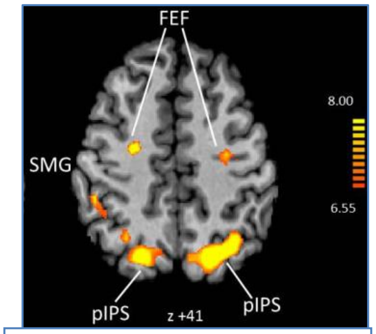


Figure 1. Activations due to spatial imagery in the frontal eye field (FEF), supramarginal gyrus (SMG) and posterior intraparietal sulcus (pIPS). Color t scale on right. From Lacey et al., 2014.

The basis for the proposed work is our published behavioral study in non-veterans showing that people with acquired blindness are significantly impaired, relative to matched controls, on a spatial imagery task requiring mental navigation through an imagined grid, directed by auditory cues (Occelli et al., 2014). Importantly, performance on this task, which was designed in our laboratory, correlated positively with scores on a validated index of real-world spatial navigational abilities, the Santa Barbara Sense of Direction Scale (SBSoDS)(Hegarty et al., 2002), demonstrating that the task indexes ecologically relevant spatial cognitive capacity. We also used this spatial imagery task in an fMRI study with normally sighted subjects (Lacey et al., 2014) and showed that this task activated regions known to be involved in spatial cognition (**Fig. 1**).

The imagery task used in these earlier studies employed a 4x4 grid with letters marking the cells of the grid. This grid required considerable effort on the part of the subject to memorize. Hence, we modified it using numbers (1-25) instead of letters, and slightly expanded the grid to a 5x5 grid to allow for more options during testing and training. Because the numbers occur in standard sequence, memorization of their positions in the cells of the grid is much easier. We used this 5x5 grid in a study comparing spatial imagery abilities of congenitally blind subjects and sighted controls (Occelli et al., 2015), demonstrating the feasibility of using this task. We are currently testing this task in blind veterans and matched controls to ensure replication of our earlier findings in non-veterans (Occelli et al., 2014).

Collectively, these studies provide evidence of our group's familiarity with behavioral and fMRI studies of spatial cognition. The consultant, Dr. Sathian, also has considerable experience with behavioral and fMRI studies of cognitive rehabilitation of patients with memory deficits (Hampstead et al., 2008, 2011, 2012 a,b) as well as with behavioral and fMRI studies of perceptual learning in normal people (Sathian & Zangaladze, 1997, 1998; Sathian et al., 2013). Critically, these fMRI studies of learning and rehabilitation controlled for non-specific effects that could stem from repeating the same task in the scanner, by including a control condition without training, with testing for a task-by-session interaction and thus enabling identification of training-specific effects (Hampstead et al., 2011, 2012b; Sathian et al., 2013). These studies therefore speak to our ability to conduct the proposed behavioral training interventions and the linked fMRI studies, as well as to analyze and interpret the data. Moreover, the Dr. Sathian has considerable prior experience in investigating behavioral and neural changes associated with blindness (Grant et al., 2000; Stilla et al., 2008) and with reviewing the literature in this field (Sathian, 2000, 2005, 2006, 2014; Sathian & Lacey, 2007; Sathian & Stilla, 2010).

In order to lay the groundwork for a future Merit Review proposal investigating the utility of spatial cognitive training in visual rehabilitation, the currently proposed SPiRE project seeks to establish the feasibility of such training in visually impaired participants over a telehealth interface, to obtain data on the effect size of the training relative to a control intervention to provide a basis for sample size estimation in a larger clinical trial, and to examine the relevant neural mechanisms so as to suggest possible synergistic interventions that would enhance the effects of spatial cognitive training. Importantly, the proposed work will examine the real-world generalizability of the training effects using physical walking spaces to assure relevance to rehabilitation.

Research Design and Methods

PARTICIPANTS

We will recruit 60 blind participants, randomized by our CVNR statistician into two groups. One group will undergo the experimental intervention (spatial cognitive training) and the other will undergo a control intervention involving letter-number matching. The participants will include women and minorities in proportion to the demographics of the veteran population attending the Atlanta VA. Working with our statistician, we calculated that this sample size has a power of 0.81 to detect an effect size of 0.9 with $\alpha=0.05$ and $\beta=0.19$. The randomization process should result in a balance between the intervention and control groups with respect to a range of variables, including age, sex, age of onset of visual loss, duration of visual loss and of loss of light perception, and comorbid conditions; any residual differences will be accounted for as covariates in statistical analyses.

Since the participants are blind or have low vision, they will need transportation to the CVNR, which will be provided via a contractual arrangement in place with the CVNR. Subjects will be compensated for their time at a flat rate of $150 for participation in all sessions of the study. If they drop out or are otherwise unable to complete the study, compensation will be prorated for the number of sessions they participate in.

Inclusion criteria: Ability to detect movement (such as hand movement), with an inability to detect details (such as the number of fingers being held up by the hand), with stable visual loss over the past year. We anticipate that causes of blindness will be ocular, including glaucoma, diabetic retinopathy and macular degeneration, the most common causes of blindness in veterans, as well as possibly late-onset Leber's optic atrophy and ocular trauma (in the absence of TBI). To minimize heterogeneity due to variations in age and the duration of visual loss, we will restrict enrollment to Veterans and Non-Veterans over the age of 50 who lost light perception within the last 5 years, and who have completed standard O&M training. From a practical standpoint, this also enables us to focus on those who can potentially benefit most from the proposed intervention.

Exclusion criteria: Participants will be excluded if they have any neurological condition, such as TBI, history of blast exposure, stroke, brain tumors, epilepsy etc. They will also be excluded if MRI scanning is contra-indicated, e.g. due to an implanted device such as a pacemaker, or foreign bodies of ferromagnetic nature. Cognitive screening will be performed using the Repeatable Battery for Assessment of Neuropsychological Status (RBANS, Randolph, 1998) and those with cognitive impairment will be excluded based on a score of 1.5 SD below the mean for the Verbal Memory Index. We will test subjects' hearing using a validated screening questionnaire (Screening Version of the Hearing Handicap Inventory for the Elderly, HHIE-S, Wentry & Weinstein, 1983, Lichtenstein et al., 1988) followed by assessment of audiometric pure tone (0.5, 1.0, 2.0, 4.0 KHz) hearing thresholds in the CVNR sound booth. Those with more than mild hearing loss (HHIE score >8 or audiometric thresholds >40dB) will be excluded (Wentry & Weinstein, 1983; Wilson, 2009), given that we are relying on audio cues. CVNR investigator Dr. Echt has considerable experience with audiometric testing and will train the research assistant working on this project to perform testing (see letter of support). We will also exclude visually impaired veterans who are dependent on a wheelchair or scooter for mobility, as they will not be able to take part in the real-world task. Although visual disturbances following TBI are clinically important, they are heterogeneous and blindness is uncommon after TBI; thus, rehabilitation of visual problems after TBI will likely require approaches differing from that in the present proposal. Given the likelihood that many veterans with visual loss will be over the age of 65, it is recognized that they may have a number of comorbid conditions, including diabetes, hypertension and cardiovascular disease. These will not, however, be automatic exclusion criteria, although such conditions will alert us to the possibility of confounding conditions such as white matter disease – if their MRI scans obtained for clinical reasons or during the course of this research show more than minimal white matter disease, they will be excluded.

Participants will be enrolled after signing informed consent according to protocols approved by the local IRB and R&D Committee. They will be recruited from a registry of visually impaired persons maintained by the CVNR, the Ophthalmology and Low Vision clinics at the Atlanta VA, as well as the community secondary to difficulty in recruiting a sufficient number of subjects from the Atlanta-based veteran population. An advertisement will be placed on the CVNR website. Based on projections modeled by Michael Williams, PhD, of the VA Blind Rehabilitation Service National Program Office, we estimate that in 2015 there are approximately 234 veterans with no light perception in the counties constituting the catchment area of the Atlanta VAMC, with this prevalence estimated to increase to 249 in 2020. Thus, we anticipate no difficulty with recruiting the required number of blind participants for this study. The research assistant will make contact with visually impaired subjects in the IRB-approved CVNR registry and with appropriate patients seen at the Atlanta VAMC Eye Clinic and Low Vision Clinic and Emory Eye Center to screen them for potential eligibility, and recruit eligible subjects. We have experience using these methods to recruit subjects for studies at the CVNR.

PROCEDURES

Specific Aim I will test the hypothesis that spatial cognitive training of blind participants on a spatial imagery task leads to improvements in **(a)** performance on the trained spatial imagery task and **(b)** real-world navigational ability, relative to a control intervention. **Specific Aim II** will use fMRI to assess the neural changes associated with spatial cognitive training, as assessed by the spatial imagery task. The hypothesis is that those in the spatial cognitive training group will show enhanced activation in and connectivity of brain regions mediating spatial processing, such as the hippocampus and dorsal frontoparietal cortex, as well as more distinct neural representations of imagined paths.

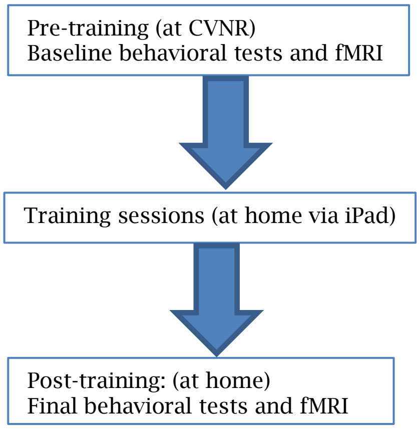
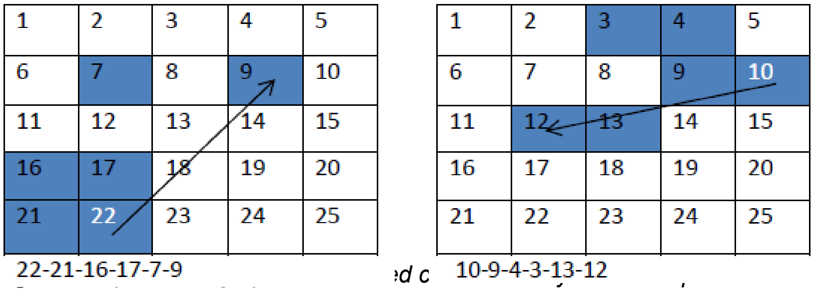


Figure 2. Study flow.

Study flow (**Fig. 2**): Participants will take part in an initial session of behavioral testing and fMRI scanning, and another similar session after training. In the intervening 3 weeks, they will attend 12 training sessions of one hour each, comprising either the experimental or control intervention. These sessions will take place each weekday from Monday-Thursday, beginning the Monday after the initial session, and will be conducted via the internet with the participant at home, using CVNR-issued iPads. The Friday of each week will be used for repeat testing on the spatial imagery task to assess the extent of improvement as a result of the preceding four days' training. This design allows 12 hours of training over 3 weeks, comparable to that used in prior studies of spatial cognitive training (Wright et al., 2008; Terlecki et al., 2008). In addition, it allows us to assess weekly improvement, thus providing crucial data for design of a larger study in the future. Importantly, CVNR investigators have experience using iPads with their built-in accessibility for those with visual impairments, and experience with this kind of telehealth application. They have found that even older, technologically naïve caregivers (mean age 78±4.1) can learn to use novel technologies such as the iPad; with a high degree of reported satisfaction (Griffiths et al., 2016). Specifically, Co-investigator Ross has expertise in use of telehealth technology with visually impaired participants in a VA project where he assessed the accessibility of smart phones including the iPhone and in an NIH SBIR project in which the accessible and award-winning MoneyReader app was developed for the iPhone and iPad. The training sessions will employ a haptic grid overlay on the iPad screen during training, and software will be developed to enable remote communications and viewing of the subject's movements and finger position on the screen of the iPad.

Spatial imagery task: The imagined grid used for the spatial imagery task as well as for spatial cognitive training will be a 5x5 grid using the numbers 1-25, with 1-5 on the first row from left to right, 6-10 on the second row from left to right, and so on (**Fig. 3**). Participants will first be familiarized with the grid using a haptic model. The spatial imagery task involves presentation of auditory cues to a four- or five-step sequence in the grid, with the constraint that there will be no diagonal sequences. Participants are asked to imagine the sequence and mentally compute the shortest path back to the start from the end-point (**Fig. 3**). This is termed path integration and is a test relevant to formation of cognitive maps, which is a key aspect of spatial navigation. Participants will use a joystick to indicate via the direction of the shortest path from the end-point to the start.



1	2	3	4	5
6	7	8	9	10
11	12	13	14	15
16	17	18	19	20
21	22	23	24	25

1	2	3	4	5
6	7	8	9	10
11	12	13	14	15
16	17	18	19	20
21	22	23	24	25

Initial positions: white numbers. Arrows: shortest paths from initial to final position, intersecting with mentally traced sequence (right) or not (left).

Real-world task: A textured 5x5 grid will be laid out on the floor of the CVNR Movement Studies Laboratory (MSL). Each cell of the grid will be a square of 32 inches side (based on an average step length of 32 inches). Subjects will be oriented to the grid by walking around the grid, just inside the perimeter, and also walking across the grid starting in the central cell of an end row, walking directly across to the central cell of the opposite end row, then back to the start, and repeating the process for the orthogonal direction. These orienting steps will be repeated a few times until the subject is comfortable with the layout of the grid and the corresponding cell numbers. Then, audio cues will be presented directing the subject to walk in sequences similar to those in the spatial imagery task. Movable lengths of 2x4's will be used to bound the specific paths to walk, the subject using his/her long white cane in a natural way to detect the 2x4's as the edge of the path being walked. The 2x4's will help the subject walk in straight lines along the path, and insure they turn at the correct points. The MSL is equipped with a WorldViz PPT tracking system that can track motion using up to 32 sensors. Once the sequence is completed, the subject will be instructed to point to the starting location using the cane. Infrared transmitters affixed to the cane for the session will detect and record the pointing angle (to an accuracy of ±4° of solid angle), and performance will be measured as the angular error of pointing.

Interventions: The experimental intervention (spatial cognitive training) will comprise repeated practice of the spatial imagery task with feedback after each trial. Training will be conducted in the participant's home using an iPad issued to the subject at the initial visit, and live video communication with a research assistant at the CVNR over the internet. The iPad will be programmed to allow administration of the spatial imagery task. As in the version of the spatial imagery task administered at initial and final testing, audio cues will trigger mental navigation through the grid using audio cues, with haptic reinforcement via tactile overlays for the screen (to permit sensory facilitation of learning). Following each sequence traced, subjects will be asked whether the shortest path back to the origin intersects with the sequence traced or not. If the answer is incorrect, the research assistant will show the correct path for the subject to trace mentally and haptically. In the control intervention, subjects will be taught letter correspondences to the numbers (e.g. 1->A, 2->B and so on until 25->Y), using a similar setup and procedure as in the experimental intervention.

Behavioral measures: The following behavioral measures will be collected before and again after training with the experimental and control interventions: (1) Performance (directional accuracy and response time [RT]) on the spatial imagery task will be acquired during fMRI scanning. (2) In addition, pointing accuracy will be measured on the real-world path integration task in the MSL, in terms of the angular difference between the target of pointing and the actual initial position. (3) We will also measure performance, with standardized neuropsychological tests, at baseline as well as at post-training, on (a) spatial memory using a haptic version (produced in the Sathian lab using textured blocks) of the Corsi block test (Kessels et al., 2000), (b) the verbal memory tests of immediate and delayed memory from the RBANS (Randolph, 1998) and (c) verbal working memory tested by the Forward and Backwards Verbal Digit Span test from the Wechsler Adult Intelligence Scale (Wechsler, 2008). A research assistant will be trained by the PI and David Ross, Co-investigator on this project, to administer all the tests, as well as the training procedures.

Imaging measures: The following imaging analyses will be conducted on data acquired before and again after training with the experimental and control interventions: (1) A univariate contrast between the experimental and control conditions will provide insight into the brain regions responsible, and the **magnitudes of activation** in key brain regions will be assessed. (2) Multivariate pattern analyses (Kriegeskorte, 2008) will be used to assess **representational similarity in the neural representations of paths**. (3) Further, we will use **multivariate effective connectivity analyses**, which our group has considerable experience with (Hampstead et al., 2011; Sathian et al., 2013; Lacey et al., 2014), to examine patterns of connectivity during task performance. (4) In addition, we will assess **resting-state connectivity** patterns using the activated regions as seeds. (5) Finally, we will also acquire diffusion tensor imaging (DTI) scans to assess **structural connectivity**.

Imaging design: The same spatial imagery task as outlined above will be used during fMRI scanning in an event-related design, with pseudorandomly interleaved trials of a control task requiring judgment of whether the majority of numbers in the audio sequence are odd or not. On each trial, the stimulus presentation will occupy 4s or 5s, depending on whether the sequence comprises 4 or 5 steps in the grid. These two trial durations will be interleaved in pseudorandom order, as will experimental and control trials. Participants will be verbally instructed to make their keypress response following the last auditory cue. A blank interval varying from 4-8s will intervene between trials: this jitter allows for better estimation of the signal on each trial than designs with a fixed inter-trial interval. Each run of trials will also include six pseudorandomly interspersed 10s blank periods for estimation of baseline signal. Functional runs will last 9min 20s, comprising a total of 40 trials (20 experimental and 20 control). 4 such runs will be conducted.

Imaging parameters: Imaging will be conducted on the Siemens Magnetom Prisma 3T MR scanner in the Biomedical Imaging Technology Center at Emory University Hospital. **Structural** scans comprise a T1- and T2-weighted (T1w, T2w) scan. The T1w scan uses a 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence (repetition time (TR)=2400 ms; echo time (TE)=2.14 ms; inversion time=1000 ms; flip angle (FA)=8°; bandwidth (BW)=210 Hz/Px). The T2w scan uses a 3D T2-SPACE sequence (TR=3200 ms; TE=565 ms; variable FA; BW=744 Hz/Px). For both sequences, field of view (FOV)=224×224 mm; 0.7mm isotropic voxels; iPAT factor=2. **Functional** scans, which measure the blood oxygenation level-dependent (BOLD) signal, are acquired using gradient-echo echoplanar imaging (EPI) sequences (TR=1000 ms; TE=25 ms; FA=52°; field of view (FOV)=208×180 mm; 72 slices; 2.0 mm isotropic voxels; multi-band factor (MBF)=8; echo spacing (ES)=0.58 ms; BW=2290 Hz/Px). **DTI scans** use a spin-echo EPI sequence (TR=5520 ms; TE=89.5 ms; FA=78°; refocusing FA=160°; FOV=210×180 mm; 111 slices with 1.25 mm isotropic voxels; MBF=3; ES=0.78 ms; BW=1488 Hz/Px; phase partial Fourier 6/8).

PROTECTION OF HUMAN SUBJECTS

Sources of materials

No specimens will be obtained. Research data consist of performance data acquired during behavioral and scanning studies and MR imaging data, all obtained solely for the purpose of the research outlined. Upon enrollment, participants will be assigned code numbers and all data acquisition and analysis will be performed using these de-identified code numbers, with the keys linking to individual identifiers being secured along with any private health information and individually identifiable information on password-protected computers and in locked file cabinets within locked laboratories.

RISKS TO HUMAN SUBJECTS

Potential risks

MRI scanning

A risk of MRI scanning, which is in very wide general use, is the possibility of damage created by movement of a ferromagnetic metallic implant or foreign body such as a pacemaker or aneurysm clip. As is routine, any subject with such an implant or foreign body will be excluded by meticulous screening of subjects by an experienced MRI technologist. There is also a small risk of thermally induced burns caused by electromagnetic loops; care will be taken by an experienced MRI technologist running the scanner to exclude such loops. With these precautions, MRI scanning is safe.

Behavioral

The blind participants are at somewhat higher risk of falling, compared to sighted people, during testing, particularly during the real-world assessment in the Movement Studies lab. However, a trained member of the research team (the research assistant) will be present at all times to closely watch the participants and ensure they do not fall. Other than this, there are essentially no risks to the behavioral tests. Confidentiality is routinely protected by coding all imaging and other data. Publications do not identify individual subjects.

ADEQUACY OF PROTECTION AGAINST RISKS

Recruitment and informed consent

Participants will be enrolled after signing informed consent according to protocols approved by the local IRB and R&D Committee. They will be recruited from a registry of visually impaired research participants maintained by the CVNR, as well as from the Ophthalmology and Low Vision clinics at the Atlanta VA and The Emory Eye Center. An advertisement will be placed on the CVNR website. Consent will be obtained by a trained staff member. The consent form and all advertising material will be IRB-approved. All risks and the research nature of the study will be clearly explained to each potential subject, whose consent will be completely voluntary.

Protections against risk

Subjects with metallic implants or foreign bodies will be excluded. A screening questionnaire is administered by an individual trained in MR safety, to ensure this. In case of doubt regarding a foreign body, we obtain 2-view X-rays of the affected region (e.g. eye); these are reviewed by a clinical radiologist to be cleared for MRI scanning. Electromagnetic loops will be avoided through careful examination of the participant by the MRI technologist. With these precautions, MRI scanning is safe.

Confidentiality is routinely protected by coding all imaging and other data. Publications do not identify individual subjects. Investigators, staff and students working with participants and their data are required by our IRB to undergo training on human subjects protection, and maintain certification by refresher courses every 3 years. All personnel working in the MRI environment also undergo MRI safety training and are supervised by a licensed MRI technologist.

Incidental findings

All the structural MRI scans will be initially reviewed by the MRI technician and if needed, will consult with Dr. Sathian, a neurologist with experience in reviewing clinical neuroimages. In the event incidental findings are noted that might be abnormal, the images will be further reviewed by a clinical neuroradiologist. Any verified abnormalities will be communicated to the participant by the PI or Co-I, and an appropriate course of action will be recommended. Depending on the finding, this recommendation may vary from no action (e.g. in case of a small arachnoid cyst) to obtaining a full clinical series and neurological or neurosurgical consultation. This procedure will be disclosed to participants on the informed consent forms, along with a reminder that the scans to be obtained on the project are not intended for clinical diagnosis.

POTENTIAL BENEFITS

Participants randomized to the experimental intervention may experience some improvement in their spatial skills, which may help them navigate their environment better. Those randomized to the control intervention are not expected to show such gains, but will be offered the opportunity to undergo the experimental intervention after they complete participation. Participants will experience the satisfaction of contributing to scientific knowledge and ultimately to better methods of rehabilitation.

IMPORTANCE OF KNOWLEDGE TO BE GAINED

Vision loss is a highly significant problem in the veteran population, and the long-term goal of this research is the application of current neuroscientific insights to design novel rehabilitative approaches for visual rehabilitation of veterans with vision loss. We propose that spatial cognitive training would be a very useful training intervention for rehabilitation of veterans with low vision and blindness, to complement and enhance existing O&M training programs. **Specific Aim I** will test the hypothesis that spatial cognitive training of blind veterans on a spatial imagery task leads to improvements in **(a)** performance on the trained spatial imagery task and **(b)** real-world navigational ability, relative to a control intervention. If the hypothesis is supported, this would be a simple method of spatial cognitive training with real-world benefits that could eventually be administered via telemedicine. **Specific Aim II** will use functional magnetic resonance imaging (fMRI) to assess the neural changes associated with spatial cognitive training. The hypothesis is that those in the spatial cognitive training group will show enhanced activation in brain regions mediating spatial processing, such as the hippocampus and parietal cortex, as well as more differentiated neural representations of imagined paths. The benefit of pinpointing the neural loci of change is the identification of potential targets for application of converging rehabilitation approaches, e.g. transcranial magnetic or electrical stimulation over parietal regions; enhancing hippocampal neurogenesis through aerobic exercise. If the present proposal is successful, subsequent research will be needed to determine how best to incorporate such training into programs that complement current O&M training.

ANALYSES

In **Specific Aim I**, each behavioral measure will be subjected to a repeated-measures ANOVA with a between-subjects factor of group (experimental, control) and a within-subjects factor of session (pre-training, post-training); the null hypothesis will be rejected in case the interaction is significant at $\alpha=0.05$. If the interaction is non-significant, the Bayes factor will be calculated to ascertain whether this (less likely) supports the null hypothesis or (more likely) reflects insufficient power (Dienes, 2014); in the latter case, the data can be used to estimate the sample size for a subsequent study. In **Specific Aim II**, the imaging measures acquired (except for DTI) will be subjected to similar two-factor ANOVAs as in Aim I, and statistical interpretations will follow similar lines.

We predict that spatial cognitive training, but not the control intervention, will lead to improvements in performance on the spatial imagery task, its analog in the MSL, and the various functional neuroimaging measures. There may be transfer of spatial learning to the spatial memory task, but we do not expect transfer to the verbal memory and working memory measures, indicating the spatial specificity of training. We hypothesize that spatial cognitive training, but not training on the control intervention, will lead to increases in activation in cortex along the IPS and in the FEFs as well as in the hippocampus, increased strength of connectivity between these regions in the task and resting states, and also to more differentiated representations between different paths (i.e. their representations will show higher dissimilarity). The behavioral and neuroimaging measures obtained at baseline, including DTI measures of structural connectivity between the activated brain regions, will be tested as regressors to establish whether they predict changes in the repeated measures. This will be useful to examine the impact of individual differences in pre-training spatial and verbal abilities on the effects of training, and in the design of further studies aimed at targeting interventions tuned to individual performance in specific domains.

TIMELINE
First 2 months: Set up tasks and initiate recruitment
Next 20 months: Test and train 2 subjects per month, one in each group
Last 2 months: Analyze data and prepare publications

FUTURE DIRECTIONS

If this project is successful, the data will be used to support application for a fuller study of spatial cognitive training for visual impairment, using automated versions of the training procedures implemented on iPads and interfaced to the CVNR via the internet. We plan to seek VA Merit or NIH funding for such a study. Subsequent steps would involve incorporation of such training into programs that complement current O&M training. Thus, additional training could involve efficiently learning to navigate the VAMC using remote tele-device training, with subsequent testing and further training of real-world path integration and navigation skills at actual visits to the VAMC. While the focus of the current proposal is limited to participants without light perception in order to minimize heterogeneity, spatial cognitive training and its future developments will be potentially helpful not only for this group of veterans without light perception, but also to the much larger group of legally blind veterans, estimated to number 2336 in the Atlanta VAMC catchment area and 131,581 veterans in the US as a whole in 2015.

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