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ORIGINAL ARTICLE

Characterization of functional brain connectivity towards optimization of music selection for therapy: a fMRI study

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ABSTRACT

Background: Music therapy, a nontraditional approach to patient care, has long been used to achieve a wide variety of positive results. To deepen our understanding of the connection and therapeutic potential of music, the effect of music therapy and music medicine (music administered to individuals without an interactive therapeutic relationship) on the brain remains a topic of active research.

Objective: This study is aimed at investigating the effect of different music genres and individualized music selection on brain functional connectivity (FC) measured by functional magnetic resonance imaging (fMRI).

Methods: Twelve healthy subjects listened to five excerpts: Bach with and without visual guide (unfamiliar), self-selected familiar music, Gagaku (unfamiliar music) and Chaplin (spoken word) while undergoing a block design fMRI study. fMRI datasets were imported into CONN (Matlab toolbox) and graph networks were created for 132 anatomical regions in MNI space. Group connectivity for each soundtrack was quantified and statistically analyzed using the R package.

Results: Complex interactions between brain regions, cerebellar regions (713), superior frontal gyrus (178) and parahippocampus (223), were highest for self-selected music. Brain regions involving sound processing, memory retrieval, semantic processing and motor areas were continuously activated for all five excerpts; however, most connections were formed in language processing regions for the Bach excerpt.

Conclusion: Functional brain connectivity varied by soundtrack with the largest degree of connectivity found consistently for self-selected and unfamiliar (Bach, Gagaku) music. Incorporating individualized music listening into existing therapy paradigms may positively contribute to standard protocol for stroke rehabilitation and prevention.

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Introduction

Stroke, the third leading cause of death in the United States, is the primary cause of long-term mental and physical disabilities [1]. More than 50% of individuals who have suffered a stroke have residual motor deficits [2]. In addition to the debilitating physical effects, once individuals have suffered a stroke, they become extremely susceptible to emotional, cognitive and consciousness disorders [3]. In fact, the rehabilitation period for stroke recovery patients harbors frequent emotional cognitive instabilities that manifest in emotional symptoms such as fear and physical symptoms such as rapid breathing, dry mouth and increased pulse [4]. The focus of care during the rehabilitation period, therefore, is the prevention of secondary brain injury and maximizing cerebral perfusion [5]. Secondary brain injuries are largely facilitated by the emotional and mood disorders stroke patients suffer as a consequence of their acute stroke.

Recent studies have shown that systematic music listening, a music medicine treatment, during stroke recovery can induce brain plasticity that translates into a significantly shorter recovery period and a better long-term prognosis [6]. Music-supported therapy has been repeatedly shown to stimulate cortical areas of the brain associated with memory, motor function and auditory and visual circuits on the normal brain [7]. In one premier example, chronic stroke patients who suffered from resulting hand paralysis showed significant functional improvement using music-supported

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therapy through increased activation and connectivity between auditory and motor regions measured by fMRI imaging [7]. Moreover, melodic intonation therapy (MIT), a music therapy treatment that facilitates expressive language in patients with aphasia by capitalizing on preserved singing functions and the natural musical elements of speech (melody and rhythm), has shown considerable success in improving conversational speech skills [8]. Specifically, patients who have suffered a unilateral, left-hemisphere stroke may benefit most significantly from repeated stimulation of language-capable regions in the undamaged right hemisphere. By incorporating intonation and pitch modulation exercises with rhythmic motor movements in the patients' left hand, MIT is a promising avenue to language and speech recovery in aphasic patients [9]. In this manner, music therapy can induce plasticity and significantly hasten recovery in stroke patients by both encouraging multimodal processing and stimulating the integration of auditory, motor, visual and cognitive systems.

Furthermore, the specific effects of music therapy for musicians, as opposed to nonmusicians, may be far deeper than what has been studied to date. In studies regarding the response to tonal stimuli involving neuroplastic components of the auditory evoked potential (AEP), the auditory cortical responses have been found to be larger in skilled musicians than nonmusicians [10]. These increased neuroplastic mechanisms shown in musicians may be due to modified synaptic connections and neural growth processes in response to sensory inputs that are heightened during musical stimulation. In a separate study, a voxel-based morphometry analysis showed significant structural brain differences between skilled pianists and nonmusician controls in which pianists showed greater gray matter volume in the right thalamus, right superior temporal and right postcentral gyri [11]. These results point to the highly complex mechanism of neural plasticity in individuals with sustained musical training, a phenomenon that can be considered for the treatment of musicians who subsequently suffer stroke. By systematically determining the ways in which music and music therapy affects musicians and nonmusicians alike, music interventions may be customized to provide the best treatment option for patients' specific needs.

In this context, understanding the exact areas of the brain that certain music stimulates through determining functional connectivity and brain activation can pave the way for individualized treatment for stroke patients to emphasize the therapeutic effects of music rather than pharmaceuticals.

This study investigated the effects of listening to five different sound tracks on the functional connectivity in brain regions during fMRI listening sessions. Previously, we have reported on the fMRI BOLD activation created by these sound tracks [12]. To determine functional connectivity in the brain on baseline patients to aid in the selection of musical pieces that elicit the greatest neurological response is the focus of this study. The goal is to optimize how music listening may support therapy by judiciously selecting certain musical pieces that will enhance the pattern of blood flow in stroke subjects and may therefore pave the way for future efforts to improve outcomes.

Materials and methods

Subjects

In this study, approved by our internal review board, 12 healthy volunteers (four males, average age 44 ± 15 years) participated as previously reported [12].

MRI acquisition protocol

After acquisition of a T1-weighted high-resolution 3D image set for anatomical reference (turbo field echo, FOV = 24 cm × 24 cm, resolution = 1.0 mm isotropic, TR = 8.2 ms, TE =3.8 ms), covering the entire brain in axial orientation, echo planar imaging (EPI) contiguous axial slices were acquired of the entire brain (FOV = 22 cm × 22 cm, resolution = 1.5 mm × 1.5 mm, slice thickness 3 mm, TR = 2400 ms, TE = 35 ms). The auditory stimulus was presented in 6 periods (24 seconds duration each) separated by silence (also 24 seconds each, total duration: 5 min 12 sec, total number of acquired brain volumes: 130). Images were acquired on a full body human scanner (Ingenia 3T, Philips Healthcare, Best, The Netherlands).

Auditory pieces

The number of auditory pieces presented to the subject varied depending on tolerance of the total scan duration by the subject. A maximum of seven auditory pieces were presented to the subject. Here, we investigate the relationship of five of these pieces; the four music pieces and a language piece in contrast to the music:

1. *Self-selected emotional music ('self'):* the subject was asked to name a music piece they had a strong positive emotional attachment (which was

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then played from iTunes, Apple Inc., Cupertino, USA during the exam) (12 subjects)

2. *J. S. Bach Invention #1 ('Bach'):* an instrumental piano piece. Selected for its medium level of rhythmic and melodic variation and novelty/ unfamiliarity to the listener. [J.S. Bach: *Two-Part Invention in C Major, Glenn Gould, piano, Sony BMG, 2009*] (12 subjects)
3. *J. S. Bach Invention #1* ('Bach visual') here, the score sheet was displayed simultaneously on a monitor visible by the subject to keep their attention engaged (9 subjects)
4. *Gagaku ('Gagaku'):* (12 subjects). This music from a Japanese opera is largely unfamiliar to Western listeners. [Jussuiraku (Oshiki-cho-Gagaku), "Musical Treasures of Japan," Essential World Masters, 2012] (12 subjects)
5. *Emotionally spoken language ('Chaplin'):* An excerpt of Charlie Chaplin's strongly emotional speech from the movie 'The Great Dictator' [Charlie Chaplin: *The Great Dictator*, United Artists, 2:01:28–2:02:26, 1940] (7 subjects)

MRI analysis

BOLD activation analysis

The AFNI software [13] was used to apply the Generalized Linear Model (GLM) to the fMRI image data. Standard pre-processing was performed (motion correction and spatial smoothing). Averaged fMRI activation maps were created for each auditory piece in Talairach space. Statistical significant activation in these maps was identified by the student *t*-test ($p < .05$).

Functional connectivity analysis

fMRI datasets were imported into CONN and subsequently evaluated with igraph package of the R project. Graph networks were created as gml files with the voxels as vertices and the CC values as edge weights.

Using the connectivity software package 'CONN' (NITRC, matlab), brains were transferred into MNI space and divided in 132 anatomical distinct regions. Functional connections and their strength (expressed as a *t*-value from a Student *t*-test over all subjects, negative and positive) were calculated for all regions for each auditory piece. For further analysis, the following regions were selected: hippocampus, amygdala, superior temporal gyrus, lingual gyrus, supplementary motor area, parahippcampal gyrus, planum temporale, Herschel's gyrus, superior parietal lobe, cerebellum, anterior cingulate, posterior cingulate, precuneus, insula, superior frontal gyrus, middle frontal gyrus and inferior frontal gyrus. The selection was motivated by the intent to investigate functional connectivity in brain regions that may be evolved in auditory and emotion processing. The total number of functional connections averaged over all subjects for these regions was calculated. The strength of each connection was determined as the sum of *t*-values taking into account the connections of each brain region with the others in each subject. The relative strength of connections was expressed by the ratio of the sum of the FC strength and the number of connections.

Similarity of functional connectivity

To gain a measure for the similarity of the connectivity patterns, the correlation coefficient between the number of functional connections for each auditory piece across the different brain regions was chosen. Connectivity patterns with similar number of connections in the same brain regions are therefore considered more similar. In this way, a correlation matrix between auditory pieces was obtained. This correlation matrix was visualized by a network graph (R project), where similar auditory pieces are drawn closer together.

Results

BOLD activation patterns

The BOLD activation patterns for all pieces showed large increase of blood flow bilateral in the superior temporal gyrus (Figure 1A) during music listening. For the unfamiliar pieces (Gagaku and Bach), decreased blood flow during listening (or increased blood flow during the rest periods) was pronounced in the parietal lobe. The visual presentation of the cursor in the score sheet results in increased blood flow in many areas in the cortex. The language piece (Chaplin) resulted in the smallest BOLD effect (least number of participating brain regions).

Functional connectivity

Number of functional connections

FC patterns varied greatly between musical pieces (Figure 1B). The cerebellar regions showed the largest number of connections of all regions (549), followed by the lingual gyrus (348), the inferior frontal gyrus (264), the parahippocampus (223), the supplementary motor area (179), the superior frontal gyrus (178),

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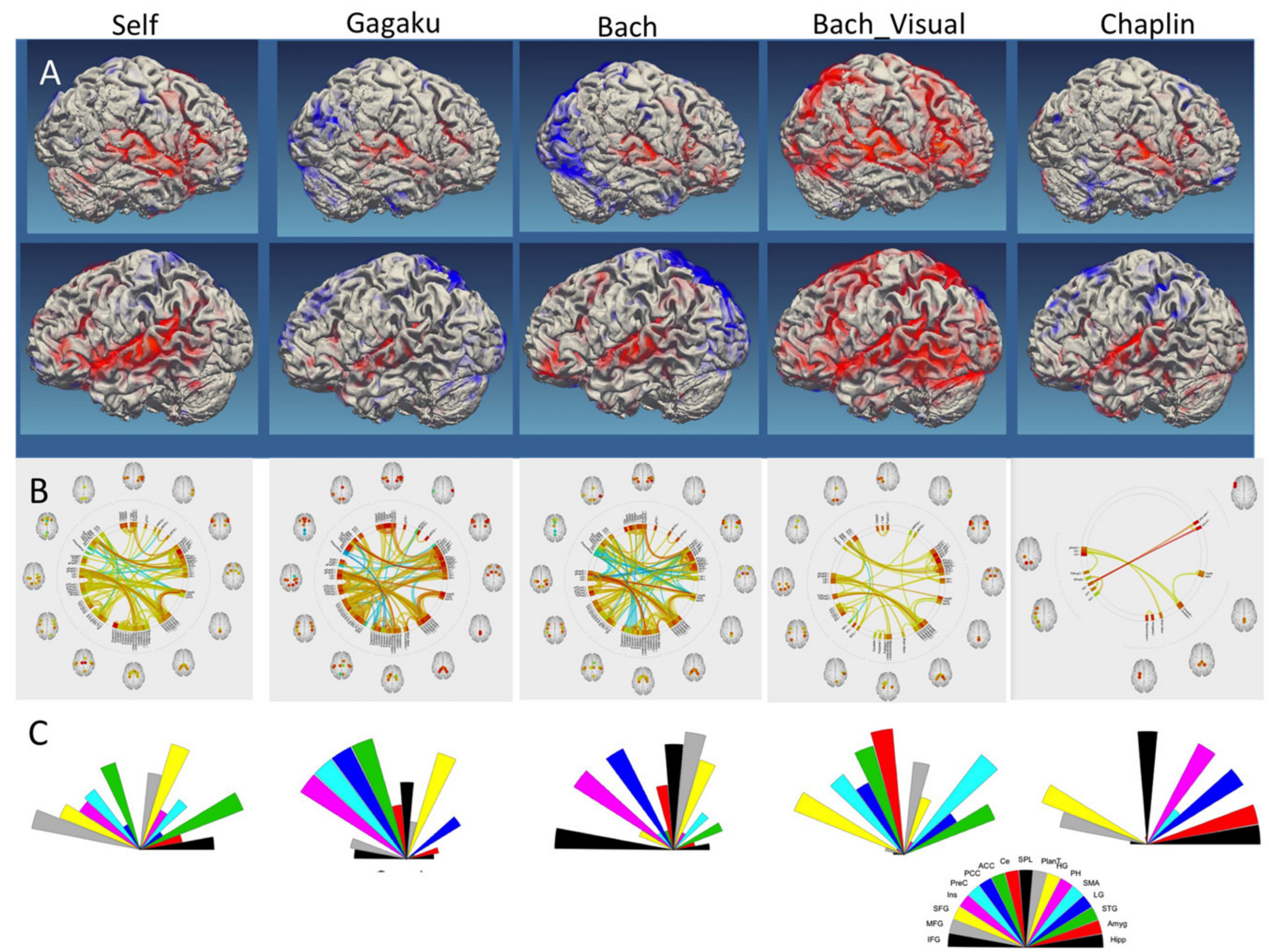

Figure 1. A: BOLD activation patterns (red: increased blood flow, blue: reduced blood flow during listening periods) for all auditory pieces. Similarities, in particular for the superior temporal gyrus region (bilateral) can be acknowledged. The unfamiliar pieces (Bach, Gagaku) expressed reduced blood flow during listening periods (or increased blood flow during silent periods). The visual presentation (Bach visual) resulted in wide-spread BOLD activation of the cortex. The Chaplin piece (spoken language) showed the smallest BOLD effect. B: FC graphs for each auditory piece averaged over all subjects. Distinct differences can be observed, the small number of functional connection for the language piece compared to the other pieces is apparent. C: Segment diagrams of the number of functional connections for each auditory piece. Different colored segments correspond to different brain regions as indicated in the legend below ((Hipp: hippocampus, Amyg: amygdala, STG: superior temporal gyrus, LG: lingual gyrus, SMA: supplementary motor area, PH: parahippcampal gyrus, PlanT: planum temporale, HG: Herschel's gyrus, SPL: superior parietal lobe, Ce: cerebellum, ACC: anterior cingulate, PCC: posterior cingulate, PreC: precuneus, Ins: insula, SFG: superior frontal gyrus, MFG: middle frontal gyrus, IFG: inferior frontal gyrus). Each diagram is individually normalized for display purposes. The variation in FC that is visible in the connection graphs in C is reflected in the variation of these segment diagrams.

Table 1. Total functional connections per brain region.

	Hipp	Amyg	STG	LG	SMA	PH	HG	PlanT	SPL	Ce	ACC	PCC	PreC	Ins	SFG	MFG	IFG
Bach	37	11	13	67	41	49	19	38	21	173	3	15	27	23	40	30	78
Self	61	23	25	96	54	73	30	36	13	18	18	5	50	22	54	49	65
Bach Vis	19	3	12	61	34	33	8	21	7	137	11	7	39	6	31	22	38
Gagaku	37	15	9	95	39	46	23	18	19	181	19	17	52	25	41	37	68
Chaplin	16	11	2	29	11	22	0	2	6	40	0	0	6	2	12	10	15

hippocampus (171) and the precentral gyrus (165) (Table 1 and Figure 1C). Connections for the self-selected (692), Gagaku (741), Bach (685) and Bach visual (489) excerpts were all considerably larger than for Chaplin (184), the only spoken word (Figure 2A).

Strength of functional connectivity

The cerebellum showed the largest strength of connections (3112) over all excerpts and subjects, followed by the lingual gyrus (1310), the inferior frontal gyrus (1162), the parahippocampus (1137), the superior

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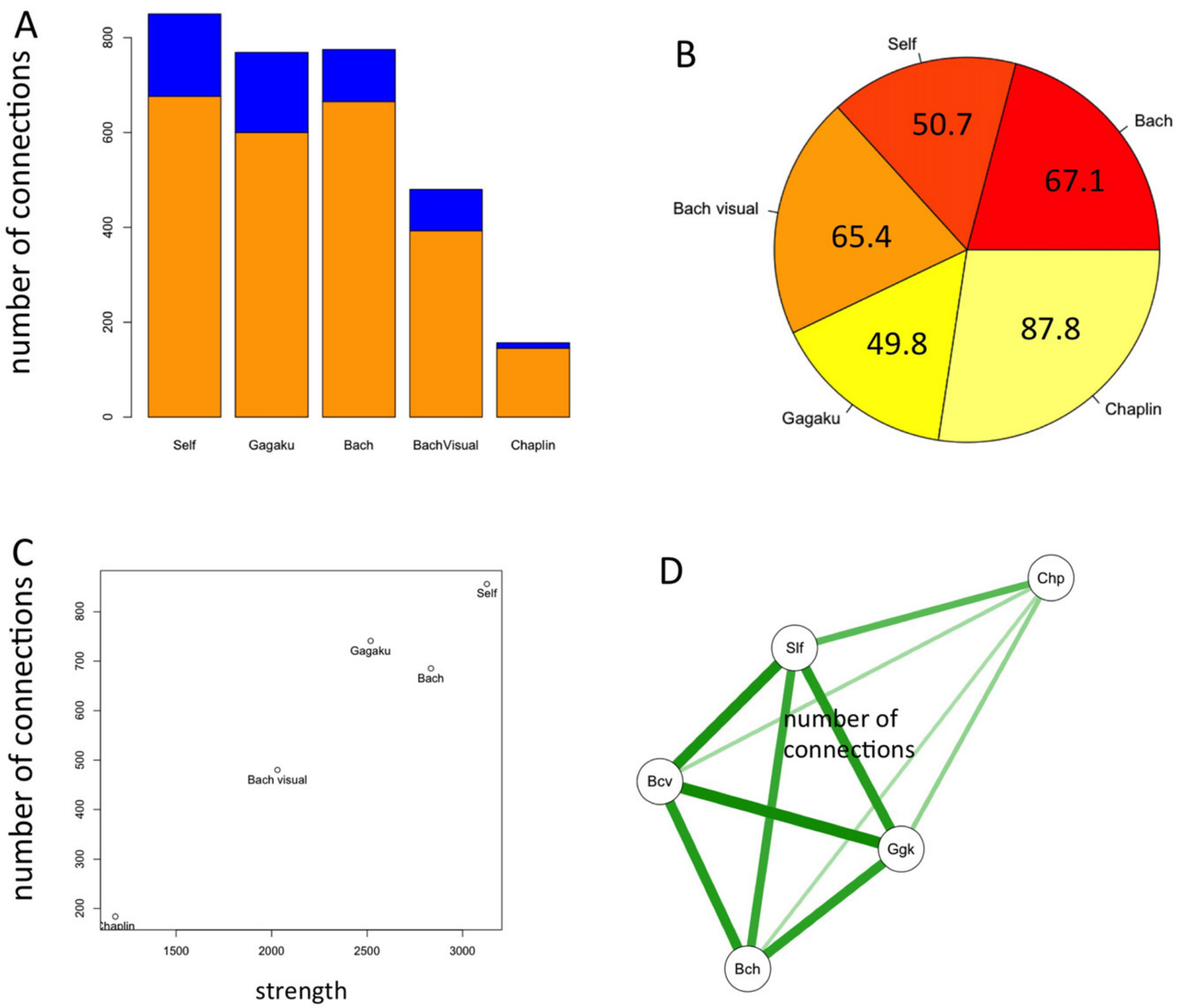

Figure 2. **A:** Number of connections formed during listening periods (bright orange) and during resting periods (dark blue). The self-selected music ('Self') showd the most number of connections for both. **B**: Relative connectivity strength for all auditory pieces. **C**: relation between the number of connections and connectivity strength (R = 0.97, p = .005). **D**: Similarity of connection patterns: While the music pieces are grouped together, the language piece appears separated indicating a much different functional connectivity pattern (Bch: Bach, Bcv: Bach visual, Slf: Self, Chp: Chaplin, Ggk: Gagaku).

frontal gyrus (868), the supplementary motor area (816), the hippocampus (759) and the middle frontal gyrus (629) (Table 2). Total connectivity strength for self-selected (3128), Bach (2834), Gagaku (2518) and Bach visual (2030) were higher than for Chaplin (1182).

Relative strength of connectivity

Relative strength of connectivity varied between brain regions and excerpts. The inferior frontal gyrus showed the highest relative strength (5.4), followed by the parahippocampus (5.3), superior frontal gyrus (5.1), supplementary motor area (4.9), cerebellum (4.8), amygdala (4.8), hippocampus (4.7) and middle frontal gyrus (4.5) (Table 3). The largest relative strength was observed for Chaplin (87.8), then Bach (67.1), Bach visual (65.4), Self (50.7) and Gagaku (49.8) (Figure 2B). A linear trend between the total connectivity strength s and total number of connections was found (R = 0.97 and p = .005) (Figure 2C).

Similarity of functional connectivity

In the network graph representing similarity of FC patterns of the different auditory pieces, the music pieces are clearly separated from the spoken language piece (Chaplin). This pattern indicates that although listening to all five music pieces may have produced somewhat similar BOLD activation patterns, the spoken piece

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Table 2. Total strength of connections.

	Hipp	Amyg	STG	LG	SMA	PH	HG	SPL	Ce	ACC	PCC	PreC	Ins	SFG	MFG	IFG
Bach	134	62	23	264	196	238	92	74	781	18	−5	40	94	239	134	296
Self	270	84	86	328	254	313	132	26	728	−13	−13	80	58	239	178	252
Bach Vis	98	15	34	275	146	162	30	34	618	14	6	35	16	179	147	163
Gagaku	164	59	25	290	144	273	53	31	706	17	−4	104	56	142	130	293
Chaplin	94	63	11	153	77	152	0	28	279	0	0	25	16	71	41	158

Table 3. Relative strength of connectivity.

	Hipp	Amyg	STG	LG	SMA	PH	HG	PlanT	SPL	Ce	ACC	PCC	PreC	Ins	SFG	MFG	IFG
Means	4.7	4.8	3.3	4.0	4.9	5.3	3.8	3.9	3.3	4.8	1.9	1.0	2.0	3.9	5.1	4.5	5.4

showed a fundamental difference in functional connectivity as compared to the music pieces (Figure 2D).

Discussion

This study aimed to investigate the effects of five different auditory excerpts on the activation and functional connectivity of the brain through fMRI. The degree of variation and similarity in functional connectivity differed considerably. The self-selected excerpt induced the most connections in the cerebellar regions, lingual gyrus, superior temporal gyrus, inferior frontal gyrus, hippocampus, parahippocampus [14] and precentral gyrus. In particular, cerebellar regions showed the highest number of connections for all excerpts, indicating that these motor regions are very likely often involved in processing music. Participants may have subconsciously and involuntarily generated rhythmic tapping movements based on the musical excerpts that required significant stimulation of cerebellar regions. Damage to the cerebellum has even been shown to severely compromise one's ability to maintain temporal consistency and evenly-paced intervals in such tapping actions [15]. The activation of the supplementary motor area additionally mirrored that of cerebellar regions; however, the SMA controls movements that are internally generated, thus illustrating the involuntarily generated tapping motion by the music pieces [16]. These rhythmic tappings, where the listener anticipates the rhythmic accents in a selected piece of music, are known as 'feed-forward' interactions, characterized by the primary influence of the auditory network that stimulates the motor output, often in a predictable manner. Rhythmic auditory stimuli have even shown significant promise in improving walking ability for patients who have suffered acute stroke [17]. In this manner, this study presents notable potential to differentiate connectivity patterns upon listening to music and spoken excerpts based on the degree of cerebellar activation. Cerebellar stimulation has been known to improve compromised motor and higher cognitive functions. The ability of music to stimulate a significant increase in cerebellar activation from our results suggests that the incorporation of music into motor and cognitive rehabilitation may be an invaluable tool for patients to regain normal functioning faster [18].

Exposure to the self-selected piece induced a degree of familiarity that likely facilitated either a positive or negative emotional response, which in turn stimulated blood flow to specific brain regions [19]. This phenomenon indicates that not only was the brain highly involved in active processing of the familiar self-selected piece, but cognitive function was also still preserved even when the auditory piece stopped playing. This significant finding suggests that familiar musical pieces may be optimal in facilitating continuous stimulation to particular neural regions, an application suitable for both normal or cognitively disabled patients.

Likewise, several studies have shown that merely listening to a familiar melody triggers a semantic processing network, including the inferior frontal gyrus, in addition to the activation of auditory brain regions [20]. The activation of Broca's and Wernicke's area reflects the distinct need for dynamic semantic and syntactical processing when listening to Bach, Bach visual, and self-selected pieces as compared to the Chaplin spoken excerpt. These select musical pieces present intricate rhythmic fluctuations that require a significant level of insight and concentration to process. Bach's compositions, in particular, are associated with high-level linguistic processing in the brain and rhythmic processing, indicating the remarkable overlap between language and nonlinguistic tasks [21]. Gagaku, however, presented with no distinct tempo and an unpredictable, erratic rhythm. The strength of the functional connections of Gagaku, therefore, fell short of Bach's due to the decreased need for complex rhythmic perception. Both unfamiliar pieces showed increased blood flow during resting periods, most

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likely in an attempt to understand the just heard pattern. This effect was largest for these two excerpts, while it was also present for the familiar (self-selected) piece. Furthermore, Chaplin showed the least number of connections and activation in cognitive areas due to the exclusively linguistic and spoken nature of the excerpt. Musical melodies require the same cognitive control as word formation and language processing do, manifesting in the large number of connections for the superior and inferior temporal gyri. The activation of planum temporale, predominantly activated for language processing, was also high for the Bach and self-selected pieces. Various neuroimaging studies demonstrated the importance of this region, in addition to the insula, regarding aspects of musical pitch processing such as melody [22]. Pitch, the indication of a sound's perceived frequency, closely parallels rhythm, a strong and regular pattern of sound [9]. The intricate rhythmic nature of Bach induced a highly complex network of linguistic and melodic processing that simultaneously prompted the listener to pay particular attention to the pitch and melodic intonations of the piece. This outcome triggered increased blood flow to the planum temporale, insula, IFG and SFG based on fMRI imaging.

The parahippocampus presented one of the highest relative strength connectivity despite the region's significantly lower number of total connections compared to other activated areas. Part of the limbic system, the parahippocampus is largely responsible for memory encoding and retrieval and may play a prominent role in paralinguistic elements of verbal communication [14]. As a clear demonstration of the anti-correlation between connection number and relative strength, the activation of the parahippocampus suggests that the types of music presented most likely stimulated a memory formation process in which the participant drew upon previous memories associated with the melody or formed new memories from the musical piece in association with past experiences. A significant negative linear trend was found between the relative connection strength and total number of connections. The anti-correlation of strength and number indicate stronger connections have more influence in a neurophysiological context; however, the number of total connections for a certain brain region significantly limits the strength.

Music induces a mode of plasticity in the brain that can be capitalized on to form deeper functional connections between specific areas of the brain and promote conscious emotional healing [20]. Previous work, for instance, has demonstrated the importance of the activation of the medial prefrontal cortex (MPFC) for music improvisation, self-expression and personal experiences [2]. The current study, however, was limited by a small sample size (n = 12) and treatment size in that only five excerpts were used for fMRI analysis. To broaden the potential of this therapy, the range of music pieces may be expanded to analyze the effects of familiar music versus unfamiliar music in order to create a comprehensive listening regimen catered to the specific needs of every patient. Subjects who have suffered brain injury from stroke or other means are primary candidates for future studies as well as music that induces similar modes of auditory-motor, emotional, and cognitive plasticity.

This research primarily demonstrated that familiar pieces generate the most positive effects in normal brains, a notion that may be considered in passive or active music medicine or therapy for stroke patients. Familiar pieces, however, can still pose the risk of recalling memories associated with negative emotions that may subject the patient to additional emotional difficulties than what is normally suspected. Having a music therapist present during the self-selected music choosing session and a follow-up session could lessen this risk and ensure the therapy is most beneficial to the patient. The activation of specific brain regions prompted by the musical pieces in this study can be employed to produce individualized therapeutic perspectives for the treatment of different clinical conditions. Further implications for the field of music therapy include a more informed model for musical choice in the session. Music therapists use a variety of improvisation, original, and pre-composed songs within the therapy session. By developing an understanding of how one's relationship with music affects activation within the brain, the music therapist can make a more informed choice on when to use specific songs from one's personal discography. Additionally, the music therapist is able to emphasize different characteristics of music in order to encourage activation in the brain.

Most importantly, stroke patients who've suffered damage to specific brain regions may benefit most significantly from this application of music. Interventions with highly rhythmic musical pieces that generate plasticity in the brain can be modified to stimulate the activation of auditory-motor circuits particularly in stroke patients who have suffered paresis or deficits in motor skills after acute or chronic stroke. Incorporating targeted music may also lower the risk of emotional disorders and prevention of secondary

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brain complications may therefore potentially revolutionize stroke rehabilitation.

Conclusion

Music, as a multimodal stimulus, shows tremendous potential in promoting brain plasticity and connectivity in structures related to sensory processing, memory formation, motor function and stimulating complex cognition and multisensory integration. These effects may be translated into targeted music therapy or music medicine interventions for patients undergoing stroke rehabilitation or other forms of physical or psychological neurologic rehab. Stimulation of semantic processing networks, auditory-motor circuits, and positive emotional pathways through differential applications of music may foster long-term plastic changes in the brain that drastically improve correlated stroke-related deficits. This study demonstrated that largely familiar and highly rhythmic music pieces generate the most functional connections that stimulate these potential functional networks. After determining the exact genre and type of music that a patient responds best to, musical approaches may be thoroughly customized to bring a revolutionary avenue of individualized care for stroke patients.

Disclosure statement

No potential conflict of interest was reported by the authors.

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