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Keys to staying sharp: A randomized clinical trial of piano training among older adults with and without mild cognitive impairment☆

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ABSTRACT

Background: The prevalence of dementia, the most expensive medical condition (Kirschstein, 2000 and Hurd et al., 2013 [1,2]), and its precursor, mild cognitive impairment (MCI) are increasing [3]. Finding effective intervention strategies to prevent or delay dementia is imperative to public health. Prior research provides compelling evidence that central auditory processing (CAP) deficits are a risk factor for dementia [4–6]. Grounded in the information degradation theory [7, 8], we hypothesize that improving brain function at early perceptual levels (i.e., CAP) may be optimal to attenuate cognitive and functional decline and potentially curb dementia prevalence. Piano training is one avenue to enhance cognition [9–13] by facilitating CAP at initial perceptual stages [14–18].

Objectives: The Keys To Staying Sharp study is a two arm, randomized clinical trial examining the efficacy of piano training relative to music listening instruction to improve CAP, cognition, and everyday function among older adults. In addition, the moderating effects of MCI status on piano training efficacy will be examined and potential mediators of intervention effects will be explored.

Hypotheses: We hypothesize that piano training will improve CAP and cognitive performance, leading to functional improvements. We expect that enhanced CAP will mediate cognitive gains. We further hypothesize that cognitive gains will mediate functional improvements.

Method: We plan to enroll 360 adults aged 60 years and older who will be randomized to piano training or an active control condition of music listening instruction and complete pre- and immediate post- assessments of CAP, cognition, and everyday function.

1. Introduction

Cognitive impairment and dementia are the most feared signs of aging [19–21]. In addition to the obvious health and quality-of-life ramifications for older adults, there are high economic costs when older adults can no longer live independently [1,2,22]. The prevalence of mild cognitive impairment (MCI) and dementia are increasing [3]. Therefore, finding effective strategies for intervention to prevent or delay dementia is imperative to improve public health. Among individuals with and without MCI, cognitive interventions may enhance cognition and maintain everyday functioning, thereby reducing dementia risk [23]. However, little is known about the mechanisms of effective cognitive interventions. One avenue to enhance cognition is the facilitation of central auditory processing (CAP) at initial perceptual stages [14], which may potentially be achieved by piano training.

Deficits in central auditory processing present as impaired sound localization and lateralization, auditory discrimination, auditory pattern recognition, temporal aspects of audition, including temporal integration, temporal discrimination (e.g., temporal gap detection), temporal ordering, and temporal masking auditory performance in

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competing acoustic signals (including dichotic listening), and/or auditory performance with degraded acoustic signals [24] and are thought to be specific to the auditory domain. Diagnosis of a central auditory processing disorder requires abnormal performance in at least two of these areas.

Decades of research have established that CAP is fundamentally linked with memory and executive functioning [14,25–27], which are the primary deficits in MCI and dementia [28,29]. In support of this premise, CAP longitudinally predicts MCI and dementia such as Alzheimer's disease [4,30,31]. Prior research (e.g. [32,33],) and our pilot data confirm that measures of CAP are strong, independent predictors of cognitive function (e.g., memory, executive function), and that adults with MCI show significant CAP deficits [34,35]. Although CAP is a strong longitudinal predictor of cognitive decline, MCI, and dementia [4–6,32], prior research has not examined the effects of interventions targeting CAP on the cognitive and functional abilities of older adults with and without MCI. *Re*-establishing and/or maintaining adequate CAP may be the first crucial step in efforts to improve cognitive abilities of older adults. Given that multiple studies have shown music experience is strongly associated with better CAP [16,18,36–39], it is likely that piano training enhances CAP, leading to better cognition. Our scientific premise is that piano training will enhance CAP, resulting in improved cognition and subsequently everyday function.

We hypothesize that improving brain function at early perceptual levels (i.e., CAP) may be optimal to attenuate cognitive and functional decline. This premise is grounded in the information degradation theory [7,8], which posits that age-related changes cause initial sensory/perceptual processing errors that lead to difficulties with downstream information processing (i.e., CAP) and cognition (i.e., memory/executive function). Accordingly, cognitive interventions that target basic perceptual processing may be most effective. Furthermore, cognitive gains will be mediated by improvements in perceptual processing (i.e., CAP). Our recent analyses support this assertion, indicating that an intervention targeting perceptual processing is more effective to reduce dementia risk than other approaches [40]. The proposed research will test the efficacy of piano training among older adults with and without MCI. We hypothesize that piano training will improve CAP and cognitive performance, leading to functional improvements. We expect that enhanced CAP will mediate cognitive gains. We further hypothesize that cognitive gains will mediate functional improvements.

2. Study design and methods

A randomized clinical trial with two arms (piano training and music listening instruction) across two levels of cognitive functioning (cognitively intact older adults and those with MCI) is being conducted. This is a phase II trial to test the efficacy of a promising behavioral intervention (i.e., piano training) in a research setting [41]. Potentially eligible participants will complete telephone screening, in-person baseline, and if needed, a clinical assessment to diagnose MCI. Those eligible will be randomized to complete piano training or music listening instruction, and will complete immediate post-test assessments.

2.1. Inclusion and exclusion criteria

Inclusion and exclusion criteria are designed to enroll older adults available and willing to comply with study demands who are capable of benefitting from the intervention and are novice to music training. Inclusion criteria are aged 60 years or older, willingness to complete up to 23 study visits at USF, and ability to speak and understand English. After providing informed consent at the baseline visit, participants must demonstrate a Montreal Cognitive Assessment (MoCA) score of 20 or higher, binocular near visual acuity of 20/50 or better (with correction, if worn), and adequate hearing acuity (hearing thresholds < 70 dB HL at 1000 and 2000 Hz in at least one ear).

To include only those novice to music training, individuals who have four or more years of formal music training, who report the ability to read music on two or more clefs (i.e., Treble, Bass, Alto), who have played a specific musical instrument for four or more years, or are currently participating in music activities (e.g., music performance, reading, lessons, or courses) are excluded. At the baseline visit, participants who score 19 or higher on the Music Reading Assessment [42] are excluded.

Individuals who previously participated in USF Cognitive Aging Lab or Music Research and Testing lab intervention studies and those concurrently enrolled in another research study are excluded. Those who report completing 10 or more hours of a computerized cognitive intervention program (e.g., Lumosity, Posit Science Brain Fitness, InSight, or Brain HQ; Lace, CogMed, CogniFit, Happy Neuron, Dakim, DriveSharp, or Staying Sharp by AARP programs) within the last five years are excluded. Individuals planning on being away for two or more weeks or undergoing anesthesia, chemotherapy or radiation treatment within the study period (~5 months) are excluded. Participants who may have difficulty using a keyboard due to pain, neuropathy, or tremor in hands or fingers, or who are missing any finger or portion thereof are excluded. Those who self-report diagnosis of dementia, stroke, serious brain injury, a transient ischemic attack within the past 18 months, or other neurological disorder are excluded. Finally, exclusion criteria assessed at the baseline visit are moderate or worse depressive symptoms [i.e., Geriatric Depression Scale short form (GDS-S) score greater than or equal to 5], clinical diagnosis of dementia, or a Clinical Dementia Rating Scale score of 1 or greater.

2.2. Procedure

Participants are primarily recruited through the community, the Cognitive Aging Lab registry, listserves, and mailing lists of older adults residing in the area. We may also use the Byrd Alzheimer's Institute Community-Based Memory Screening program and referrals from the Department of Psychiatry and Behavioral Neurosciences Memory Disorders Clinic to enroll participants in the study. Advertisements for the study are placed in media outlets including social media.

Individuals who express interest in our research are telephone screened and those deemed initially eligible schedule a study visit. At the baseline visit, participants complete the MoCA, GDS-S, hearing and vision screenings, and MRA to determine eligibility. Those not eligible due to MoCA, GDS-S, hearing (including outer or middle ear pathology as determined by otoscopy), or vision scores are referred to the appropriate professionals for treatment. Eligible participants are enrolled in the study and further complete thorough assessments of CAP, cognition, and everyday function (See Table 1 for list of assessments). Demographic and health questionnaires are also completed.

Those potentially eligible who score between 20 and 25 on the MoCA will also complete a clinical evaluation visit. The purpose of the clinical evaluation is to determine if participants have MCI or dementia by administration of the National Alzheimer's Coordinating Center Uniform Data Set (NACC) neuropsychological battery subtests and an exam by a study physician (See Table 1 for list of assessments). We apply the Alzheimer's Association/National Institute on Aging guidelines for diagnoses or exclusion of MCI as described in detail by Alberts et al. [43]. The criteria include a) evidence of change in cognition obtained from an informant or a skilled clinician, b) cognitive performance on one or more cognitive domains at least 1 standard deviation lower than expected based on age and education, c) preservation of independence in functional abilities despite some cognitive problems, and d) no dementia.

Participants are asked to bring an informant (a relative or spouse or close friend who has regular contact with them and can report on their everyday activities) to the clinical evaluation. Informants are interviewed by telephone, if unable to attend in-person. The physician reviews lab results available from the past year or orders lab tests to examine potential treatable causes of cognitive impairment (e.g.,

Table 1
Schedule of evaluations.

Evaluation	Measure Type	Telephone Screening	Baseline	Clinical Evaluation	Randomization	Intervention	Post-Test
Inclusion/Exclusion Criteria Confirmed	I/E	X	X	X			X
Geriatric Depression Scale-Short Form (GDS-S)	I/E, C		X				
Demographic Questionnaire	C		X				
Montreal Cognitive Assessment (MoCA)	I/E, C		X				
Hearing and Vision Screening	I/E, C		X				
Pure-tone Hearing Thresholds							
Speech Recognition Threshold							
Near Visual Acuity							
Music Reading Assessment	I/E		X				
Central Auditory Processing (CAP)	O		X				X
Time Compressed Speech 65%							
Words-in-Noise Test							
Dichotic Digits Test							
Dichotic Sentence Identification test							
Adaptive Tests of Temporal Resolution							
Cognitive Assessment Battery	O		X				X
Trail Making Test							
Digit Coding							
Verbal Fluency							
- FAS, Animals/Boys' Names, Vegetables/Musical Instrument (baseline)							
- BHR, Clothes/Girls' Names, Fruits/Furniture (post-test)							
Everyday Functional Assessment	O		X				X
Timed IADL Test							
Test of Everyday Attention							
Questionnaires	SC						
Health Questionnaire			X				
Medication Audit			X				
Health Changes							X
Clinical Evaluation	SC			X			
National Alzheimer's Coordinating Center (NACC) Uniform Data Set assessments:							
- Clinical Dementia Rating Scale							
- Craft Story 21 Recall -Immediate and Delayed							
- Benson Complex Figure Copy and recall							
- Multilingual Naming Test							
- Functional Assessment Scale							
- Clinician Diagnosis form							
Lab Assessments	IV			X			
CBC, Metabolic panel, Thyroid Stimulating Hormone, B12, D, Folic Acid							
Advanced Measures of Music Audiation (Day 1 of training)	E					X	
Basic Piano Measure or Music Listening Measure (Days 1 and 20 of training)	E					X	
General Self-Efficacy and Music Performance Self-Efficacy (Days 1 and 20 of training)	E					X	
NICT Expectations Questionnaire (Between days 17 and 20 of training)	IV, C					X	

C = covariate, E = exploratory, I/E = inclusion/exclusion, IV = internal validity, O = outcome, R = regulatory, SC = sample characterization.

vitamin deficiencies, thyroid dysfunction). Those without dementia or any clinically significant abnormalities that may interfere with their ability to benefit from intervention will continue in the study.

Enrolled participants with and without MCI are randomized in a 1:1 ratio to either piano training or the active control condition of music listening instruction. To ensure balance throughout enrollment, randomization is stratified by MCI status (present vs. absent) and conducted in permuted random blocks using R. Couples are randomized together to protect the blind.

The intervention and active control group are detailed below in Section 3. Both conditions attend group training two times a week for 10 weeks with the goal of completing 20 sessions. Several prior studies of piano training have successfully used the group format [9,10,44,45]. Training is being administered in group format for feasibility and potential scalability of the intervention. The two training conditions are equivalent in terms of frequency and duration of each session (90 min/day, two days/wk., 10 weeks) and social contact (led by trainer and conducted in groups of up to 10 persons). At least one five-minute break occurs in each session. Both conditions are described to study participants as “music training”. Participants are encouraged to complete training two times a week without missing two or more consecutive sessions. All training sessions must be completed within 15 weeks of training start date. Participants are considered adherent if they complete at least 80% of the assigned sessions (i.e., at least 16 of 20 sessions). Classes are arranged such that those with MCI primarily train together within the randomized condition. The intervention phase will continue until 20 total sessions are completed or 15 weeks have passed.

Concurrent participation in cognitive interventions aimed toward enhancing or maintaining cognitive abilities is not allowed. Formal music training, such as private music lessons or group music classes or courses related to music (as example voice instruction or musical instrument instruction or a music appreciation class) outside of the

assigned activities is not allowed. Participants are instructed not to participate in such activities during the entire study period. Participant are deemed ineligible at the time such an incident occurs and are dropped from the study. Only data points prior to such participation will be included in analyses.

If the participant opts to undergo a surgical procedure that requires general anesthesia or chemotherapy or radiation, we will attempt to complete post-test prior to the procedure/treatment. If the participant undergoes general anesthesia, chemotherapy, radiation, experiences a head injury, stroke, or heart attack, the participant will be withdrawn from the study. The participant will be deemed ineligible at the time of the incident. All available data points prior to the incident will be used in analyses.

Participants complete a post-test visit immediately after the intervention phase and are encouraged to complete post-test regardless of adherence. Post-test is completed within 60 days of training completion, or within 18 weeks of baseline if the intervention phase was not completed. At the post-test visit, cognition, CAP- and everyday function outcome measures are re-administered by blinded testers. Alternative forms are used, as available (See Table 1 below).

3. Interventions

3.1. Piano training

Piano training consists of basic piano technique, dexterity exercises, piano literature, and music theory. At each bi-weekly training session, participants are trained in groups and are expected to perform all technique (scales/finger dexterity exercises), piano repertoire (Alfred Basic All-in-One Method), and complete music theory assignments. Each class session is structured with a short review followed by an intense focus on new skill development (e.g., scales; chord progressions) and concept formation (e.g., intervals).

3.1.1. Piano training rationale

Engagement in learning challenging new skills, such as learning to play the piano with training, is a promising cognitive intervention approach. Piano training can be defined as systematic sequential instruction to acquire piano skills that includes technique (scales/arpeggios/chords), music theory, and piano repertoire. Verghese et al. observed that older adults who reported playing musical instruments were 69% less likely to develop dementia [46]. Increasing neuroscience evidence indicates positive, longitudinal associations of music training with enhanced structures and function in the brain [47,48]. Thus, music training (piano training, in particular) has been proposed as a viable means to attenuate age-related cognitive decline [49,50]. Piano training may be an efficacious cognitive intervention because it requires the simultaneous coupling of sensory processing, motor skills, and complex cognitive operations to be executed with temporal precision [51]. We propose that piano training is a promising cognitive intervention because piano training enhances CAP. Numerous studies indicate that music experience is associated with better CAP (e.g. [16,18,36–39]). Correlational studies indicate superior CAP for adults with formal music training compared to non-musicians [52–54]. Studies show that adult musicians have enhanced CAP, indicated by faster neurophysiological processing of sound, than their nonmusician counterparts [15,16]. Similarly, older musicians do not show age-related neural timing delays, indicating better CAP [17]. Zendel and colleagues also demonstrated that CAP (i.e., auditory processing speed and speech-in-noise perception) is less susceptible to age-related decline in musicians [18].

Furthermore, piano training is associated with improved cognitive performance [9,11–13,55]. Hanna-Pladdy and Gajewski conducted cross-sectional research in non-musicians and musicians matched on age and education. Older adult musicians performed better on memory (letter number sequencing, verbal learning test) and executive function measures (phonemic fluency) [56]. Seinfeld and colleagues found that older adults randomized to piano training showed improved speed of processing and executive function [47]. Bugos published two pilot randomized trials [9,55] indicating small to medium effects of piano training relative to controls for improved speed of processing and executive function. Improvements in speed of processing were sustained three months after training. These data demonstrate enhanced speed of processing and executive function among older adults subsequent to piano training relative to controls [9,55].

In summary, we chose piano training because it is a novel cognitive engagement approach that shows promise to enhance CAP and cognition. Although prior epidemiological research and our pilot studies indicate the potential efficacy of piano training [9,11–13,55], statistically powered experimental studies are lacking.

3.2. Music listening instruction

Participants randomized to the music listening instruction condition engage in music listening and appreciation. The participants read about, listen to, view diagrams of, and answer questions about the music. Each lesson covers chapters from Music Listening Today [57]. Each lesson is structured as follows: overview of chapter material and group listening activity, participants review chapter on their own, active listening activity, and a five question quiz for each chapter. This structure is equivalent to the switching between ensemble/individual approaches to teaching in the piano training condition. We chose music listening instruction as an active control condition that equates social contact and activity and appears to participants as a viable intervention. Indeed, recent studies have documented the positive effects of music listening on biomarkers [58].

At the first training session (for both conditions) the trainers administers assessments of music audiation and general and music performance-self efficacy. The self-efficacy measures are completed again at the end of training. To assess internal validity and learning from the intervention, those in the music listening instruction group complete a music listening measure while those in piano training complete a basic piano measure at the beginning and again at the end of training. Between sessions 17 and 20, the trainers administerthe The Cognitive Training Expectations NICT questionnaire [59] to examine participants' attitudes and expectations about the potential effects of the intervention completed.

4. Measures

4.1. Covariates

After initial telephone screening, eligibility is further assessed in-person by measuring near visual acuity, hearing, cognitive status (MoCA), Music Reading Assessment, and depressive symptoms (GDS-S). These variables and demographic information may be considered as covariates in analyses.

Near Visual Acuity is measured at 40 cm using standard procedures with a Sloan letter chart, and the log minimum visual angle resolvable will be quantified [60]. Hearing thresholds and speech recognition thresholds (SRTs) are assessed for each ear using standard procedures and calibrated equipment [61]. An otoscopic exam is performed prior to inserting ear phones for pure tone and SRT testing. Pure tone air conduction thresholds in dB are measured at 250, 500, 1000, 2000, 4000, 6000, and 8000 Hz in each ear. For future analyses, pure-tone averages (PTAs; average threshold at 500, 1000, and 2000 Hz) are calculated for each ear. The SRTs are used to set presentation levels of several auditory tests as noted below. At post-test, the SRTs are verified and presentation levels of auditory tests using this as a reference (TCS, DDT, DSI) are adjusted if the SRT in either ear varies by more than ± 5 dB.

The MoCA is used to examine participants' cognitive status [62]. This assessment has good internal consistency, Cronbach's $\alpha = 0.83$,

and test-retest reliability, $r = 0.92$ [62]. A cut-point of 20–25 on the MoCA is indicative of probable MCI, while < 20 is suggestive of dementia [62]. The GDS-S is used to screen depressive symptoms. The GDS has 92% sensitivity and 89% specificity to detect depression and has good test-retest reliability of $r = 0.75–0.81$ [63,64]. The Music Reading Assessment [42] consists of a 40-item measure of basic music reading ability with 20 treble clef items and 20 bass clef items.

4.2. Sample characterization

A health questionnaire is administered at baseline to characterize the sample. Participants are asked whether a doctor or nurse has ever told them that they have any of the following conditions: arthritis, asthma and/or other breathing problems, cancer (other than skin cancer), chronic skin problems, diabetes, heart disease, heart problems (other than heart disease), high cholesterol, hypertension or high blood pressure, mood problems or anxiety, multiple sclerosis, osteoporosis, Parkinson's disease, stroke, mild cognitive impairment or memory impairment, neuropathy, or any other significant illness. At the baseline visit, a list of prescription medications that the participants' are taking is recorded. For those completing a clinical evaluation, the medication list is provided for the study physician to review. The study physician uses this information in the clinical diagnosis of MCI or exclusion of dementia.

A questionnaire is administered at post-test to assess if any health changes are experienced by the participants during the trial that could affect cognitive or functional performance. Participants are asked if they experienced any significant changes in health conditions such as head injury, chemotherapy or radiation treatment, heart attack or myocardial infarction, changes in vision or hearing, or underwent general anesthesia. They are also asked if they had any new diagnoses of stroke, mini-stroke, TIA, heart disease or congestive heart failure, Parkinson's disease, mild cognitive impairment or memory impairment, Alzheimer's disease, or Multiple Sclerosis.

4.3. Central auditory processing outcome measures

Outcomes include CAP measures of: Time Compressed Speech 65%, Words-in-Noise, Dichotic Digits Test, Dichotic Sentence Identification, and Adaptive Tests of Temporal Resolution. All tests are presented binaurally and the presentation level is recorded for each measure. If any participant expresses discomfort with the presentation level, it is adjusted to a comfortable level.

4.3.1. Time Compressed Speech test (TCS)

The TCS test assesses both auditory temporal processing and degraded speech understanding. It is a word recognition task in which the Northwestern University Auditory Test Number 6 recorded monosyllabic words with a static preceding sentence (e.g., “Say the word jug”) have been digitally manipulated to resemble rapid speech [65–67]. TCS performance worsens with age [68]. The listener must repeat the last word (test item), after the introductory sentence “Say the word”, which precedes every test item. The talker is female and approximately 4 s of silence separate the stimuli. The 65% compression condition was used. Participants are asked to repeat 50 words delivered through insert earphones at a level of 50 dB SL (re: SRT), and percent correct is calculated. Normative data on time compressed speech performance in adults have been described elsewhere [69].

4.3.2. Words-in-Noise Test (WIN)

The WIN is a test of degraded speech understanding or speech understanding in noise. It was developed as an instrument that quantifies the ability of listeners to understand speech in background multi-talker babble [70]. The stimuli are the Northwestern University Auditory Test Number 6 monosyllabic words with a static preceding sentence (e.g., “Say the word road”) and a background of multi-talker babble. The talker is female and approximately 3 s separate each sentence. Two 35-word lists are used; 5 words are presented at each of 7 signal-to-noise ratios (SNRs). The SNRs are presented in a descending manner, from 24 to 0 in 4-dB increments. The babble is maintained at a fixed level of 70 dB HL. Listeners must repeat the last word of the sentence, ignoring the babble. The WIN uses a modified method of constants to establish the SNR at which 50% correct performance is achieved on the materials. The 50% point is computed with the Spearman-Kärber equation [71,72] [50% = 26 – (#correct)(0.8); “0.8” is the attenuation step size (4 dB) divided by the number of words per step (5)]. The WIN has been established as a reliable measure (intra-class correlation coefficient = 0.88) [73,74].

4.3.3. Dichotic Digits Test (DDT)

The DDT is a test of dichotic processing that uses a closed set of stimuli (numbers), thus having a relatively low linguistic load. The DDT consists of verbally presented words representing the numbers one through nine, excluding the two-syllable word “seven” (test-retest reliability $r = 0.79–0.97$) [75]. Two number-words are presented to the right ear while two number-words are presented simultaneously to the left ear, for a total of four numbers. The participants are instructed to repeat the four numbers that are presented to them, in any order. The talker is male. Approximately four seconds of silence separate each set of four numbers, and approximately one second separates the individual pairs within a set of four. Twenty-five sets of four numbers each are presented, for a total of 100 stimuli. The test is scored as a percent correct out of the 100 numbers presented.

4.3.4. Dichotic Sentence Identification (DSI)

The DSI test is used to assess dichotic speech understanding and also falls into the broad category of degraded speech understanding. The DSI stimuli [76] are recorded meaningless sentences (e.g., “Small boat with picture has become”). A sentence is delivered to one ear while a different sentence is delivered to the contralateral ear. The DSI is presented at a level of 50 dB SL (re: SRT) via insert earphones; the talker is male and approximately 8 s of silence separate the sentences. Participants are required to select both sentences heard from a closed set list of 6 sentences, and results are scored as percent correct. Test-retest reliability of the DSI is high in older adults, $r = 0.79–0.97$. Deficits in DSI performance may be predictive of cognitive decline [32].

4.3.5. Adaptive Tests of Temporal Resolution (ATTR)

The ATTR [77] is a copyrighted and freely downloadable test of auditory temporal processing. Details regarding the ATTR have been published previously [77–79]. Briefly, the ATTR is used to measure gap detection thresholds using a three-interval, two-alternative forced-choice adaptive procedure targeting 70.7% correct gap detection. The stimuli used to define the silent gaps are ¼ octave narrow bands of noise (NBN) centered on either 1 kHz or 2 kHz. Before the silent gap, the NBN is 300 ms in duration. After the silent gap, the NBN varies randomly in duration between 250 and 350 ms. The participant is presented with three intervals of sound, a reference interval, a standard interval identical to the reference interval, and a target interval. In the reference and standard intervals, two NBNs separated by a 1-ms gap are presented. In the target interval, two NBNs separated by a gap of adaptively varying duration are presented. The reference interval is presented first and the standard and target intervals are presented in random order, following the reference interval. The participant's goal is to select the target interval from among the standard and target intervals. The participant is not allowed to select the reference interval. Two subtests of the ATTR are used in the present study, the within-channel subtest for which NBNs before and after the gap are both centered on 2 kHz and the across-channel subtest for which the NBN before the gap is centered on 2 kHz and the NBN after the gap is centered on 1 kHz. The ATTR is presented at a high, comfortable level, self-selected by each participant as described by Cox [80]. Reliability for the ATTR has been established with intraclass $r = 0.58–0.87$ [77].

4.4. Cognitive outcome measures

Outcomes also include cognitive measures: Verbal Fluency Test (phonemic fluency, category fluency, and category switching), Trail Making Test, and Digit Coding

4.4.1. Verbal fluency

Executive function is assessed with phonemic, category, and category switching verbal fluency tasks [81]. Phonemic fluency consists of three, one-minute trials during which the examinee names as many words as can be thought of that begin with a given letter, excluding proper nouns, numbers, and the same word with a different suffix will also be assessed (test-retest reliability = 0.88) [82]. Category fluency is designed to measure the speed and flexibility of verbal thought processes ($r = 0.82$; sensitivity = 0.88; specificity = 0.96) [81,83]. A switching condition is included that requires participants to alternate between sets (e.g. naming fruits and furniture) ($r = 0.51$). Different versions of this measure are administered at baseline and post-test. At baseline, participants are asked to say as many words they can recall that start with the letters F, then A, and then S for subtest 1. Subtest 2 asks participants to recall Animals and Boys' names, and subtests three asks participants to recall Vegetables and Musical Instruments. At post-test, participants are asked to say as many words they can recall that start with the letters B, then H, and then R for subtest 1. Subtest 2 asks participants to recall Clothes and Girls' names, and subtests three asks participants to recall Fruits and Furniture. The recorded score is the number of correct items for each task.

4.4.2. Trail Making Test

Speed of processing is evaluated using the Trail Making Test Part A. This test ($r = 0.53$–0.64), requires participants to draw a line connecting a series of numbers in sequential order (1–2-3, etc.) [84]. The recorded score is the time required to complete the task [85]. Executive function is evaluated using the Trail Making Test Part B, which is a reliable measure ($r = 0.54$–0.62) that requires participants to draw a line connecting a series of number and letters in alternating, sequential order (1-A-2-B, etc.) [84]. The recorded score is the time required to complete the task [85,86].

4.4.3. Digit Symbol Coding

Cognitive speed of processing is evaluated using Digit Symbol Coding [81]. This test consists of 135 blank squares that are paired with a number from one to nine. A reference key links each number to a different geometric figure. Using the reference key, participants have 120 s to copy the geometric figure assigned to the number into the blank boxes. Scaled scores are obtained by subtracting the number of errors from the number of correct responses. Lower scores indicate better performance. Psychometric properties are reported in the manual.

4.4.4. Everyday functional outcome measures

Outcomes of everyday function include the Timed Instrumental Activities of Daily Living (IADL) Test and Test of Everyday Attention (TEA).

4.4.5. Timed IADL

Timed IADL involves timed performance of five tasks encountered in daily life. The previously validated tasks [87] utilize real-world stimuli and represent five IADL domains, including communication (finding a telephone number in a phone book), finance (making change), cooking (reading the first three ingredients on a can of food), shopping (finding two items on a shelf of packaged foods) and medication management (reading the directions on a medicine bottle label). Scores are generated by combining the completion time and error code for each task per standard procedure. Task scores are combined into a single composite by taking the average of *z* scores computed for each of the five tasks after error correction. Test-retest reliability of the Timed IADL is $r = 0.85$ [87].

4.4.6. The Test of Everyday Attention (TEA)

The TEA [88,89] consists of eight subtests designed to measure attention. The subtests are designed to mimic everyday tasks that encompass both visual and auditory domains. The test-retest reliability of versions A to B range from 0.59–0.86 [88]. Four of the eight subtests are administered in this study and include: *Visual Elevator*. Participants count up and down floors as they follow a series of visually presented doors and arrows. Accuracy (how many final floor numbers the participant gets correct out of 10) and timing scores (total time taken for the correct items) are obtained. The reported score is the total time taken divided by the number of switches for the correct items and the scaled score. This subtest measures attentional switching [89]. *Elevator Counting with Reversal*. As with the Visual Elevator subtest, participants count up and down as they follow a series of visually presented doors. In this subtest however, participants also hear tones presented at a fixed speed. Participants are asked to indicate what floor the elevator is on based on the tones they hear and visually presented doors. The recorded score is the number of correct answers out of 10 and the scaled score. This subtest measures auditory-verbal working memory [89]. *Telephone Search*. Participants search for symbols while searching for entries on a replicated page of a telephone directory. The recorded score is the time per target score (number of correctly detected symbols divided by the time taken to identify the correctly detected symbols) and the scaled score. This subtest measures selective attention [89]. *Telephone Search While Counting*. Participants search the telephone directory while counting strings of tones simultaneously. The recorded score is obtained by the combined performance on the Telephone Search and Telephone Search While Counting gives a measure of divided attention, as well as the scaled score. This subtest measures sustained attention [89].

4.5. Exploratory measures

Exploratory measures include a measure of music aptitude and two self-efficacy measures. Advanced Measures of Music Audiation (AMMA) consists of 30 paired piano melodies that is used to evaluate music aptitude [90]. Test–retest reliability for music majors is $r = 0.89$ and non-music majors, $r = 0.83$ [90].

The General Self-Efficacy [91] scale is comprised of 23 positive and negative items on a 14-point Likert scale ranging from strongly disagree (1) to strongly agree (14). Internal reliability is established ($\alpha = 0.86$–0.71). Items are designed to reflect elements of effort, initiation, and persistence as described in Bandura's social cognitive theory.

An adapted version of the Music Performance Self-Efficacy Measure [92] is administered. This questionnaire ($\alpha = 0.97$) consists of 24 items to which participants respond by selecting a number ($0-100$) to reflect strength of agreement to a specific statement regarding musical beliefs (0 = strongly disagree … 100 = strongly agree). The items included are based on Bandura's sociocognitive theory and assess domains: mastery experiences (eight items), vicarious experiences (five items), verbal/social persuasion (six items), and physiological state (five items). An example of an item from this measure is, “I have had positive experiences performing music in the past”. This measure has been used in studies with older adults [44]. The adaptation from the original version includes a change in the order of the questions and changes in the wording of 7 questions. More specifically, the question, “I have improved my music performance skills by watching professional musicians, who are similar to me in some way, perform well”, was changed to “I have improved my music performance skills by watching professional musicians perform well”. The question, “My friends think I am a good performer on my primary instrument”, was changed to “My friends think I am a good performer on my piano”. The question, “I have had positive experiences performing in large ensembles” was changed to “I have had positive experiences performing in large ensembles

(more than 11 performers)". The question, "I have improved my music performance skills by watching other students, who are similar to me in some way, perform well" was changed to "I have improved my music performance skills by watching someone I know perform well (parent, brother, sister, church member, etc.)". The question "I have had positive experiences performing solo, or, in a small ensemble" was changed to "I have had positive experiences performing music solo". The question, "I have had positive experiences performing music in large ensembles" was changed to "I have had positive experiences performing music in a small ensemble (2-10 performers)". Lastly, the question "Performing with my instrument makes me feel good" was changed to "Performing on piano makes me feel good".

Participants' expectations about the effects of intervention/control exercises on post-test outcomes are examined as a potential covariate. During the last week of intervention, the trainers administer a modified version of The Cognitive Training Expectations questionnaire to examine participants' attitudes and expectations about the effects of the intervention received on cognition and everyday function [59]. The NICT questionnaire was modified to refer to "music training" or "piano training", and the "memory" and "reasoning" questions were omitted since we are not assessing these abilities. The questionnaire explains that cognitive function refers to abilities such as attention, memory, visual perception, information processing, and reasoning; and that cognitive training refers to activities that aim to improve cognitive functions by training within a specific timeframe (i.e., several weeks or months). The questionnaire then asks participants to rate what effects they expect the intervention exercises to have including whether the exercises will result in improved general cognitive function, memory, concentration, distractibility, reasoning, multi-tasking, and everyday performance. Ratings are on a 7-point Likert scale ranging from completely unsuccessful (1), to no expectations (4), to completely successful (7). Participants also rate the degree to which the intervention was engaging, enjoyable, and challenging on a 7-point scale ranging from very strongly agree (7), to neither agree or disagree (4), to very strongly disagree (1). Finally, participants rate whether or not they were satisfied with the program ranging from extremely satisfied (7), to neither satisfied or dissatisfied (4), to extremely dissatisfied (7) and indicate whether they felt that they had "trained their brain" (yes/no). This questionnaire has been successfully implemented in our pilot study and prior studies [59].

5. Data analytic plan

5.1. Power

Statistical power analysis using G*Power [93] in consideration of our pilot data effect sizes as well as attrition was conducted to estimate power. We will control type I error at 0.05 to achieve at least 80% statistical power. We expect up to 20% attrition after the initial in-person visit across the time period in which cognitive intervention study protocols are administered.

To examine the efficacy of piano training to improve CAP, cognition, and everyday function among older adults, a final n of 198 participants ($n = 99$ per randomized condition) will achieve 95% power to detect a significant group × time interaction across baseline to immediate post-test, with an alpha of 0.05. This assumes a small effect size (f) of 0.10[94] (Cohen's f effect sizes are 0.10- small, 0.25- medium: f is roughly equivalent to ½ of d when comparing two groups) [94]. To examine the moderating effects of MCI on intervention efficacy, a final n of 168 will have 0.95 power at alpha 0.05 to detect medium effects ($f = 0.25$) for significant group x time x moderator three way interactions.

5.2. Interim analyses

Interim analyses will be conducted in June of 2019, after the pilot, first, and second replicates are completed. We expect that 140 participants will have completed post-test at this time. Interim analyses will be conducted to ensure the safety of the trial and feasibility of study intervention adherence. The purpose will be to confirm feasibility of the training conditions, to assess effect size on cognitive measures from pre- to post- training and adapt number of sessions, if warranted, and to monitor safety. If at interim analyses, < 75% of participants randomized to an arm complete at least 16 sessions (80% of prescribed 20), the intervention arm will be deemed not feasible. If this occurred for both arms, the study will end. Finally, interim analyses will examine the potential efficacy of the piano training arm. Effect sizes and confidence intervals for all cognitive outcomes will be calculated for pre- to post-training relative to controls. We expect that the piano training arm will produce an improvement of at least $d = 0.25$ from baseline to post-test on at least one of the cognitive measures of verbal fluency (phonemic, category or switching), Trails A or B, or Digit Coding, relative to active controls. If at interim analyses, an effect size of $d = 0.25$ or greater reflecting improvements from piano training relative to controls is not observed on at least one of the cognitive outcomes measures (verbal fluency, Trails, Digit Coding) relative to controls, we will randomize the remaining participants to 25 sessions (i.e., 37.5 h) instead of 20 sessions (i.e., 30 h) of training. In this instance, number of training sessions completed will be examined as a covariate in final analyses.

5.3. Primary analyses

We will inspect the distribution of scores to confirm that parametric statistical testing is appropriate. In the event that distributional properties do not support parametric tests, we will compare the results from conventional parametric analyses with (a) results from similar non-parametric testing (e.g., Wilcoxon signed ranks test), (b) results from parametric analyses conducted after the non-normally distributed variables are transformed to improve normality to compare the results with the conventional parametric analyses, and (c) any illegal values or outliers of $\geq \pm 3z$ will be checked for accuracy with the raw data.

We will conduct one-way ANOVA or Chi-square analyses as appropriate comparing the randomized groups at baseline on age, race, education, sex, MoCA, GDS-S, hearing, and vision, to ensure that the study randomization procedures are successful. We will also confirm the equivalence of the two randomized conditions by comparing the NICT questionnaire responses. The total across the six items relevant to cognition will be calculated and examined in analyses. If even a marginally significant ($p < .1$) difference is observed for any of these study variables, the pertinent variables will be included as covariates in subsequent analyses.

Primary data analyses will follow the intent-to-treat principle. Sensitivity analyses will further examine effects of piano training relative to music instruction among those who are adherent (i.e., who completed 16 or more hours) in both conditions.

The primary objective is to assess the effects of piano training as compared to music listening instruction on CAP, cognition, and everyday function. CAP includes Time Compressed Speech, Words-in-Noise, Dichotic Digits Test, Dichotic Sentence Identification, and Adaptive Tests of Temporal Resolution: all are parametric tests of perception. Cognition includes Verbal Fluency (phonemic, category, and switching), Digit Coding, and Trail Making test: all are parametric tests of cognitive function. Everyday function includes the Timed IADL Test and TEA, both parametric measures.

Data reduction in the form of principal component factor analysis (PCA) will be used to derive composite outcomes of CAP, cognition, and everyday function for analyses to reduce the number of comparisons. Baseline data across CAP, cognitive, and everyday function outcomes will be factor analyzed using pairwise deletions. Based on the number of factors derived and factor loadings of the individual measures (0.4 or greater), outcome composite scores will be calculated after transforming the baseline data to z scores while taking into account the directional scaling of the items. Post-test scores will be standardized

based upon the baseline mean and SD. The baseline factors and loadings will be applied to calculate post-test composite scores.

To examine the efficacy of piano training to improve CAP, cognition, and everyday function among older adults, we will compare changes in performance for piano training relative to music listening instruction across the two measurement points (baseline, immediate post-test). We will use the PCA-derived composites of CAP, cognition, and everyday functioning as outcomes. We will use repeated measures analyses of variance within the mixed effects models, examining group as the between-subjects factor and time as the within-subjects factor. The group x time interaction will indicate whether the participants randomized to piano training change at differential rates over time relative to those randomized to the control group. This output will be obtained for each of the composite outcomes (CAP, cognition, and functional abilities). We will apply Holm-Bonferroni adjustments [95] to reduce Type I error. Specifically, the Holm-Bonferroni procedure uses a step-down process whereby *p*-values are sorted from lowest to highest, then the lowest p-value is used in it raw version, the second lowest p-value is multiplied by two, the third lowest *p*-value is multiplied by three and so on until the adjusted *p*-value reaches or exceeds the pre-specified threshold for statistical significance, in our case a two-tailed *p* value of 0.05.

5.3.1. Intent-to-treat approach

We expect that some participants will not complete their assigned training and/or post-test for a variety of reasons, generating missing values. Participants are encouraged to complete post-test regardless of adherence to their assigned training. Intent-to-treat (ITT) analysis will be applied. To maximize available information, we will employ statistical techniques that allow for the inclusion of missing data. Specifically, we will use linear mixed effects models to analyze data. This advanced analytical method allows for the inclusion of participants with missing data, so long as data are missing at random and offers flexibility with regard to the specification of the variance/covariance structure, which often leads to improved fit of the analytical model to the actual data. If there is non-ignorable missing data, we will apply pattern-mixture mixed effects models to assess the sensitivity of our findings with regard to missing data [96].

5.4. Secondary analyses

A secondary objective is to examine the moderating effects of MCI on piano training efficacy. Moderating effects of MCI status will determine if piano training is effective for older adults with and/or without MCI. We do not have a directional hypothesis for this objective. We will test for moderation effects to determine at what stage along the cognitive status continuum—without MCI vs. MCI—intervention is most effective. To do so, we will examine three-way interactions (MCI x training group x time) for the CAP, cognitive, and everyday function composites. When an interaction is significant, we will stratify analyses by MCI status and examine effect sizes. Effect sizes from pre- to post-training relative to controls will be compared for participants with/without MCI. An alpha of 0.05 will be used for these analyses.

Participants who score 26 or higher on the MoCA will be defined as no MCI (i.e., cognitively normal). Those participants who score a 20–25 on the MoCA will be defined as MCI if they score a 0.5 on the CDR and have performance at or 1 SD below their age, sex, and education norms on any of the following measures: Trails, Verbal Fluency, Digit Coding, Craft Story Recall, Multilingual Naming Test, or Benson Complex Figure. Those with MoCA scores 20–25 who score 0 on the CDR, but have performance at or 1 *SD* below expected for age, sex, and education will be adjudicated prior to analyses. If an individual scores 20–25 on the MoCA, and 0.5 on the CDR, but has performance above expected on all of the aforementioned measures, their case will be adjudicated prior to analyses. The study physicians will adjudicate such cases prior to coding of MCI status for final analyses.

Pursuant to National Institutes of Health guidelines on examining sex as a biological variable, we will examine if sex moderates any significant intervention effects identified in analyses by examining sex x group x time interactions. Effect sizes will be reported by sex if there are any significant differences (alpha 0.05).

To quantify the effects of piano training further, in addition to examining composite outcomes as detailed above, we will calculate and report effect sizes for pre-to-post change of piano training relative to controls for each individual measure of CAP, cognition, and everyday function for the sample overall as well as stratified by MCI status and among those who are adherent only (80% or more of sessions completed).

Sensitivity analyses will be conducted to examine if missing data or outliers significantly affected results. We will conduct sensitivity analysis for missing data by using pattern mixture models. The pattern of results will be compared to ITT analyses. Results will also be conducted after any outliers, defined as observations with values of greater than $+3$ or smaller than -3 z score units, are removed and compared to primary results.

5.5. Exploratory analyses

We will also explore mediators of intervention effects. We expect that enhanced CAP will mediate cognitive gains. We further hypothesize that cognitive gains will mediate functional improvements. With identification of significant effects from the primary analyses, we will examine behavioral mediators of interventions to determine mechanisms. We hypothesize that improved CAP will mediate cognitive gains. We hypothesize that cognitive gains will mediate functional gains. Formal mediation tests using a bootstrapping technique as outlined by Hayes [97] and Selig and Preacher [98] will be used to examine these hypotheses. The pre-to-post differences will be captured by a latent score, whereby the post-test score will serve as the outcome with pre-test score covaried. Results yield estimates and confidence intervals for the indirect and total effects. The procedure allows simultaneous estimation of all three pathways (M on Y; X on M; X on Y, where M = mediator (e.g., CAP score), Y = outcome (e.g., cognition), and X = predictor (e.g., group assignment) as well as adjustment for covariates (e.g., depression). The use of bootstrapping will ensure that power is not reduced from the main effect analyses [99]. An alpha of 0.05 will be used for these analyses.

Exploratory analyses will further examine effect size for the pre-to post-change of piano training relative to music listening instruction among those who are adherent (i.e., who completed 80% or more of assigned number of sessions) in both conditions. Analyses detailed above for specific aims 1 and 2 will be repeated among this subsample. Results and effects sizes among the adherent sample will be compared to the ITT derived results and effect sizes. We will further examine if effects are moderated by a better ear pure-tone average (PTA). In these analyses we will examine if there are significant training group x time x hearing interactions on CAP, cognition, or everyday function, using an alpha of 0.05.

As it is possible that training will be differentially effective for those with CAP disorders (CAPD), we will identify a subgroup of participants (regardless of MCI status) who could be diagnosed with CAPD. Diagnosis of CAPD requires performance deficits on the order of at least two standard deviations below the mean on two or more of the following tests [61,100]: temporal processing (TCS, ATTR), degraded speech understanding (WIN), or dichotic processing (DDT, DST). Analyses for the cognition and everyday function outcomes will be repeated with groups defined as with/without CAPD as an independent variable. We will examine if there are significant training group $\times$ time $\times$ ADP status interactions using an alpha of 0.05.

We may also explore moderation effects of covariates such as MCI subtype (amnestic, non-amnestic, multiple domain) to determine who is most likely to benefit from the intervention among participants with

MCI. To do so, we will examine three-way interactions (covariate ×s training group × time) stratified by MCI status, if MCI was a significant moderator in results of analyses for aim 2 described above. Effect sizes will be examined.

The self-efficacy measures (general self-efficacy and music performance self-efficacy) will be examined as exploratory outcomes by comparing the two randomized conditions across the two measurement points (before/after training). Analyses will include ordinal logistic regression analyses across levels of self-efficacy conducted within the generalized estimating equations (GEE) statistical framework to account for repeated measurements. Significant improvements on either measures demonstrated in this analyses will be followed by exploratory mediation analyses to examine if improvements in self-efficacy can account for any observed training effects on CAP, cognition, or everyday function. Thus, we will examine an alternative hypothesis that training gains can be attributed to improved self-efficacy. An alpha of 0.05 will be used.

To explore if initial music aptitude affects performance within each of the training conditions, AMMA at baseline will be examined as a covariate (i.e., modifier) of Basic Piano Measure performance (BPM) from the first to the final day of training among those in the piano training condition. Similarly, baseline AMMA will be examined as a covariate on the Music Listening Measure (MLM) across the same two time points within the control group. Again, ordinal logistic regression with GEE will be used given the ordinal scaling of the outcomes. An alpha of 0.05 will be used.

6. Discussion

We present the rationale and design of a phase II study to investigate whether piano training is an efficacious intervention to improve cognition, CAP, and everyday function among older adults with and without MCI. The contribution of the proposed research is expected to be the identification of a novel and efficacious cognitive intervention (i.e., piano training) to counter age-related cognitive and functional decline, which could potentially delay dementia onset. If we find that piano training is more efficacious than music instruction to improve CAP, cognition, and/or everyday functional abilities, then we will know that it is a viable cognitive intervention. If so, the results will indicate that cognitive interventions targeting basic sensory-motor interactions (e.g., piano training) are a superior approach to cognitive stimulation (e.g., music instruction).

The study results will also indicate who is most likely to benefit from piano training through analysis of moderating effects. If those with MCI or who meet the diagnostic criteria for CAPD do not experience improved CAP, cognition, or everyday function, results would indicate that piano training is either not efficacious in these populations or that a larger dose may be required to obtain the same benefit. It is also possible the outcomes improved by piano training could vary by MCI or CAPD status. The results will determine if those with or without CAPD or with a specific subtype of MCI benefit most, and if so, for which outcomes. If results indicate differential benefits, we will be able to tailor the intervention to specific populations and make hypotheses regarding the connection between specific pathologies and treatment effects. If pure tone hearing status moderates training effects, then we will know that it is important to correct peripheral hearing (e.g., prescribe hearing aids) prior to intervention. Prior cognitive intervention research has examined the role of self-efficacy and the effects of expectations on outcomes [101,102]. We will further explore if self-efficacy is enhanced by piano training and whether expectations about the two conditions affected outcomes. The results will also indicate if initial music aptitude determines benefits derived from piano training. Thus, the effects of several potential moderating factors will be known.

If we find that piano training enhances cognition relative to music listening, we will further examine if the mechanism for improved cognition is CAP. If we find that piano training enhances everyday function as compared to music listening, we will determine if the mechanism is improved cognition, and if so, what particular aspect of cognition. Alternatively, if only one or two of the composite outcomes are improved, we will be able to rule out potential mechanisms (e.g., results may reveal that CAP is not a mechanism). Examination of effect sizes across individual outcome measures will guide future studies to focus on the most promising outcomes and will provide further insight into possible mechanisms (e.g., only dichotic CAP measures show training effects, then divided attention may be an underlying mechanism). We will thereby elucidate the underlying mechanisms of effective interventions to facilitate maximizing cognitive gains and improving everyday function.

The contribution of this research will be significant in that if an intervention could delay the onset of Alzheimer's disease by only one year, there would be about 9.2 million fewer cases of the disease in 2050 [103], substantially lessening the burden. Results will inform subsequent research and clinical practice by facilitating the design and implementation of effective interventions to attenuate cognitive decline and thereby improve public health.

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