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Research Paper: Investigating the Effect of Music on Spatial Learning in a Virtual Reality Task

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ABSTRACT

Background: Spatial learning and navigation is a fundamental cognitive ability consisting of multiple cognitive components. Despite intensive efforts conducted with the assistance of virtual reality technology and functional Magnetic Resonance Imaging (fMRI) modality, the music effect on this cognition and the involved neuronal mechanisms remain elusive.

Objectives: We aimed to investigate the effect of familiarity with music on human's spatial learning performance in a goal-directed virtual-navigation task combined with an fMRI study.

Materials and Methods: Healthy adult participants were navigated using fMRI-compatible equipment within a 3D virtual maze developed with the MazeSuite application. This measure was taken to learn the environment and find the position of hidden objects. The fMRI data were obtained, processed, and analyzed to map the brain activity and identify the differences in the Blood Oxygen Level Dependent (BOLD) activity between the research groups during searching and finding phases. Both behavioral and image analysis were outperformed in this research. Besides, three T-contrasts were defined to compare the activity patterns between the study groups. The selected music was Mozart sonata owing to its known facilitating impact on cognition.

Results: The obtained data indicated that those who have heard music prior to the test had a better performance; they navigated faster and committed fewer errors. The activation of regions, like parahippocampal gyrus, related to spatial cognition, was observed in the searching phase and the activation of the cerebellum, superior temporal, and marginal gyrus, i.e. more probably related to music processing was observed during the finding step.

Conclusion: The active regions found in this work indicated the interplay of the neural substrate underlying to spatial-temporal tasks and music processing.

Keywords: Magnetic Resonance Imaging (MRI); Spatial learning; Patient navigation; Hippocampus; Image processing; Computer-assisted

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Highlights

● Repeated exposure to some music improved the spatial learning performance and functional neural activity of navigators when they listened to it during goal-directed navigation.

● The neural areas recruited for object-location learning and spatial memory retrieval were modulated as a function of music as well as being familiar with the music.

Introduction

To navigate in an environment, human beings and animals visualize different pathways in their brain to plan a suitable path; then, they move along the selected path to reach the target. Navigation is the process in which human/animal use multiple cue sources to determine a route (trajectory) toward a goal, then follow that route. Navigators may use various navigational strategies to find their way [1]. Sometimes, salient objects, known as landmarks/beacons are used to guide navigation [2]. Sometimes, an internal representation of the environment (i.e. cognitive map) is built. Besides, the saved abstract information is employed for orientation. The interaction of navigational strategies was further suggested by researchers stating that navigators spontaneously and flexibly use either of them while attempting to find their way in an environment [3].

Based on the classes of input (i.e. allothetic & idiothetic), two navigational strategies are defined. First spatial strategy, in which navigation in an environment is performed by using different landmarks and forming relationships between the landmarks and a navigator attempts to orient itself concerning those landmarks. Second, response strategy which depends on the ability to quickly recognize and react to situations with well-learned action-outcome relationships [4]. The first strategy (“place strategy”) is hippocampal-dependent and the second one (“response strategy”) is dorsal-lateral and striatal-dependent. Previous neuroimaging investigations indicated that employing spatial strategies increased activity and gray matter in the hippocampus. Furthermore, enhanced activity and gray matter in the caudate nucleus were observed when implementing response strategies [5].

Spatial learning indicates animal/human encodes information about the environment to facilitate navigation and retrieve the location by recalling data from memory. Learning to find a way in an environment is a process that involves perceptual, mnemonic, and executive components mediated by a large network of the brain structures. Spatial memory is formed when sensory data about the environment is integrated and processed. Learning and memory processes in the brain are caused by changes in the neuronal representation of stimuli. It is hypothesized that synaptic plasticity in the form of Long-term Potentiation (LTP) is recognized as the neuronal basis for memory formation [6]. NMDA Receptor (NMDAR)-dependent LTP or an LTP-like process in the hippocampus is almost considered as the neuronal mechanism responsible for spatial memory and learning [7, 8].

Multiple experiments on animals and human beings have revealed the facets of spatial cognition. To evaluate spatial learning and memory, cognitive tasks performing in mazes are often defined. Moreover, different scenarios are executed to indicate multiple aspects of spatial cognition. To evaluate human navigation and spatial learning abilities, Virtual Reality (VR) and Functional Magnetic Resonance Imaging (fMRI) modality are occasionally adopted. A network of activated regions compatible with those regions reported in the literature of animal navigation was identified in the fMRI studies of human spatial navigation, using virtual environments [9]. In fMRI, the Blood Oxygen Level Dependent (BOLD) signal -correlated with neural activity- is measured. Increased neuronal activity in a part of the cortex increases regional blood flow resulting in an elevated oxygen level in that area. In recent years, fMRI has been successfully employed for evaluating healthy as well as cognitively-impaired populations. Accordingly, it has been proven to be a noninvasive and reliable technique yielding valuable information about brain function in learning and memory. Decades of research have emphasized the importance of the medial temporal lobes for spatial navigation and long-term memory [10].

Moreover, listening to music could enhance cognition and learning [11]. Behavioral, neuropsychological, and electrophysiological experiments have demonstrated that listening to particular music improves spatial-temporal reasoning in the short term. In general, ex-

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perimental data have indicated that being exposed by music affects brain function. It is more probable that music modulates neurotransmitters and other neuronal mediators to induce this effect. The impact of musical stimulations on the capability of the spatial learning-memory in developing rats has also been supported by behavioral and electrophysiological techniques [12]. However, the effectiveness of music in this regard depends on multiple factors, including the complexity of the music. Indeed, music is an intrinsically complex stimulus; it is almost used in experiments that investigate several different facets of cognition. Accordingly, finding exactly how and why music worked across different studies may particularly be difficult [13]. Furthermore, different aspects of music may convey various information types; thus, correlates with different neural systems. As a result, selecting suitable music, which has less cognition and/or neuronal involvement, should be considered. Mozart sonata classical music seems to be an appropriate choice. This is because it is speculated that listening to it could improve spatial learning and memory (the Mozart effect) and could facilitate human navigators within the VR environment.

Assessing spatial learning and memory has long attracted neuroscientists' attention. A growing number of studies have been published concerning the performance of rats in the Morris water maze; a rat is trained to find the position of a platform hidden in the opaque water of the tank [14, 15]. However, human navigation studies using fMRI provided more realistic results. This is because it requires no prior learning, like animal experiments. VR technology could also provide a sense of presence and facilitate fMRI-based spatial learning experiments in humans. In this regard, some researchers have designed complex (large-scale) virtual environments and tested various navigational tasks and cognitive involvements, and their underlying neural characteristics.

The role of the visual stimulus within an environment has occasionally been investigated which could potentially influence navigation [16]. Specifically, when sets of landmarks are available, they interact in special manners or compete for associative strength to control the rats' behavior [17]. The hypotheses for cue-competition and cue-integration were tested by Zhao et al. in 2015. The research participants were required to determine the response direction in a homing task similar to an archer's one. In this task, multiple cues were either integrated to reduce response variability or compete to determine the response direction. It was concluded that that visual landmarks and path integration interact to guide human navigation [18].

Studies from overlapping fields, including electrophysiology, lesion, and imaging have indicated a network of brain regions for navigation. Several researchers have stated that spatial learning is mainly mediated with the hippocampus; although the temporal cortex and prefrontal structures also significantly impact this learning [19]. Using the fMRI scan, Aguirre et al. found that navigation in a virtual maze is associated with increased activity in the parahippocampus gyrus rather than the hippocampus [20]. They suggested that, unlike rats, the parahippocampus is the neural substrate that supports spatial mapping in humans. Supplementary results further supported that the hippocampal gyrus is activated when navigation is performed within a maze based on landmark guidance. The neural correlates of reward-based spatial learning have further been evaluated by other scholars [21]. In this fMRI-based research, a VR task was conducted to learn subjects via using extra-maze cues. Besides, they were navigating in an 8-arm radial maze to find hidden rewards. Differential contributions of the hippocampus and other temporoparietal areas were found for searching and reward-processing phases during a reward-based spatial learning task. Experimental evidence in the support of interaction among navigational strategies also exists in a few studies. A study reported that navigational strategies correlate with the gray matter when the cognitive decline occurs due to normal aging [22]. Furthermore, experiments conducted in a virtual plus-maze revealed switches between navigational strategies.

An fMRI experiment was conducted by Gron to assess and contrast male and female brain activities during a searching task within a complex Three-Dimensional (3D) VR maze. Accordingly, the research subjects attempted to find the way out. Statistical analysis on functional images revealed navigation-related activation in the medial occipital gyri, lateral, and medial parietal regions, posterior cingulate and parahippocampal gyri, as well as the right hippocampus proper. The relevant results indicated significant fMRI activity in the left hippocampus of males versus an increased activity in the right parietal and right prefrontal cortex of females. Furthermore, the behavioral analysis signified that males acted faster than females to find the exit pathway [23].

Data on the effect of music on cognition and in particular on spatial cognition are scarce. Listening to Mozart sonata (K.448) caused subsequent short-term enhancements of spatial-temporal reasoning ability in college students [12]. In addition to temporal cortex activation by the Mozart sonata vs. other music (e.g. Beethoven's Fur Elise & 1930s piano music), dramatic significant

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differences were observed in the activation in the dorsolateral prefrontal cortex, occipital cortex, and cerebellum; all were expected to be important for spatial-temporal reasoning. Additionally, the spatial learning and memory capacity of developing rats was investigated behaviorally and electrophysiologically with the effect of music stimulation by Mozart sonata for Two Pianos in D Major [24]. Exposed rats could find the platform position in the Morris water maze task with significantly shorter latencies. Furthermore, the alpha power spectral quantity of electrohippocampogram was statistically higher than that of the control rats and the rats stimulated with horror music [24]. Another study documented that a 10-week exposure to Mozart sonata for Two Pianos in D Major caused the mice to complete T-maze tasks with significantly lower working time and fewer errors [25]. Overall, these findings indicated the potential effect of music on neural plasticity. In a study, the Mozart effect was investigated where the brain regions activated by the Mozart sonata (K.448) were compared and contrasted to those activated by the 1930s piano control music. Mozart sonata activated a significantly greater number of regions, including DPC (Brodmann's areas 9 and 46), occipital cortex (Brodmann's areas 18 and 19), frontal cortex, and the cerebellum [26].

Various efforts have been made to determine the effect of music on spatial learning and cognition. However, the neural basis of spatial navigation learning in humans with the effect of music processing cognition and the exact involved mechanisms remains elusive. In this research, an fMRI experiment was conducted to explore the effect of listening to music and familiarity with it on the performance of human spatial learning. The main purpose of this research was to investigate the effect of listening to standard classical music (which makes no additional cognitive involvement) on a goal-directed navigation task; we considered this effect either by reducing the time of the search or by making fewer mistakes. We also aimed to understand whether subjects, who had repetitively listened to the music prior to the test, experience significant neural activation, compared to those who may be distracted by music when they first hear it within the fMRI scanner. Navigators who had listened to music before the test (‘mu’ group) were differentiated from the controls (‘co’ groups) via statistical analysis. Furthermore, the functional mapping of the activated regions for both study groups was acquired and compared. Such measures helped to indicate whether the activation pattern of navigation-related regions in the brain was affected by listening to the music.

Materials and Methods

Fourteen healthy volunteers (10 males, Mean±SD age: 23.4±2.1 y, age range: 21-26 y; 4 females, Mean±SD age: 22.5±2.08 y, age range: 20-25 y) without neurological or mental health disorders participated in this study. They all had a normal or corrected-to-normal vision. All study participants were biomedical engineering undergraduates and had experiences of playing computer games. The research participants were selected among those who self-declared their computer game experience (4-7 out of 10). All study participants received an examination by a physician prior to the test to exclude those with severe stress and the phobia of wearing goggles or of being presented in the fMRI scanner. Before the test, all study subjects provided written informed consent.

The research project was approved by the Ethics Committee of Iran University of Medical Sciences (Code: IR.IUMS.REC.1397.1244). The study subjects were divided into two groups. Ideally, the research subjects were randomly selected from a larger population and assigned to one of the two groups. The first group listened to Mozart's background music several times during the week (the experimental ‘mu’ group). However, the second group listened to no music recently (the ‘co’ control group) although might have been familiar with the considered music. Individuals were given all the necessary instructions by experimenters before being presented into the recording room. All study subjects were requested to navigate within a 3D virtual maze developed with the MazeSuite application [27]. They were instructed to use fMRI-compatible equipment. Their brain functional images were captured during the task to be processed later. The MazeMaker module of the MazeSuite software allows one to design different 3D mazes, including static, moving, and audio objects. This software has two other modules (MazeWalker and MazAnalyzer) which provide the possibilities of executing a defined task and analyzing the participants’ behavior while performing a task.

A rectangular environment was designed that consisted of 8 walls inside. Several distinct objects were hidden behind the walls. The research subject was given two tasks to solve in the VR-based maze. They were requested to accomplish a navigation task within the described maze: 1. To learn the environment at the search phase; and 2. To find a given target at the test phase. In general, the experiment consisted of two main experimental blocks. The training was followed by a probe trial and this order was the same for all research participants. Unlike boxcar-based design, which consists of multiple blocks of defined time and the interval between them, it was impossible to define the blocks of stimulus separated by fixation times. The free navigation in the virtual maze was conducted continuously and individually and the stimulation was not induced via images or videos; therefore, the fMRI design was not as straightforward as the majority of tasks attempting to orderly stimulate subjects. Accordingly, scans from searching and finding phases were ex-

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tracted with the timing of the image acquisition (TR) and used for the following analysis and statistical steps.

Before the main experiment, the research subjects were given a 60-seconds interval to navigate freely within a simple virtual environment. At this pretraining phase, the study subjects attempted to practice the motor aspects of the task and learn to use the 4 keys on the joysticks to be able to maneuver within the environment. As described, the task consisted of two phases of searching and finding. At the search phase, the study subjects were given 200 seconds to move around the environment and learn where the salient objects were hidden. In the second phase, the research subjects were requested to find the position of an object that had been observed in the search phase. This 60-second test trial was finished earlier than scheduled; provided that the target was found by a subject. The time delay between the two runs was two minutes for the subject to rest and to be instructed (b-d). A top view of the described environment, including an overview of the space and objects, is shown in Figure 1A. Some intramaze views of the environment are also presented in Figure 1A. As mentioned earlier, our experiment was conducted according to the hypothesis of Mozart's effect, i.e. listening to Mozart sonata as the background music could improve cognitive performance, including spatial learning. During navigation, this music was played through MR compatible headphones within the scanner.

The research subjects were scanned at the Iranian National Brain Mapping Lab (www.nbml.ir) in spring 2019 using Siemens 3.0 Tesla scanner. The required images were acquired using a 64-channel head coil. The study participants wore a goggle to directly observe the monitor located in the control room. A headphone compatible with the huge magnetic field in the scanner was used for playing music. The research participants held two fMRI compatible joysticks by hands, each consisting of two keys. They could move forward and backward as well as turn right and left using the joysticks. Each scanning session lasted approximately 15 minutes. The sessions comprised structural imaging, searching (200 seconds), and finding (maximum 60 seconds) phases. In between phases, the study participants were requested to find the position of a familiar object observed in the search phase.

To achieve the required structural data for analysis, a 10-minute T1-weighted sagittal localizing scan was initially obtained. The relevant scans were recorded with repetition time (TR)=3000 ms, echo time (TE)=3.44 ms, inversion time (TI)=1100 ms, flip angle (FA)=7°, in-plane resolution (IPR)=1×1 mm, in-plane matrix (IPM)=256×256, field of view (FOV)=256 mm with 128 sagittal slices of 2 mm thickness. Then, the func-

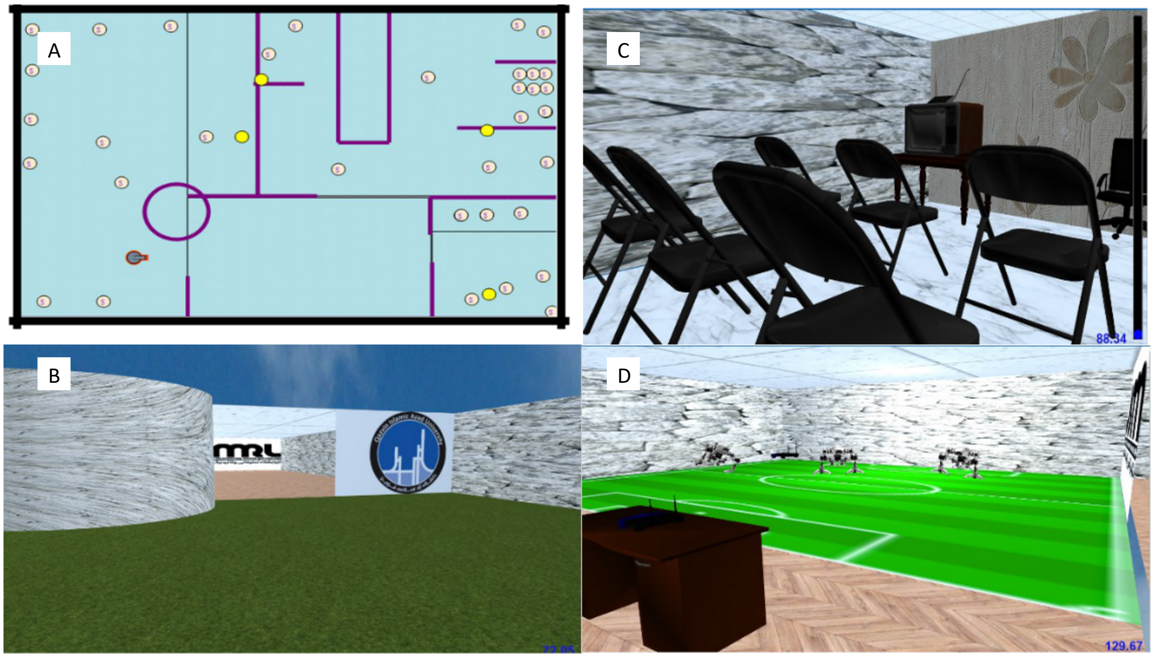

Figure 1. A top view of the described environment

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A: An extramaze view; and B-D: Some inreamaze views of the designed environment

* The designed environment is similar to the Mechatronics Research Lab at our university (MRL -QIAU)

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tional T2*- weighted BOLD images were acquired with a multi-band slice accelerated gradient-recalled Echo Planar Imaging (EPI) sequence and the following parameters: TR=3000 ms, TE=30 ms, FA=90°, FOV=220 mm, 48 axial slices of 2.5 mm thickness, IPR=3.4×3.4 mm, IPM=64×64.

Results

All studied subjects, except one of the second group's members, were able to solve the maze task. After the test, a questionnaire was obtained from the study participants about their experience within the virtual environment. Some questions were also inquired about how they solved the navigational task in the maze. Table 1 provides information related to participants' behavioral analysis and the quality of their performance in the maze. Each research participant was initially requested to score the maze (0-10), according to its complexity. The relevant mean scores and data extracted from the Maze analyzer module from the Mazesuite package are presented in Table 1. Figure 2 shows a graphical view of the MazeAnalyzer output tracing the path that a study participant has traversed in the maze. The 'mu' group members had fewer complaints about the complexity of the environment and could easily solve the maze. In this group, 71% of the cases claimed that music helped them find the object; while 29% claimed that listening to the music did not affect solving the task. No complaint of distraction was reported by the members of the first group. Of the second group members, 52% claimed that they had not paid attention to the music; 30% claimed that the background music distracted them while navigating, and 18% stated that the music assisted them to learn the environment and find the object location. Figure 3 shows these statistics by pie plots for quick comparison. Due to the limitations of fMRI imaging as well as its high cost, we failed to obtain images more subjects. However, to have a large population for statistical validation, 40 volunteers (n=20/group) participated in our test to perform the virtual-navigation task behind the computer at our lab.

The inter-group performance was compared statistically with an independent group t-test data. This test's objective was to determine whether groups differed in terms of time required to complete the task or not. The related results indicated that the subjects of the 'mu' group were significantly faster in the retrieval of the spatial memory ($t=2.8$, $P=0.05$), compared to the controls. Another statistical test was performed to find the significance of path length differences between the research groups. This test data indicated that the path length, i.e. traversed by the 'co' group members in the searching phase was significantly lower than that of the other group ($t=3.1$, $P=0.05$).

The BOLD signal has low amplitude and it is almost susceptible to noise and artifacts. Based on these characteristics, it is necessary to perform some preprocessing steps before the main processing. Preprocessing steps described here were conducted to make our fMRI data ready for further analysis and to ensure that inferences

Table 1. The behavioral performance of the spatial navigation task described in the text

Group	Complexity Score out of 10 (Mean)	Path Length		Selecting Repetitive Paths (%)	Time to Solve the Maze (Mean)	Velocity (cm/s)
		Searching	Finding			
First group ('mu')	3.82	51.02	11.83	33	24.78	29.57
Second group ('co')	5.49	56.8	13.21	41	36.29	34.48

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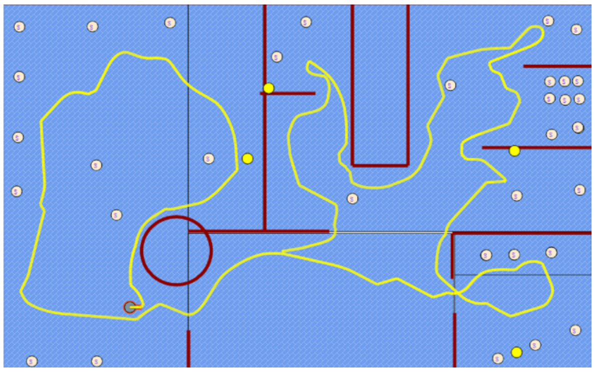

Figure 2. Navigating in an environment by a subject traced by the MazeAnalyzer

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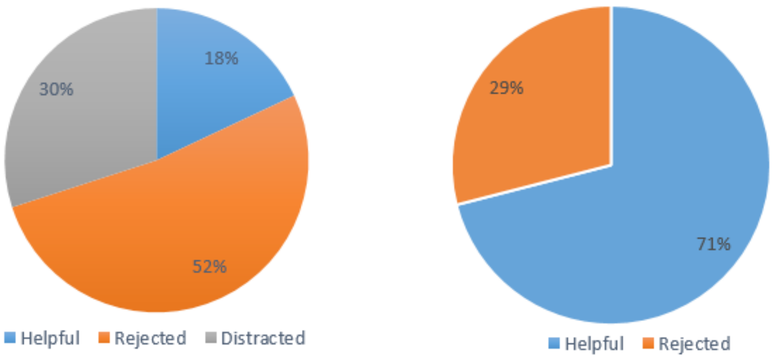

Figure 3. The study participants' self-declaration of music impact on finding the target object for the first (right) and the second (left) groups

and decisions are reliable. The acquired fMR images were analyzed using Statistical Parametric Mapping (SPM). This comprehensive MATLAB-based toolbox [28] is commonly used for analyzing functional imaging data. Images were recorded in DICOM format, then converted to NIFTI, and subsequently resliced. Reslicing is performed to modify the timing between image slices. Accordingly, images underwent slice time correction using the interleaved down to top method. Next, they were realigned and unwrapped to remove motion artifacts (Figure 4). This procedure was applied to resolve rotations and movements that occurred during imaging. To this end, images were compared with a reference image (the first slice of each run); then, they were corrected to remove rotations and translations occurred by movement. The SPM software can compute and evaluate the amount of head movement within the scanner. When the amount of movement is less than the voxel size, the obtained data is ready for analysis. Voxel size in our recording was equal to X=2mm, Y=2mm, Z=2mm. Figure 4 shows the head translation and rotation for a study participant who could pass this test. The maximum translation that occurred in the scanner was <0.5 mm along the Y-axis; the maximum rotation was about 0.7 degrees in the yaw direction. These values were less than that of the voxel size; thus, the subject's head motion was tolerable for the next analyses. Subsequently, the collected images were normalized to the standard template; Montreal Neurological Institute (MNI). Next, spatial smoothing was conducted using a full-width Gaussian kernel at half a maximum 8 mm.

After preprocessing, data analysis proceeded. A standard computational model for fMRI data, known as the General

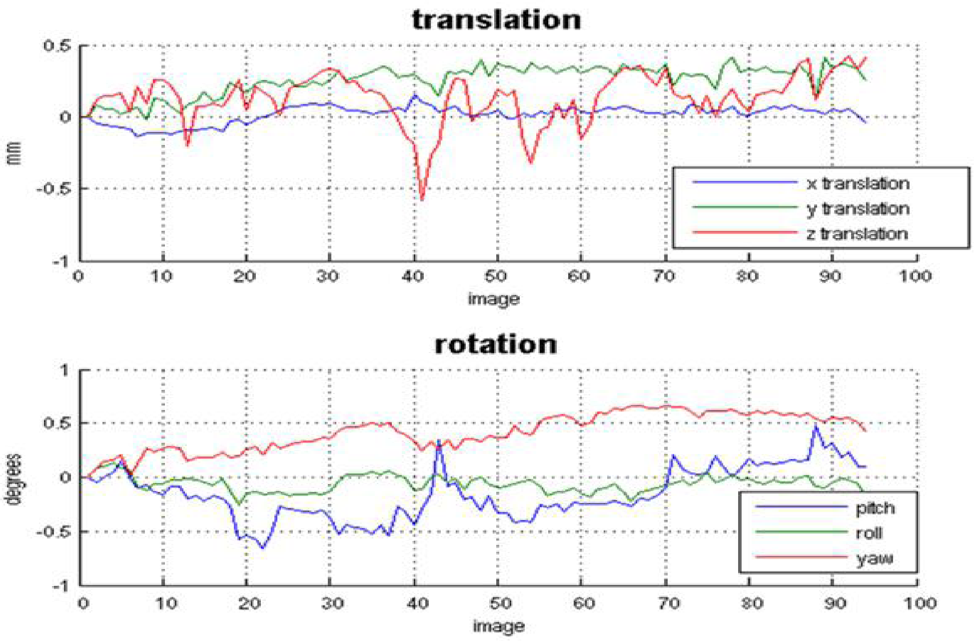

Figure 4. A study participant's head movement and rotation in the scanner

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Table 2. Significant clusters found for contrast-1 (regions with increased activity during searching with music exposure effect)

Active Region	Hemisphere	K	t	Z	X (mm)	Y (mm)	Z (mm)
Lateral ventricle	R	5763	32.86	21.04	28	-46	10
Parahippocampal gyrus	R	651	28.06	19.67	36	-24	-26
Parahippocampal gyrus	L	432	26.02	17.48	-34	-22	-28
Cerebral white matter	L	144	16.25	12.73	-10	-12	62
Middle frontal gyrus	R	117	13.75	11.52	50	40	22
Inferior frontal gyrus	R	92	11.64	11.28	54	36	16
Precentral gyrus	L	66	9.64	11.05	-42	-4	54
Cerebral white matter	R	86	10.20	9.11	42	4	24
Temporal pole	R	73	7.14	7.04	52	18	-18
Middle frontal gyrus	L	57	7.10	7.01	-28	20	52
Posterior insula	R	52	5.48	5.44	44	-12	8

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The table has been extracted from SPM software and rewritten for a better view. The following items are settings for the test: Contrast (first group>second group); Height threshold: T=8.53; P=0.001; Expected voxel per cluster, <K>=46.19; Degrees of freedom [10., 94.90]; FWHM=(8.7 mm, 8.7 mm, 8.3 mm); Voxel size (2 mm 2 mm 2 mm).

Linear Model (GLM) was constructed for each subject to perform first-level parametric analyses. The GLM models, observed signals using one or more explanatory variables, are recognized as regressors. For data modeling, regressors were scaled and aggregated to enable the best explanation of the observed data. In this work, the GLM was designed, including the conditions of events, i.e. formed by both phases of our experiment. In other words, the GLM included two regressors related to each phase of our experiment (i.e. searching & finding). Regressors were convolved with a canonical Hemodynamic Response Function (HRF) to generate the design matrix. Furthermore, to remove slow signal drifts, the time series were first filtered using a high pass filter with a minimum cutoff period 128 s. The modeling of the time series was then conducted by weighting and summing of the regressors representing the effects of interest and the potential confounding factors. The two regressors employed used as covariates in the GLM and entered into the design matrix along with time series of the 6 estimated realignment parameters (head movement parameters). By considering regressors related to movement estimates (i.e. nuisance regressors), one could provide conditions that

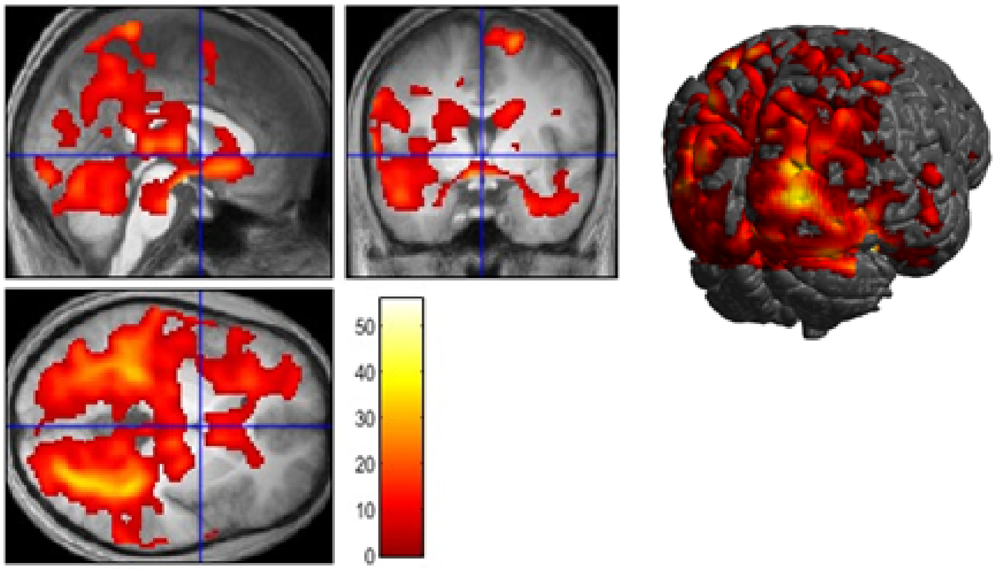

Figure 5. The activated regions for the main effect of searching (contrast-1) displayed

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Left: On the axial, coronal, and sagittal views and on the cortical surface via whole-brain three-dimensional rendering; Right: The activation of parahippocampal gyrus, precentral gyrus, temporal pole, insula, and frontal gyrus is noticeable.

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Table 3. Significant clusters found for contrast-2

Active Region	Hemisphere	K	t	Z	X (mm)	y (mm)	z (mm)
Cerebellum white matter	L	4352	8.62	8.09	-10	-28	-34
Cerebellum white matter	R	1023	8.55	6.83	14	-50	-34
Fusiform gyrus	R	582	8.53	6.54	48	-8	-34
Middle temporal	L	159	6.12	6.06	-64	-30	-14
Middle frontal	R	111	5.86	5.81	28	60	-4
Middle frontal	L	83	5.62	5.579	-28	62	-2
Super marginal gyrus	R	144	5.01	4.98	62	-14	40
Cingulate	L	75	4.96	4.92	-8	28	-14
Middle temporal	R	68	4.89	4.86	58	-8	-20
Inferior temporal	L	53	4.70	4.67	-48	-54	-26
Medium orbital	R	54	4.68	4.65	26	42	-16
Superior temporal	L	51	4.44	4.42	-62	-40	10
Post central gyrus	L	63	4.33	4.31	-62	-4	18

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the estimated parameters for the effects of interest would not be affected by confounding factors. By fitting the best model, subject-specific parameters on each regressor (βs) were calculated for each voxel under the GLM assumption. The most common technique to find the beta values is to minimize the sum of squared residuals (the difference between observed & predicted values). These error terms, with unexplained variances, were minimized in SPM when attempting to fit the best model to the input data.

The T-contrast approach was implemented to compare the activity patterns between the study groups. In general, three T-contrasts were applied for each subject, including contrast-1 (first group vs. the second group in searching), contrast-2 (first group vs. the second group in finding), and contrast-3 (searching vs. finding). To illustrate the activity of brain regions, the mean structural images of 14 study participants was obtained. MNI-space group-level Family Wise Error (FWE) corrected clusters ($P<0.05$) were acquired for each test.

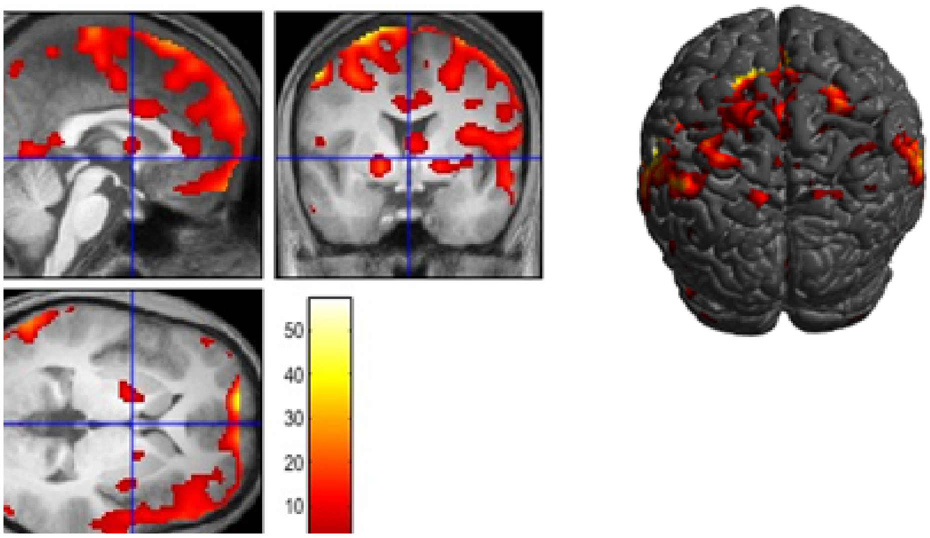

Figure 6. The activated regions for the main effect of finding (contrast-2) displayed

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Left: On the axial, coronal, and sagittal views; Right: On the cortical surface via whole-brain 3D rendering; The activation of frontal, temporal, orbital fontal cortices, as well as cingulate and cerebellum is noticeable.

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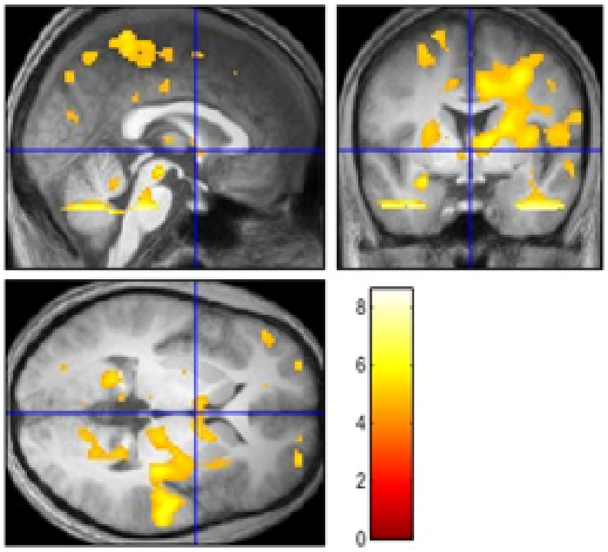

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Figure 7. Contrast 3 (searching vs. finding) was mapped indicating no significant activity at the uncorrected cluster level

*P<0.05

The neural activity of the "mu" group, compared to the "co" group during searching in the maze was contrasted with the t-test. The relevant results are presented in Figure 5 and Table 2. Statistically, significant activation was observed in the neural regions, including bilateral parahippocampal gyrus (P<0.001), middle, and inferior frontal gyrus (P<0.005, P<0.01& P<0.05, respectively), right temporal pole (P<0.05), and right insula (P<0.05). The maps of neural activity in Figure 5 display the activated regions, graphically. The highlighted voxels in these maps were significant at corrected P<0.05.

The study groups' neural activity contrast during the finding of an object in the maze, with the effect of listening to Mozart sonata (contrast-2), was next mapped (Figure 6 & Table 3). The research participants mainly engaged in bilateral cerebellum activation (P<0.001), bilateral middle frontal (P<0.01), and middle temporal (P<0.001) cortices, as well as left cingulate (P<0.05) and orbital cortex (P<0.05). Superior and inferior temporal cortex was also activated, although not significantly. The active areas for the second contrast differed from those activated for the first contrast. The neural regions involved with searching the maze seem to be mostly specific to navigation cognition; this si while regions got active in the finding phase were more corresponded to music-related cognition.

Table 3 lists the regions with increased activity during finding an object with the music effect for group1>group2. The table signifies Talairach coordinates (X, Y, Z), the t-values referred to the peak voxel of each cluster, and the cluster size given as the number of functional voxels.

Neural activity for contrasting searching and finding steps (phase 2 vs. phase 1), named contrast-3 in this work, was also evaluated; the obtained data suggested no significant effects on BOLD activation at the corrected cluster level (P<0.05). Figure 7 shows the mapping results for this test obtained by the SPM software. To run this test, a software program was written to match the images of both research phases. The number of scans varied between both phases and from subject to subject in the finding phase. This algorithm extracted the same number of scans for each phase by discarding several scans from the searching phase to enable the contrast phases via a one-sample t-test.

Discussion

Both behavioral and image analyses were conducted in this research to investigate the effect of repeated exposure pre-test to Mozart sonata on spatial cognition. Two groups were contrasted while performing a navigational task in a simple non-confusing VR environment. Evaluations indicated that those who have heard music before the test presented no problem with the background music when navigating. They demonstrated a better performance in completing the task and achieved less run time with fewer mistakes.

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On the other hand, some of those who have not heard the music before the test were distracted when they were stimulated with the music in the scanner. They presented a relatively poor performance, compared to the first group members. This matter must be further evaluated with larger sample sizes and different music types. Such measures could determine whether the music stimulation within the scanner for the first time (i.e. hearing the Mozart music during the task) was destructive or not. This effect could be interpreted with the familiarity principle (i.e. the "more exposure effect"). This principle suggests that familiarity or repeated exposure to music makes sense of liking and provides an emotional and hedonic response in the brain [29].

This study aimed to identify the brain neural regions engaged with spatial learning by the effect of repeatedly heard music stimulation. In our work, bilateral parahippocampal gyrus activation related to spatial learning and navigation was highlighted. This activation was considerable during the searching phase. Furthermore, frontal regions, prefrontal cortex, and cerebellum were also activated; as it was expected to occur for a navigation task in simple environments. Insula activation during searching is also justifiable. It is because this region's activation is related to consciousness and cognition. Additionally, spatial memory for retrieving and finding an object in the maze was associated with the right orbitofrontal cortex BOLD activity, i.e. observed in the second contrast. The activation of some regions in the second contrast (for memory retrieval & finding an object), including cerebellum, superior temporal, and marginal gyrus are mostly related to music processing. In general, the activation patterns obtained by contrast-1 and contrast-2 revealed that the degree of familiarity with a stimulus (i.e. the Mozart music) affects the processing capacity of the brain. The pattern of brain activity at early learning (the searching phase of our task) was more intensified than the spatial retrieving phase (the finding phase of our task). This finding could be interpreted either by being more familiar to music in the finding phase or by less cognitive involvement to the retrieval of simple cues and signs from the environment to find a given object. The former states the familiarity principle and the latter indicates that the brain has less processing load to solve a relatively simple navigational task and subsequently, less BOLD activity occurs.

The active regions we found in this work correspond partially to the results [30] previously reported for a spatial-temporal task. In studies on music stimulation effect [26, 29, 30], increased cortical activity in prefrontal, frontal, parietal, and occipital cortices in addition to temporal lobes was reported for listening to Mozart's sonata. Furthermore, a large network of brain regions correlated with music processing was previously identified; they include orbital front lateral and ventrolateral premotor cortices, inferior frontal and supramarginal gyrus, anterior insula, as well as the anterior and posterior areas of the superior temporal gyrus and superior temporal sulcus [31]. Our results highlighted activation in some of these regions; these activations occurred either when the brain encoded the levels of music information during learning a high level spatial cognitive task, or when the spatial memory was tested with repeated exposure to Mozart music.

Conclusion

Our results suggested that repeated exposure to Mozart sonata could improve the functional activity of navigators when listening to it during goal-directed navigation. The patterns of functional neural activity related to music stimulus during spatial learning and memory retrieval were characterized in this work. Besides, the neural areas recruited for object-location learning and retrieval were modulated as a function of music as well as being familiar with the music. Indeed, a large network of neural regions cooperated to encode the environment, the objects in it, also the music information. This network was smaller when retrieval was under investigation.

Investigating different cognitions, such as spatial learning and navigation as well as the spatial memory capacity provided an opportunity to understand and develop the brain potentials. Furthermore, this finding could be helpful for those with cognitive decline, and specifically Alzheimer's disease sufferers. There are some suggestions for future works. It is worth evaluating whether the result is specific to Mozart sonata or other kinds of music that could also produce similar effects. Overall, it may be assessed which specifications music should have to be a facilitator for navigation. The complexity of the task and its effect on results should also be evaluated. Moreover, the simple task considered in this work required no participants to process the details of the spatial cues or be involved in the cooperation and competition of navigational strategies. It remains unclear whether and how the interaction of music-related cognition and spatial navigation cognition is impacted when a complicated task is defined or when other factors, such as reward or navigational strategies interaction are involved.

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Ethical Considerations

Compliance with ethical guidelines

This study was approval by the Ethics Committee of Iran Medical University (Code: IR.IUMS.REC.1397.1244). All study procedures were in compliance with the ethical guidelines of the Declaration of Helsinki 2013.

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Authors' contributions

Conceptualization, investigation, writing-review & editing: Somayeh Raiesdana; Methodology: Mohammad Raouf; Funding acquisition, resources: Somayeh Raiesdana, Mohammad Raouf.

Conflict of interest

The authors declared no conflicts of interest.

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