Building Capacity for Music Therapy Research: Revealing the Neural Basis of Music Skill Learning Using MR-Safe Instrumentation

Subject of Research

Rationale. The importance of learning and practice for skilled musicians and performers is universally known and undisputed. Jokes like "Q: How do you get to Carnegie Hall? A: Practice, practice, practice" and story-telling songs like Bryan Adams' *Summer of '69*, which depicts its protagonist practicing his guitar until his fingers bleed, illustrate the well-known importance of practicing for musical performers. Importantly, however, recent research suggests that music practice may not only boost artistic performance, but may also have enormous therapeutic potential in the treatment of neurological disorders and stroke. Practice of music in a medical setting has become a critical treatment in recent years with reported successes in therapies for neurological disorders ranging from autism[1,2] to Parkinson's disease, and in the treatment of aphasias and dyspraxia in stroke patients[3,4]. Further, general music ability and practice may ameliorate some of the neurobiological effects of normal aging.

Music therapy research has shown the importance of music practice in treating neurological conditions. However, so far, this research has been primarily based around showing proof-of-concept demonstrations that music therapy can be an effective technique for certain clinical populations. To continue to make progress in the use of music therapeutically, it will be critical to bridge music therapy research with neurobiological research on learning and memory to develop biologically principled techniques to increase the efficacy of music skill learning interventions. The present study aims to create stronger links between music skill learning and the neurobiology of learning and memory with the goal of translating effective neurobiological learning principles to therapeutic settings. As a first step toward this ultimate goal, with the present funding, we will develop equipment and procedures for measuring the neurobiological basis of music skill learning in a magnetic resonance imaging environment, and test these procedures using expert musicians, healthy young novices, and older adults. This study will directly inform music skill learning interventions in older adults through comparison to expert musicians. These results are expected to generalize to and set the stage for larger funded studies on clinical populations.

Background and Methods. Combining music skill learning with cutting edge research on the neurobiology of learning and memory promises to improve therapies by (1) using neurobiological principles to increase the efficacy of training regimens and (2) offering principled training regimens that are adapted to the unique neurocognitive capabilities of individuals and/or clinical populations. In terms of improving efficacy of training, recent studies on motor sequence learning have helped to increase the efficacy of music skill learning in expert musicians and novices. Investigations, including those conducted by members of our group, have found that music skill learning is impacted by post-training overnight sleep[5-7], the interposition of brief rest breaks during practice[8], learning of similar musical sequences in juxtaposition[9], and distribution of practice across different varied intervals of time[10]. Although findings from these music skill learning studies overlap with studies on general motor skill learning, they have not been incorporated into therapeutic approaches or integrated fully into the neurobiological literature.

The strategies that have been found to promote music skill learning by members of our team are not accidental, but rather intimately tied to the neurobiological process of consolidation that underlies more general learning and memory phenomena, including motor sequence learning[11,12]. Consolidation is a neurobiological process by which memories become permanent and is a critical property of the brain's medial temporal lobe (MTL) memory system[13-15], the neural system most strongly associated with conscious long-term memory. When events or experiences are first encountered, they elicit a cascade of effects at the cellular and molecular level to make the memory of the experience permanent[16]. However, like many biological processes, this cascade is not instantaneous, and instead unfolds over the course of hours, days, and (in some cases) years. While permanent memories for previous experiences are being consolidated, they are vulnerable to interference[17]. Just as described above for music skill learning, two experiences that are similar have the potential to interfere with each other during early stages of consolidation, leading to the destruction of memories before they are fully formed[18]. Likewise, lengthy and varied practicing sessions can be counter-productive because memories from earlier in a session can be overwritten by memories for later material. Coupled with the results from previous studies on music skill learning, knowledge of the consolidation process in the MTL can help tailor music skill learning so that there is the least loss of memory for the amount of time spent practicing. In patient and elderly populations, this knowledge of optimal practice strategies may be especially critical because fatigue places a strong limiting factor on the total number of practice and therapy hours available.

Neurobiological learning and memory research may also add important knowledge for tailoring music skill learning techniques to specific individuals and populations. Skill learning does not only depend upon the MTL, but also upon interactions between the MTL and the striatum[11], another fundamental learning system in the brain. Research from animal learning suggests that the MTL and striatum can function independently[19], raising the question of whether the role of the striatum becomes more critical in music skill learning in groups with MTL impairments. For example, the MTL is disrupted by dementias like Alzheimer's and Korsakov's, accounting for the profound memory loss observed in this patient population, yet music skill learning has lead to behavioral and psychiatric improvements in these groups[20,21]. Although less profound, total MTL volume and memories dependent on the MTL are also disrupted during normal aging[22,23]. Lower MTL volumes and capacity suggests that older adults may rely on the striatum, which is less sensitive to aging, to a larger degree than younger adults when learning new music sequences. Although the striatum is less sensitive to aging, striatal learning is perhaps more dependent on careful design of skill learning interventions because of the striatum's sensitivity to immediate reward/feedback[24,25]. If immediate feedback is not promptly provided, the striatal memory system has difficulty with learning connections between perceptual stimulation and motor outputs. Ultimately, music therapies and skill learning may achieve the same positive psychiatric and behavioral ends regardless of how an individual learns music sequences (whether using MTL or striatum), but the way in which training should be optimally structured to support effective learning is very different depending on *how* the brain is learning the sequences within an individual.

One of the main obstacles to doing effective neurobiological work on music practice at TTU is a lack of infrastructure to combine neurobiological measurement with measures of music performance. We have state-of-the-art environments for doing both music performance and neurobiological measurement separately, but they will need to be effectively combined in order to get pilot data to leverage for grants on the neurobiology of music skill learning. The reason why it is so difficult to combine neurobiological measurement with music skill learning is because of the magnetic resonance imaging (MRI) environment. Most musical instruments are made out of or contain metal, which can be disruptive or even dangerous in the strong magnetic environment. For example, ferrous metal objects can become projectiles when subjected to high magnetic fields. Data quality-wise, the subtle biological signals that fMRI measures in the brain can be obliterated by proximity of even non-ferrous metal to the scanner because of the way that metals interfere with the magnetic fields.

For these reasons, neurobiological researchers interested in music performance have created MRI-safe instruments that are designed specifically for the MRI environment by removing any metal in the instruments and replacing it with plastics and fiber optics. For example, leading schools such as Johns Hopkins University and McGill University have recently created MRI-safe piano keyboards to record music performance inside MRI. These MRI-safe pianos are not available commercially, however, and require advanced engineering knowledge of fiber optics, digital controllers, and materials science to create.

Our plan is to expand the capacity of TTNI to perform music research by adding capabilities for vocal recording inside the scanner through commercially available MRI-safe microphones and to build our own non-commercially available MRI-safe piano keyboard. For the MRI safe keyboard, we will develop and extend previously published plans for MRI-safe piano keyboards from McGill[26] to allow testing of neurobiological theories of music learning and performance. Dr. Li and the student from Electrical Engineering will coordinate the development of the MRI-safe piano keyboard and preliminary testing in the MRI environment.

After expanding TTNI's capacity for simultaneous measurement of music performance and neurobiological activity, we will test these devices on several imaging studies that will be intended to probe the neurobiological basis of music skill learning in music experts, healthy music novices, and older adults. We plan to conduct two neuroimaging experiments, which will be designed and coordinated by Dr. Davis, Dr. Cash, Dr. Brookes, Dr. Li and the graduate students from Psychological Sciences and Electrical Engineering. In the first experiment, we will examine the effects of practice spacing and timing of feedback (information about whether participants performed a sequence appropriately) on piano sequence learning in expert musicians (n = 25), novices musicians (n = 25), and older adults (n = 25) during fMRI scanning. Successful learning/retention of sequences will be measured outside of the scanner immediately after the session and one day later in a behavioral session in Dr. Davis' laboratory. Sequences that were retained in the subsequent memory tests will be used to isolate brain activity associated with successful memory formation[27,28] during learning. We predict that expert musicians will learn new piano sequences primarily through the MTL, and further, the degree of MTL activation during learning will be predictive of their overall susceptibility to interference between learning sequences due to consolidation. We expect that novice participants will use a combination of MTL and striatal systems, and will thus be sensitive to both interference and feedback timing effects. In older adults, we expect that the MTL system will be used less due to its loss of volume during aging, and thus older adults will be impaired at learning sequences when the timing of feedback delayed or feedback is not presented.

In the second experiment, we will extend what we learned in the first experiment to vocal sequence learning, which has proven critical for treating aphasias in stroke patients[29]. The key questions in vocal sequence learning will be how multiple types of information can be used to encourage learning in the MTL or striatum. To this end, we will have participants (25 expert, 25 novice, and 25 older adults) learn (during fMRI scanning) brief vocal sequences either with lyrics, with the MR-safe piano, or with only tonal auditory information and music notes. Participants will perform the vocal sequences in all cases by humming (to avoid excessive head motion) and visual instructions for key sequences (for sequences learned with the MR-safe piano) will be presented on a screen inside the scanner to facilitate performance in novices. As with the first experiment, learning/retention of sequences will be measured outside of the scanner immediately after the session and one day later to isolate brain activity associated with successful memory formation during learning. We expect that adding lyrics will improve music performance above only tonal information and will specifically increase use of the MTL because it will add to the contextual features of the learning experience that will help the MTL isolate the memory from overlapping sequences. We expect use of the MR-safe piano to also improve performance relative to only tonal information but via increases in striatal involvement by providing an additional, self-generated feedback signal during learning. Dr. Davis, Dr. Li, and the graduate students from Psychological Science and Electrical Engineering will perform the analysis of the fMRI data. All personnel will be involved in writing manuscripts and presenting the results.

Significance. As a unique combination of music pedagogy, neurobiological measurement and theory, and engineering, this study has the potential to inform a wide range of disciplines. Our primary goal is to inform practices in music therapy by testing how basic components of training like sequence spacing, sequence similarity, feedback, inclusion of lyrics, and multimodal training impact the brain systems used and participants' rate of learning. We believe there will be strong interest in the medical community for these results as the precise neurobiological measurements will be informative for tailoring music therapy to specific groups depending upon the brain regions impacted by neurological disorders and stroke. Because we include older adults in the sample, the results will be directly transferrable to music therapy work in elder care, where we anticipate increasing demand for inexpensive therapies like music therapy as the population continues to grey over the coming decade.

In terms of contribution to basic science, because there have been no studies yet that thoroughly combine all of these areas, we expect that our results will be of interest within each of our fields. Indeed, although some work has been done on the neurobiology of music performance, almost no work has been done on the neurobiology of music learning, which means that even our results from expert musicians and novices will be of interest to both the neurobiological and music pedagogy communities. Further, although parts of our design for the MRI-safe keyboard are inspired by similar efforts at top universities, our plan will be the first to allow for real time feedback and sub-millisecond recording precision. Thus we expect our design to be innovative, and potentially marketable for use in treatment and diagnosis, when combined with our proof-of-concept data.

Expertise of the Investigators

The current investigators all bring critical expertise to the experiment and are fully committed to the success of the project. Three members of the group have previously submitted a related grant to CH Foundation in 2015 (Drs. Davis, Cash, and Li), and Drs. Davis and Li have worked together as part of the neuroimaging cluster and in service roles at Texas Tech Neuroimaging Institute. Although Dr. Brookes is new to the group, he brings vital experience from his work on memory mechanisms in vocal training. The strong track record of collaboration suggests that we will be successful in the current project.

Tyler Davis. Dr. Tyler Davis will coordinate the group and lead the fMRI design, data collection, and analysis. Dr. Davis is an expert on the neurobiology of learning and memory and has published papers on changes in neurobiology and learning performance due to healthy aging. His primary research focus involves combining computational models of learning and memory systems with functional neuroimaging to reveal systems-level algorithms the brain uses to learn new categories and concepts. His work on related large-scale neuroimaging studies of older adults will prove critical to the success of the project as neuroimaging data from older adults requires specialized procedures and analysis techniques due to neurobiological changes that occur with aging.

Carla Cash. Dr. Carla Cash will develop the music skill learning interventions and sequences used in the fMRI studies. Dr. Cash's research centers on the processes by which novice and expert musicians learn and refine motor skills. Her line of inquiry regarding the behavioral effects of skill practice and procedural memory consolidation has added unique and valuable perspective to the existing body of research pertaining to music learning. Dr. Cash's previous work in motor sequence learning will provide a strong basis for designing the music-related experimental tasks and performance measures used in the fMRI study.

Changzi Li. Dr. Changzhi Li brings expertise in design and testing of electronic systems for biomedical applications. Because of his research and education activities in this area, he has received the ASEE Frederick Emmons Terman Award in 2014, the IEEE-HKN Outstanding Young Professional Award in 2014, and the NSF Faculty Early CAREER Award in 2013. Besides publishing a book "Microwave Motion Sensing and Analysis" (John Wiley & Sons), he has published over 170 journal and conference papers and holds four US patents. In this project, Dr. Li will supervise an engineering student to build and electronically test the MRI-safe keyboard system. Dr. Li's work also incorporates state-of-the-art time series analyses, which will add a critical dimension to the fusion of the fMRI data and real-time performance data.

Gregory Brookes. Dr. Gregory Brookes brings expertise on vocal training and singing and song repertoire. Dr. Brookes teaches undergraduate and graduate vocal pedagogy at Texas Tech University. Previous research includes factors that influence the memorization of song. Dr. Brookes will provide expertise in terms of singing and song repertoire. He is an active performer having sung as a soloist throughout the United States, Canada, France, China and Honduras and performances being heard on NPR, CBC and the BBC. Dr. Brookes' work will provide a strong basis for designing the vocal sequence training experiment and providing insight into how to integrate vocal work with fMRI effectively.

Deliverables.

As a novel combination of music pedagogy, neurobiology, and engineering, the present study will offer many opportunities for manuscript publications in field specific and general science journals, as well as conference proceedings and presentations. The data that we generate will also be used to leverage two grant submissions to the NIH and one submission to the NSF. We expect that one NIH submission and the NSF submission to occur within the 18 month funding range and the second submission to NIH shortly after.

Grant Submissions. The pilot data generated by this study will be used to support grant submissions. The first submission will be to the National Institute of Aging, which funds grants on cognitive performance in healthy aging as well as strategies to ameliorate the negative cognitive affects of aging. We anticipate that the pilot data we generate from this study will be a critical proof-of-concept for a large-scale longitudinal study aimed at testing the efficacy of our optimally designed training regimens on brain health, cognitive function, and well-being in older adults. A second submission is planned to the NSF's Cognitive Neuroscience program and will be primarily aimed at developing a better understanding of the basic science behind optimal music sequence learning in novices and experts. The SBE directorate at NSF has expressed great interest in developing a better understanding of music learning and performance due to the well-known cognitive benefits of music skill learning across the lifespan. Finally, we expect that our initial findings with older adults can be leveraged for grants extending this work to populations with neurological disorders and stroke. After the funding period, we plan to submit a proposal to NINDS that will allow us to extend these results to patients in groups with neurological conditions.

Manuscripts and Conference Presentations. We expect at least 5 manuscripts to be generated by the present activity: two full empirical papers on the results from of each study to be submitted to top-tier neuroimaging journals (e.g., Neuroimage); two cross-experiment review papers, one to be submitted to a journal on music pedagogy and one to a music therapy journal; and one methodological paper on the analysis techniques and equipment to a neuroimaging methods and/or engineering journal. Finally, the results will generate numerous presentations and proceedings at conferences in each PI's field.

Budget and Justification.

$149,905 is requested for the 18-month funding period to be spent on student support, equipment, scanner fees, and participant incentives.

Student Support ($43,500). Two graduate students will be paid through this grant, one student from Electrical Engineering and one student from Psychological Sciences (one full year each). The student from Electrical Engineering will work on the development and field testing of the MRI-safe piano. The Psychological Sciences student will coordinate data collection, participants, and will assist in fMRI analysis and data processing.

Equipment ($16,405). Parts and equipment will be needed to build the MRI-safe keyboard. In addition, we will purchase MR-safe voice recording microphones and headphones for delivery of auditory information from the MR-safe piano. Currently TTNI is only equipped with a general PA system that is not sufficient for voice recording or precise delivery of auditory stimulation.

Scanner fees ($82,500). The proposed studies will recruit 75 participants each (150 total). Each participant will require one hour of scanning at the current rate of $550 per hour. Sample size is based off of standard minimum sample size requirements for within subject fMRI studies[30] extrapolated to a three condition, between subjects one-way ANOVA design. For reference, with the present sample sizes in a purely behavioral one-way ANOVA design, we would expect correct rejection of the null hypotheses approximately 80% of the time if the underlying effect sizes were medium (f = .37).

Participant incentives ($7,500). Participants will be paid $50 at the time of data collection as an incentive to participate in the study. Incentives are necessary due to the time commitment and general effort required to participate in the study.

References

1. Whipple J. 2004. J Music Ther. 41:90-106.
2. Reschke-Hernández AE. 2011. J Music Ther. 48:169-207.
3. Schlaug G, et al. 2008. Music Perc. 25:315-323.
4. Altenmüller, et al. 2009. Ann New York Acad Sci. 1169:395-405.
5. Allen SE, & Duke RA. 2013. Application Research Music Educ. 32:67-73.
6. Simmons AL, & Duke RA. 2006. J Research Music Educ. 54:257-269.
7. Duke RA, Davis CM. 2006. J Research Music Educ. 54:111-124.
8. Cash CD. 2009. J Research Music Educ. 57:252-266.
9. Allen SE. 2012. Psychol Music. 41:794-803.
10. Simmons AL. 2012. J Research Music Educ. 59:1-12.
11. Albouy G, et al. 2008. *Neuron*. *58*:261-272.
12. Walker MP, et al. 2005. Neuroscience. 133:911-917.
13. Alvarez P, & Squire LR. 1994. *PNAS*. *91*:7041-7045.
14. McGaugh JL. 2000. *Science*. *287*:248-251.
15. Müller GE, & Pilzecker A. 1900. *Experimentelle beiträge zur lehre vom gedächtniss* (Vol. 1). JA Barth.
16. Bekinschtein P, et al. 2007. *Neuron*. *53*:261-277.
17. Robertson EM. 2004. Curr Biol. 14:R1061-R1063.
18. Wixted JT. 2004. Annu Rev Psychol. 55:235-269.
19. Poldrack RA, & Packard MG. 2003. Neuropsychologia. 41:245-251.
20. Koger SM, et al.1999. *J Music Ther*. *36*:2-15.
21. Raglio A. et al. 2008. *Alz Disease Assoc Disord*. *22*:158-162.
22. Petersen RC, et al. 2000. *Neurology*. *54*:581-581.
23. Davis et al. 2012. *Learn Mem*.*19*:325-329.
24. Hollerman JR, & Schultz W. 1998. *Nature Neurosci*. *1*:304-309.
25. Maddox WT, et al. 2003. J Exp Psychol Learn Mem Cognit. 29:650.
26. Hollinger A, et al. 2007. In *Proc 7th Intl Conf New Interf Music Exp.r* 246-249.
27. Wagner AD, et al. 1998. *Science*. *281*:1188-1191.
28. Kim H. 2011. *Neuroimage*. *54*:2446-2461.
29. Yamaguchi S, et al. 2012. Internat J Rehab Res. 35:78-81.
30. Desmond JE, & Glover GH. 2002. J Neurosci Meth. 118:115-128.