Collaborative Research Grant Initiative: Mental Wellness in Seniors and Persons with Disabilities

Ideas Fund Final Report

May, 2014 – Giuseppe Iaria & Aiden Arnold
EXECUTIVE SUMMARY

Previous research has documented an age-related decline in different cognitive skills that are critical for spatial orientation and navigation. These declines are especially pronounced in later adulthood and can have a negative impact on the autonomy of senior citizens.

This project had two main objectives. The first was to investigate a brain training paradigm using software developed by Lumos Labs, Inc., which is designed to train numerous cognitive skills that are critical for effective spatial orientation. The training program was designed to run with a group of Mild Cognitive Impairment (MCI) patients referred from the Cognitive Neuroscience Clinic (CNC) at Foothills Hospital, as well as an age-related control group. The second objective was to investigate the neural mechanisms that underlie accurate spatial navigation in order to develop more comprehensive theories on why training different cognitive skills would influence a MCI patient’s capacity to spatially navigate.

Due to a low referral rate of MCI patients from the CNC, we were unable to complete the first objective. The second objective was met and our data provides a novel perspective on how spatial navigation operates in the brain. This has important future implications for understanding how changes in the brain that occur with MCI and Alzheimer’s Disease (AD) may influence spatial navigation ability.

RESEARCH OVERVIEW

Objective(s)

The goal of this project is to investigate the impact of cognitive training on a variety of spatial navigation skills that are known to deteriorate with age and in people with MCI and AD, and to investigate the neural mechanisms associated with spatial orientation.

Background

Previous research has documented an age-related decline in different cognitive skills that are critical for spatial orientation and navigation (i.e., attention, perception, memory, mental imagery and decision-making skills) (Kirasic, 2000; Iachini, Ruggiero, Ruotolo, & Pizza, 2008). This has an impact on the most complex spatial orientation skill - the ability to form a mental representation of an environment – that shows the largest decline in later adulthood (Iaria, Palermo, Committier, & Barton, 2009). This loss of spatial skills increases with age (Liu, Levy, Barton, & Iaria, 2011) and can have debilitating effects on the autonomy of senior citizens (Burns, 1999).

These impairments of spatial skills are especially pronounced in people diagnosed with Mild Cognitive Impairment (MCI) (Mapstone, Steffenella, & Duffy, 2003) and Alzheimer’s Disease (AD) (Braak, & Braak, 1991). MCI is a mild form of cognitive disability and has been proposed to be a precursor for AD (Morris et al., 2001). Recently, studies documenting the spatial impairment resulting from MCI/AD have concluded that training the cognitive skills involved in spatial orientation may have therapeutic value, especially as a preventative measure during the early stages of disease progression (Iachini et al., 2009).

In the context of aging and dementia (MCI transitioning to AD), it is essential to develop an understanding of how cognitive training can be used to prevent and reverse the decline of spatial skills in order to promote well-being and autonomy, as well as to slow disease progression for people with MCI/AD.

Critically, it is important to further investigate the neural mechanisms underlying spatial navigation in humans so that theoretical models can be developed to account for changes in neural function that
result from disease, aging and brain training. Such accounts are imperative to understanding why brain training works, and potential therapeutic influences it has on slowing the age and disease related decline of cognitive skills such as spatial navigation.

**Approach and Methods**

The initial brain training project involved collecting behavioural data from a group of MCI patients, as well as an age-matched healthy control group. We intended to collect pre-training data on performance using a testing battery assessing numerous spatial navigation skills (Arnold et al., 2013), which was then to be followed with a five week training program using Lumos Labs, Inc. software and a final post-training behavioural assessment. However, despite our efforts we received no patient referrals from the CNC. As such, we were unable to conduct this portion of the study.

The neuroimaging phase of the study was conducted at the Seaman Family MR Centre at Foothills hospital. We recruited 14 healthy young individuals (mean age = 22 years), 9 persons with a cognitive deficit termed Developmental Topographical Disorientation (DTD; mean age = 52.67), and 9 healthy control participants age and gender matched for the DTD group (mean age = 51.33). Each group was scanned using magnetic resonance imaging (MRI). We acquired high resolution anatomical images, task-based fMRI while participants completed a series of orientation tasks, and resting-state fMRI.

Our first analysis looked at the neural mechanisms underlying the capacity to make accurate orientation judgments in familiar environments using the sample of 14 healthy young individuals. This skill is critical for supporting autonomous lifestyles throughout all stages of life, and has been shown to have age-related declines (Iaria et al., 2009). To analyze the data, we used a partial least squares (PLS) algorithm to identify the regions of neural activity associated with orientation decisions. We found that the whole group engaged a pattern of neural activity representative of a canonical spatial navigation brain system. Importantly, we then correlated accuracy scores with neural activity and found that high performing individuals engaged additional brain areas known to be critical for spatial navigation (e.g. hippocampus). This suggests that individuals differ in how they configure functional systems during spatial orientation, and the composition of those systems has important implications for explaining variability in orientation skills.

We then followed the preceding analysis with one based on graph theory. Here, we looked at the global efficiency (i.e. the capacity of a network to integrate information) and the centrality (i.e. the importance of a specific region to a network) of the orientation systems we identified in the first analysis. We found that high performing individuals had more efficient networks, and the degree of efficiency was correlated with orientation accuracy ($R^2 = 0.66$). Additionally, we found that the brain regions engaged only by high performing individuals were more central to the networks, suggesting that they facilitate information processing that contributes to accurate orientation. These results have important implications for understanding how rehabilitative strategies targeting age and disease related declines in orientation and navigation relate to changes in the brain. Specifically, our results suggest that as a person ages into the later stages of life, or is affected by a neurodegenerative disease such as AD, the capacity of spatial memory networks to integratively process information diminishes, plausibly due to a reduced centrality of brain regions such as the hippocampus.

Our second neuroimaging study involved looking at the neural mechanisms associated with DTD. DTD is a developmental cognitive deficit that is associated with a lifelong inability to encode the spatial layouts of environments (Iaria & Barton, 2010). This manifests as a decreased ability to spatially navigate and has a wide reaching impact on personal autonomy. Importantly, understanding how DTD operates at a neural level has the potential to develop theories about how spatial memory operates in the brain.

Our analysis with the DTD and associated control group involved investigating the functional connectivity of brain regions using resting-state fMRI data. Here, we looked at the patterns of functional connectivity associated with the hippocampus. We found that the hippocampus of persons with DTD had reduced connectivity with areas in the prefrontal cortex, which are important for the selection, storage and monitoring of spatial information during navigation. Because the regions of
decreased functional connectivity in the prefrontal cortex overlapped with a widespread brain network known as the default mode network (Biswal et al., 2012), we conducted a follow up analysis to investigate potential changes in default mode network connectivity associated with DTD. We found that the medial prefrontal cortex, a central hub in the brain, had decreased functional connectivity to the right and left superior frontal gyrus, as well as the right inferior parietal lobe. Critically, there were no volumetric differences in brain structures between the DTD and control group. These data suggest that aberrant patterns of functional connectivity between the hippocampus and prefrontal cortex may underlie the cognitive deficits in DTD, and that changes in default mode network connectivity may act as a biomarker to assist in the identification of persons with DTD.

**Key Findings**

The key finding from our first MRI study is that the ability to spatially orient is critically dependent on both the capacity of spatial memory networks to integrate information. As previously noted, this suggests that either positive (i.e. brain training) or negative (i.e. disease related) changes in orientation ability may be related to changes in the efficiency of spatial memory networks. This has important implications for future research, as our perspective provides a quantifiable measure through which to track the impact of training and rehabilitative paradigms. The table below summaries this key finding: (A) shows the topology of the spatial memory network analyzed, while (B) shows the correlation between accuracy in spatial orientation and the global efficiency of the network.

![Image A](image1.png)

![Image B](image2.png)

The key finding from our second MRI study is that DTD appears to be related to decreased functional connectivity between the hippocampus and the prefrontal cortex. This is an important finding as it suggests that deficits in the ability to spatially orient and navigate may be the results of variability in the interaction between brain regions, rather than the activity of a single region alone. Critically, this finding was extended into a default mode network analysis that identified decreased functional connectivity between prefrontal and parietal regions. The default mode network is one of the most pervasive brain networks measurable (Biswal et al., 2012) and changes in its connectivity have been linked to AD, autism spectrum disorder and schizophrenia. This suggests that the patterns of functional connectivity observed in the present study may provide an important biomarker to assist in the identification of persons with DTD. These two results are summarized in figures below. The first figure shows the areas within prefrontal cortex that have decreased functional connectivity with the hippocampus in persons with DTD.
The second figures shows the pattern of functional connectivity within the default mode network (left side) and the difference in correlations between medial prefrontal cortex and the right/left superior frontal gyrus and right inferior parietal lobe between the DTD and control group (right side).

**Conclusions**
Although we could not complete the brain training portion of the study due to a low referral rate, we were able to provide important advances in understanding how spatial orientation operates at a neural level. These findings have important future implications for measuring the influence of brain training paradigms in the healthy population and rehabilitative strategies for persons showing deficits in spatial abilities. Additionally, our DTD study provided the first insight into how the disorder operates at a neural level and provides a potential biomarker that can be developed through future studies to assist clinicians in correctly identifying persons with DTD.

**Implications for Policy or Practice**
As previously stated, the implications for our results are twofold. First, by using network level measures of efficiency and centrality, future studies investigating the influence of brain training and rehabilitative paradigms will be able to quantify the impact of those paradigms on the capacity of cognitive networks to
process information effectively. This provides a novel means to assess the impact of such paradigms on individuals and target populations.

Second, the results from our DTD study suggest that patterns of functional connectivity may be used to assist clinicians in properly identifying persons with DTD from other cognitive conditions that also show deficits in spatial orientation ability. This will be critical for developing proper rehabilitative strategies that properly target the underlying deficit.

DIRECTIONS FOR FURTHER RESEARCH
The most important follow up study from our data is to evaluate the relationship between brain training, neural plasticity and clinical rehabilitation. Future studies can use our results to investigate the correlation between brain training paradigms in healthy and clinical populations (i.e. MCI and DTD) and changes in structural and functional connectivity in spatial memory networks. Such an evaluation would be able to identify how brain training alters the neural functioning of mechanisms critical for spatial orientation, and allow researchers and clinicians to quantify the efficacy of training paradigms.

KNOWLEDGE DISSEMINATION AND TRANSLATION ACTIVITIES
We have published some of our results in a major international journal and are in the process of publishing additional manuscripts. Our data has also been presented at provincial and international conferences. See publications/presentations section below for details.

PRINCIPAL APPLICANT (TEAM LEADER)

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<tr>
<th>Name</th>
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<th>Topics of interest</th>
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<td>Lumos Labs Inc</td>
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PUBLICATIONS AND PRESENTATIONS

Publications


Presentations


ABOUT THE ALBERTA ADDICTION AND MENTAL HEALTH RESEARCH PARTNERSHIP PROGRAM

The Alberta Addiction and Mental Health Research Partnership Program is comprised of a broad-based multi-sectoral group, representing service providers, academic researchers, policy-makers and consumer groups, working together to improve the coordination and implementation of practice-based addiction and mental health research in Alberta.

The mission of the Research Partnership Program is to improve addiction and mental health outcomes for Albertans along identified research priority themes, by generating evidence and expediting its transfer into addiction and mental health promotion, prevention of mental illness, and innovative service delivery.

The Research Partnership Program sets out to increase Alberta’s excellence and output of addiction and mental health research findings, and to better translate of these findings into practice improvements.
REFERENCES


