Increased Functional Connectivity After Listening to Favored Music in Adults With Alzheimer Dementia

J.B. King[1,2], K.G. Jones[1], E. Goldberg[3], M. Rollins[2], K. MacNamee[4], C. Moffit[4], S.R. Naidu[5], M.A. Ferguson[6], E. Garcia-Leavitt[7], J. Amaro[7], K.R. Breitenbach[8], J.M. Watson[4,9], R.K. Gurgel[5,10], J.S. Anderson[1,2,11], N.L. Foster[7,12]

1. Interdepartmental Program in Neuroscience, University of Utah, Salt Lake City, UT, USA; 2. Department of Radiology and Imaging Sciences, University of Utah, Salt Lake City, UT, USA; 3. Jewish Family Services of Utah, Salt Lake City, UT, USA; 4. Department of Psychology, University of Utah, Salt Lake City, UT, USA; 5. Department of Communication Sciences and Disorders, University of Utah, Salt Lake City, UT, USA; 6. Berenson-Allen Center for Noninvasive Brain Stimulation, Division of Cognitive Neurology, Department of Neurology, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, MA, USA; 7. Center for Alzheimer Care, Imaging, and Research, University of Utah, Salt Lake City, UT, USA; 8. Genetic Science Learning Center, University of Utah, Salt Lake City, UT, USA; 9. Department of Psychology, University of Colorado Denver, Denver, CO, USA; 10. Department of Otolaryngology, University of Utah, Salt Lake City, UT, USA; 11. Department of Bioengineering, University of Utah, Salt Lake City, UT, USA; 12. Department of Neurology, University of Utah, Salt Lake City, UT, USA

Corresponding Author: Jeffrey S. Anderson, 1A71 School of Medicine, 50 N Medical Drive, Salt Lake City, UT 84132, andersonjeffs@gmail.com

Abstract

BACKGROUND: Personalized music programs have been proposed as an adjunct therapy for patients with Alzheimer disease related dementia, and multicenter trials have now demonstrated improvements in agitation, anxiety, and behavioral symptoms. Underlying neurophysiological mechanisms for these effects remain unclear.
METHODS: We examined 17 individuals with a clinical diagnosis of Alzheimer disease related dementia using functional MRI following a training period in a personalized music listening program.
RESULTS: We find that participants listening to preferred music show specific activation of the supplementary motor area, a region that has been associated with memory for familiar music that is typically spared in early Alzheimer disease. We also find widespread increases in functional connectivity in corticocortical and corticocerebellar networks following presentation of preferred musical stimuli, suggesting a transient effect on brain function.
CONCLUSIONS: Findings support a mechanism whereby attentional network activation in the brain's salience network may lead to improvements in brain network synchronization.

Key words: Personalized music, dementia, supplementary motor area, fMRI, functional connectivity.

Introduction

Individualized music programs have been proposed as adjunct treatments for a large and growing population of individuals with Alzheimer disease and related dementias (1). Approaches to formal interventions utilizing personalized music therapy consist of identifying favorite music of an individual through interviews with the individual, friends, and family, and training on a personalized music device, as well as observation of symptomatic improvement and evaluation for other causes of agitation or anxiety (2).

Specific benefits from listening to personalized or favorite music, rather than background or "relaxation" music, have been shown (3, 4).

Several studies have investigated symptomatic improvements associated with personalized music therapy or listening programs. While an intervention that was not personalized for individual participants involving live music did not show benefit on levels of depression or quality of life (5), in contrast, personalized music programs have resulted in improvements in depression (6, 7), anxiety (6-9), agitation (10, 11), and behavioral symptoms (9, 12), although mixed results have also been observed (13, 14). In a retrospective study examining over 25,000 patients in long-term care facilities, those with individualized music programs showed decreased rates of antipsychotic medication, decreased anxiolytic medication, and reduced behavioral problems (15).

Even in patients with advanced dementia, music recognition appears to be a relatively spared domain of memory function (16). Memory of musical selections is preserved in patients with impaired verbal memory (17). There may be integration of music and autobiographical memory in the medial prefrontal cortex, facilitating retrieval of personally salient episodic memories when listening to familiar musical excerpts (18). Familiarity of music is directly related to engagement of brain resources in response to music (19), and positive valence of musical selection also enhances how memorable music may be (20).

Brain mechanisms for symptomatic benefits from individualized music programs are not well understood. Early reports of symptomatic improvement through personalized music therapy proposed a "Progressively Lowered Stress Threshold Model" as a conceptual framework (3, 21). This hypothesis posited that impaired sensory perception and processing lowered a stress threshold and heightened anxiety, and that familiar

or personally meaningful music might be more easily perceptible than unfamiliar or background stimuli, resulting in decreased anxiety. More recent studies of emotive content of music have emphasized the role of brain reward circuits and dopamine responses as a mechanism for pleasure associated with listening to favorite music (22). Alternatively, benefits may be secondary to effects on brain attentional systems or through stimulation of brain regions associated with autobiographical stored memories. To discriminate among putative neurophysiological mechanisms, we performed functional brain imaging in a cohort of patients with mild Alzheimer disease.

Methods

All experimental procedures were performed following informed consent for research participants in accordance with protocols approved by the University of Utah Institutional Review Board and the Code of Ethics of the World Medical Association for protection of human subjects in scientific research.

Participant Selection and Characteristics

A total of 22 individuals participated in the evaluation and scanning portion of the study. After all data was collected, fMRI scans were visually inspected and pre-processed to account for head motion. Subjects with high motion during the resting-state (<100 motion-free volumes, n=4) or visible artifacts on BOLD images (n=1) were excluded from further processing, giving a final subject pool of n=17. Of these participants, there were 11 males and 6 females with a mean age of 71.82 ± 5.96 years.

Personalized Music Training

Each individual completed a period of personalized music training that consisted of meeting with the patient and caregivers, identifying favorite songs and music styles, training of patient and caregivers on an iPod device with personalized music, and confirmation over at least 3 weeks following the training that patients had used the device independently following the training.

Preferred Music for Participants

Participants submitted a list, in advance, of music that had personal significance to them. From each song, 20 second segments were selected to be played for the participant during a scan. The 20 second selections were taken from the most iconic and recognizable moments in each song. For popular music selections (i.e. country, jazz, rock, etc.), show tunes, and other modern lyrical songs selections were taken from the chorus, the first verse, or the opening of the song. For instrumental popular music,

selections were taken from the refrain, introduction, or at the beginning for an iconic solo. For pieces of western art music (baroque, classical, romantic, etc.) selections were taken from easily recognizable statements of the main or secondary theme in exposition and recapitulation sections, as well as strongly defined introductions to developmental sections, and climactic cadential moments with loud dynamics. Lastly, choral selections were made similarly to popular music (choruses and introductions), but sometimes selections came from instrumental interludes with clear statements of a main theme.

Auditory Evaluation

We measured pure tone averages (PTA) in a sound booth. Subjects with a four-frequency (0.5, 1, 2, and 3 kHz) PTA greater (worse) than 40dB HL were not considered for the imaging portion of the study. This cutoff was chosen so that only subjects with relatively normal hearing or only mild hearing loss were included in the study. Subjects with hearing thresholds worse than 40dB HL could potentially confound the imaging data as we evaluate the central processing of sound because they lack peripheral (cochlear) acuity to deliver the stimulus to the brain.

For those subjects with a PTA less than 40dB HL, we measured standard word recognition scores to test peripheral auditory function. As per previously published protocols, we also administered three behavioral central auditory tests based on their standardization, ease of use, likelihood of being affected by dementia, and testing of different central auditory skills (23). The tests included the Synthetic Sentence Identification with Ipsilateral Competing Message test (SSI-ICM) (24) and two dichotic tests involving speech: the Dichotic Sentence Identification test (DST) (25) and the Dichotic Digits Test (DDT) (26). The sequence of test presentation was randomized to prevent an order effect.

MRI Acquisition

Imaging was performed in the sagittal plane on Siemens Trio 3T MRI Scanner with Siemens 32 channel head coil. Structural imaging consisted of MP2RAGE sequence (TR = 5 s, TE = 2.91 ms, TI = 700 ms, GRAPPA acceleration factor = 2, 1 x 1 x 1 mm resolution). Functional imaging consisted of one task fMRI sequence (8 minutes duration) and 2 resting-state fMRI sequences (10 minutes duration each). Resting-state fMRI acquisitions were acquired with participants' eyes open and instructions to "allow your mind to wander and let thoughts pass through your mind." fMRI sequences were acquired using multiband acquisition (multiband factor = 8, TR = 800 ms, TE = 33 ms, 2 x 2 x 2 ms resolution).

Structural MRI Processing

The FreeSurfer imaging analysis environment (v6.0.0), which is documented and freely available for download (http://surfer.nmr.mgh.harvard.edu/), was used to process structural scan data to obtain subject-specific subcortical regions of interest given characteristic volume loss in dementia patients and risk of volume averaging with the ventricles using a voxelwise atlas-based approach to region selection (27). A detailed description of the FreeSurfer pipeline can be found on the FreeSurfer website.

fMRI Music Task

A passive listening task consisted of 24 blocks of 20 seconds each presented in random order with instructions to listen to the musical selections. 8 blocks each of the music selection presented forward, 8 blocks with the same selections presented in reverse, and 8 blocks of silence were presented. Four preferred musical selections were chosen from each subject's favorite musical selections by a professional classical composer (KB) to include iconic clips of the selected music (as detailed above). Song clips and reversed selections were created using Logic Pro X software.

Activation maps for forward music > silence, reverse music > silence, and forward music > reverse music were obtained for each subject using a general linear model in the SPM12 software suite (Wellcome Trust, London) following postprocessing that included motion correction (realign: estimate and reslice), coregistration to MP2RAGE image (coregister: estimate), normalization to MNI space (normalize: estimate and reslice), and smoothing (FWHM: 6 mm kernel). Second level estimates were obtained across 17 subjects using 2-direction t-tests for each of the three selected contrasts. Statistical significance was assessed using cluster-defining threshold of $p < 0.001$ with familywise error corrected cluster-level significance to account for multiple comparisons.

Resting-state fMRI Processing

A postprocessing pipeline was selected to optimize correction for head motion and physiological artifacts, and physiological waveforms from heart rate and respiration were explicitly recorded for each subject during each resting state acquisition to use as regressors. Motion correction, coregistration, segmentation, and normalization of MP2RAGE and BOLD to MNI template was performed in SPM12 software (Wellcome Trust, London) for MATLAB (Mathworks, Natick MA). Phase-shifted soft tissue correction (28) was used to regress physiological waveforms as well as regressors obtained from 6 detrended subject motion parameters, degraded

white matter, degraded cerebrospinal fluid, and soft tissues of the face and calvarium. Censoring of frames showing greater than 0.2 mm (motion scrubbing) was performed as a final step prior to analysis with concatenation of remaining frames (29). No significant differences were seen in root-mean-square head motion between initial and final resting state acquisitions for each subject using paired t-test across subjects.

Region of Interest Selection

Resting-state fMRI data were analyzed using brain parcellations at 2 levels of granularity. Average time series were extracted from each of 7 distributed brain networks associated with the cortical parcellation of Yeo et al. (30) and cerebellar parcellation of Buckner et al. (31). Cerebellar time series were extracted from left-lateralized and right-lateralized voxels in each of the 7 networks. Each network was treated as a single region of interest, and BOLD time series was averaged across all voxels for each of the 7 networks for each of the 740 volumes in each of the 2 runs for each subject after excluding the first 20 volumes of each run.

A finer parcellation consisted of 333 regions in the cerebral cortex (32). Fourteen subject-specific subcortical regions were added using FreeSurfer-derived segmentation (33) of bilateral thalamus, caudate, putamen, amygdala, hippocampus, pallidum, and nucleus accumbens, segmented independently for each subject. Fourteen cerebellar regions were also added (31) comprising left- and right-hemispheric representations of a 7-network parcellation. This combined parcellation scheme covering cortex, subcortical structures, and the cerebellum comprised a total of 361 regions. Average BOLD time series were extracted for each volume in each run for each subject.

Results

Auditory Testing Results

The average pure tone thresholds for the right and left ears were 24.9dB and 24.6dB, respectively, indicating normal peripheral hearing (average <25dB or the volume of a whispered voice). Average dichotic sentence scores for the right and left ears were 91% and 45%, respectively. Average dichotic digit scores for the right and left ears were 94% and 90%, respectively. Average Synthetic Sentence Identification test results with a 20dB, 0dB, and -20dB signal-to-noise ratio were 91%, 71%, and 40%, respectively.

Imaging Results

Participants listened to favorite musical selections, personalized for each individual, compared to the same

Table 1. Significant activation associated with fMRI music contrasts

| Music Forward > Silence						
Region	**p-Value (Cluster, FWE)**	**T-Statistic**	**Voxels**	**MNI: X**	**Y**	**Z**
Left Auditory Cortex	8.9 e-16	12.82	2169	-56	-2	-6
Right Auditory Cortex	4.4 e-16	9.99	2224	56	-8	-6
Right Inferior Frontal	0.015	6.45	166	50	20	18
Supplementary Motor Area	0.012	5.82	175	6	2	70
Right Premotor Cortex	0.020	5.67	156	50	-2	44
Left Cerebellum	0.022	5.59	152	-22	-72	-32
Music Reverse > Silence						
Region	**p-Value (Cluster, FWE)**	**T-Statistic**	**Voxels**	**MNI: X**	**Y**	**Z**
Left Auditory Cortex	5.38 e-14	10.19	1710	-62	-16	6
Right Auditory Cortex	2.49 e-14	8.41	1770	56	4	-8
Music Forward > Music Reverse						
Region	**p-Value (Cluster, FWE)**	**T-Statistic**	**Voxels**	**MNI: X**	**Y**	**Z**
Supplementary Motor Area	0.00036	5.72	295	-8	2	60

selections played in reverse. When selections were played in reverse, auditory content was preserved while iconic motifs, language, and familiarity of the music was disrupted. Functional activation associated with forward and reversed musical stimuli is shown in Figure 1. Both forward and reverse musical stimuli elicited activation within bilateral auditory cortex and areas of left lateral frontal lobe, and cerebellum. There was specific activation seen in the bilateral, left greater than right, supplementary motor area for musical stimuli played forward, with a significant cluster for forward vs. reverse stimuli. Details of activated regions are displayed in Table 1.

To evaluate functional connectivity before and after the music task, we performed 10-minute resting-state fMRI acqisitions and calculated functional connectivity between mean time series of 7 brain networks from a previously published parcellation of the cerebral cortex (30) and cerebellum (31). The cerebellar time courses were calculated separately for left and right cerebellar hemispheres. Mean functional connectivity for each pair of cortical and cerebellar network time series was calculated as the correlation coefficient between the time series. A paired t-test across subjects was performed to identify network functional connectivity that differed significantly after the music task compared to before the music task, with results shown in Figure 2.

Significantly higher functional connectivity was observed after the music task for the visual network compared to somatomotor, salience, and executive networks, and for numerous cerebellar and corticocerebellar network pairs as shown. All results were corrected for multiple comparison corrections using false discovery rate approach. No network pairs showed

significantly decreased functional connectivity after the music task.

Figure 1. Response to Favorite Music. Images show significant activation across participants to preferred musical selections played forward and in reverse greater than to blocks of silence (above), and to forward greater than reversed musical selctions (below). Results were cluster corrected using family-wise error, with display threshold set at p<0.001
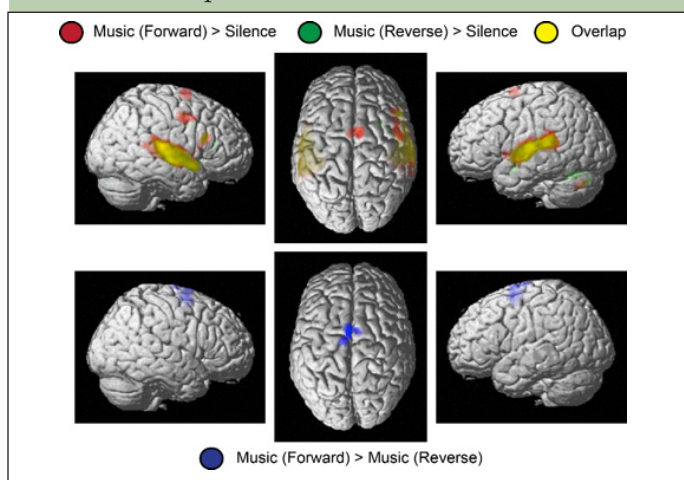
To evaluate at a finer spatial distribution changes in functional connectivity, we computed time courses for 361 regions comprised of a 333-region functional brain parcellation of the cerebral cortex (32), 14 subcortical regions derived from subject-specific FreeSurfer segmentation, and the 14 cerebellar regions from the Buckner et al. parcellation shown in Figure 2 (31). Results

for comparison of functional connectivity after vs. before the music test show in Figure 3 that for almost all brain region pairs functional connectivity after the music task was equal to or higher than before the task. While no individual connections were significant following full multiple comparison correction across all 361 x 361 region pairs given the modest sample size, the mean functional connectivity averaged across all region pairs was higher after the task compared to before (p=0.0167, paired t-test over 17 subjects).

Figure 2. Changes in functional connectivity after listening to preferred music. Colored squares show functional connections between 7 cortical networks and corresponding networks within the left and right cerebellum that showed greater connectivity after musical task than before, corrected by false discovery rate <0.05 across all connections. Color scale shows t-statistic from bidirectional paired t-test across 17 subjects
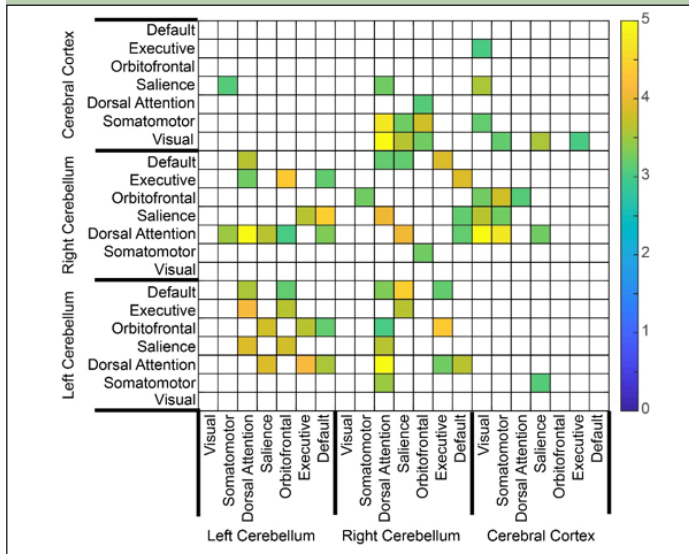

Discussion

In a cohort of patients with Alzheimer disease related dementia, we find that listening to preferred musical selections is specifically associated with activation of the supplementary motor area when compared with the same selections played in reverse such that passages were not clearly recognizable. After a period in which favorite musical selections were played, there were widespread increases in fMRI connectivity involving both corticocortical and corticocerebellar connections, particularly involving sensory and attentional networks.

These findings directly support previous research identifying the supplementary motor area as a region associated with selective activation to more familiar musical stimuli (34, 35). This region, in addition to the anterior insula that was also more active for familiar music, may play an important role in the preservation

of musical memory in Alzheimer disease related dementia given that these areas tend to be relatively spared from neurodegenerative processes in the disease (34). Recognition of famous musical passages has also been associated with preservation of brain tissue in the anterior temporal lobes in Alzheimer and semantic dementias (36).

Figure 3. Changes in functional connectivity after listening to preferred music. Results from connections between 361 x 361 gray matter regions of interest, grouped by functional network. Warm colors represent greater connectivity after the music task and cool colors represent greater connectivity before the music task
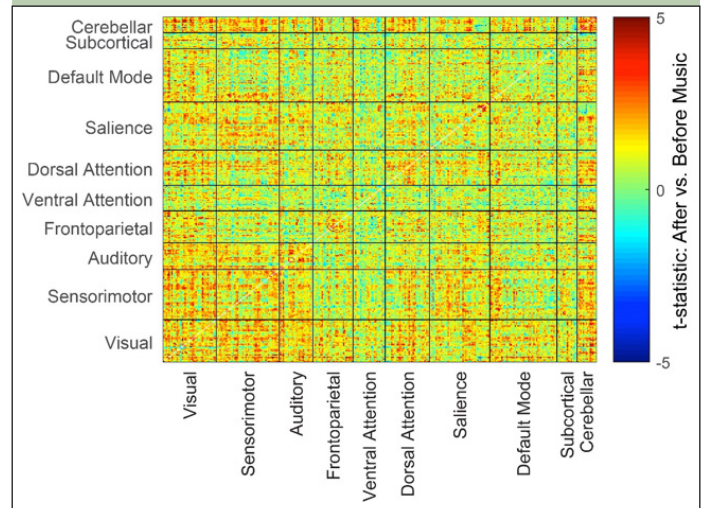
The dorsal anterior cingulate, supplementary motor area, and frontal insula comprise a brain network known to process stimulus salience across multiple sensory and cognitive domains, and form a core part of the brain's ventral attention network engaged in response to novel or unexpected stimuli (37). The specific activation of the supplementary motor area for favorite musical selections may suggest an attentional mechanism for symptomatic improvements associated with music listening whereby preferred musical selections evoke brain attentional responses, at least for a window time following the musical stimuli.

The brain's salience network is closely associated with reward circuits in the ventral striatum, also known to play a key role in both salience processing and music appreciation. Activation of dopaminergic pathways in the ventral striatum is associated both with salience and valence of sensory stimuli (38), with dopamine signaling salience of rewarding stimuli (39). Selective activation of the ventral striatum has been associated with responses to musical stimuli evoking emotional chills (40), and specific activation of the dopaminergic striatum has been demonstrated in response to favorite music (22).

Widespread decreases in functional connectivity have been observed in Alzheimer disease related dementia, with earliest involvement of the brain's default network

(41-46). In contrast, the brain's salience network is relatively preserved until late in Alzheimer disease and given the specific ability of familiar music to engage these circuits (34) may facilitate attention, reward, and motivation associated with the salience and mesolimbic networks (47).

Increased functional connectivity in our results associated with a personalized musical intervention suggests recruitment of brain networks that were highest among sensory regions and corticocerebellar circuits. Given that Alzheimer disease related dementia is typically associated with decreased functional connectivity (48), it is plausible that symptomatic relief observed after musical interventions may be related to such connectivity increases that occur in the context of apathetic and amotivational states observed in dementia. Anecdotal evidence from observation of music listening programs has highlighted precisely this type of "awakening" associated with musical interventions (49).

It remains unclear from our results the duration and generalizability of the effect on brain connectivity and attentional activation seen in our results. We studied only a single imaging session, and while participants had been trained for a period of weeks on a music-listening program, it is unknown whether such training was required to see an effect, whether such an effect persists beyond a brief period following stimulation, or whether other functional domains such as memory or mood may be enhanced by the specific changes in neural activation and connectivity in our results. Given the modest sample size in our study and known heterogeneity of symptoms in patients with early Alzheimer Disease, these results serve primarily a heuristic value in suggesting mechanisms for neurophysiological effects that can be tested in clinical trials with larger sample sizes and control of additional variables such as psychiatric comorbidities, personal musical history, environmental support, and pharmacotherapy. Further, while we do observe widespread increases in functional connectivity following music listening, our study is not powered to specifically identify which brain networks are primarily affected.

Nevertheless, we find support for an effect in Alzheimer patients for personalized music interventions that utilize favorite musical selections of individuals to promote improved attention and function consistent with the empirical benefits seen in clinical practice (15). Given the potential benefit of adjunctive therapies such as personalized music intervention, particularly given the low cost, few reported adverse side effects, and wide potential availability of these interventions in a large and growing patient group with enormous social cost and personal impact, continued evaluation of mechanisms and potential applications of personalized music programs and music therapy is warranted.

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