Musical hallucinations: a brief review of functional neuroimaging findings

Francesco Bernardini, 1* Luigi Attademo, 2 Karen Blackmon, 3 and Orrin Devinsky 3

Musical hallucinations are uncommon phenomena characterized by intrusive and frequently distressful auditory musical percepts without an external source, often associated with hypoacusis, psychiatric illness, focal brain lesion, epilepsy, and intoxication/pharmacology. Their physiological basis is thought to involve diverse mechanisms, including "release" from normal sensory or inhibitory inputs as well as stimulation during seizures, or they can be produced by functional or structural disorders in diverse cortical and subcortical areas. The aim of this review is to further explore their pathophysiology, describing the functional neuroimaging findings regarding musical hallucinations. A literature search of the PubMed electronic database was conducted through to 29 December 2015. Search terms included "musical hallucinations" combined with the names of specific functional neuroimaging techniques. A total of 18 articles, all clinical case reports, providing data on 23 patients, comprised the set we reviewed. Diverse pathological processes and patient populations with musical hallucinations were included in the studies. Converging data from multiple studies suggest that the superior temporal sulcus is the most common site and that activation is the most common mechanism. Further neurobiological research is needed to clarify the pathophysiology of musical hallucinations.

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Introduction

Musical hallucinations (MHs) are uncommon phenomena characterized by intrusive and frequently distressful auditory percepts without an external source¹ and are described as songs, tunes, melodies, harmonics, rhythms, and/or timbres.² Five common causes of MHs include hypoacusis, psychiatric illness, focal brain lesion, epilepsy, and intoxication/pharmacology,³ but MHs also occur in people without auditory, neurological, or psychiatric disorders.⁴

The physiological basis for MHs involves diverse mechanisms, including "release" from normal sensory or inhibitory inputs as well as stimulation during seizures.⁵ Functional or structural disorders in diverse cortical and subcortical areas can produce MHs.⁶ However, in some cases, neither a localized lesion nor a functional disorder

(Email: francesco.bernardini@erasme.ulb.ac.be)

can be identified. To further explore the pathophysiology of MHs, we reviewed functional neuroimaging and neurochemical imaging studies.

Material and Methods

We searched the PubMed electronic database for all articles up to 29 December 2015. The search terms included "musical hallucinations" combined with "functional neuro-imaging" or "functional magnetic resonance imaging" or "fMRI" or "magnetoencephalography" or "MEG" or "positron emission tomography" or "PET" or "single-photon emission computed tomography" or "SPECT" or "near-infrared spectroscopy" or "NIRS." The search included all languages. Some 11 articles were identified. ^{6–16} We excluded two articles that were unrelated to the topic. ¹², ¹³ In addition to the PubMed search, nine other relevant clinical case reports of functional neuroimaging studies on MHs were identified based on bibliographies and our knowledge of the subject. ^{17–25} A final set of 18 articles, all clinical case reports, comprised the set of studies reviewed.

Department of Psychiatry, Hôpital Érasme, Université Libre de Bruxelles, Brussels, Belgium

² Department of Mental Health, ASST Papa Giovanni XXIII, Bergamo, Italy

³ Comprehensive Epilepsy Center, Department of Neurology, New York University School of Medicine, New York, New York

^{*} Address for correspondence: Francesco Bernardini, Department of Psychiatry, Erasme Hospital, Université Libre de Bruxelles, Route de Lennik 808, 1070 Anderlecht, Belgium.

Results

Among the 18 functional neuroimaging studies published on patients with MHs, 17 were single-case reports, and 1 reported 6 cases, providing data on 23 patients. Among these 23 patients, all but one were examined with a single functional neuroimage: PET (n = 10), SPECT (n = 8), fMRI (n = 2), MEG (n = 2), and SPECT and MEG (n = 1). MHs were associated with different pathologies or conditions: (1) hearing loss or deafness without other psychiatric or neurological conditions (n = 10); (2) psychiatric disorders (n = 4) (depression = 3, schizophrenia = 1); (3) epilepsy and hearing loss (n = 2); (4) depression and hearing loss (n = 1); (5) Alzheimer's disease (n = 1); (6) temporal ischemic stroke (n = 1); (7) depression and epilepsy with hearing loss (n = 1); (8) traumatic brain injury and progressive deafness (n = 1); (9) intracranial hemorrhage (n = 1); and (10) neuropsychiatric normality (n = 1). In three cases, the onset of MHs followed a new pharmacological treatment (donepezil, amitriptyline, gentamicin) in the presence of a preexisting neurological or psychiatric disorder. Patient characteristics, the clinical features of their MHs, and the functional neuroimaging findings of the reviewed articles are summarized in Table 1, in chronological order. Figure 1 overlays findings from each study on a Montreal Neurological Institute (MNI) template brain.

Discussion

Musical hallucinations involve a localized network of cortical areas, with converging data from multiple studies suggesting that the superior temporal sulcus (Figure 1) is the most common site and that activation is the most common mechanism. The superior temporal sulcus is an auditory association area that is selectively activated by music and melody (as well as speech-sound processing, such as phonological mismatch²⁶) versus such other acoustic features as pitch²⁷ and melody.^{28,29}

Other cortical areas activated within the network underlying MHs include the orbitofrontal, precuneus, and basal ganglia. Activation of these areas, which are all reciprocally connected with the auditory association cortex, may occur passively via efferents from the superior temporal sulcus, actively through the same pathological process that stimulated the superior temporal sulcus, or through other mechanisms. Activation of the orbitofrontal cortex may contribute to some of the emotional features associated with MHs. 30,31 The precuneus is involved in several aspects of higher-order processing of music, such as harmonic elements of melody³² and musical transformations of pitch and time, 33 as well as retrieval of auditory images³⁴ and memories.³⁵ Basal ganglia activation may reflect timing elements of musical hallucinations, such as beat and rhythm³⁶ but likely reflect secondary activation of these subcortical structures from temporal lobe efferents and other cortical regions activated by an MH.

Diverse pathological processes and patient populations with MHs were included in the studies we reviewed. Therefore, activation of the superior temporal sulcus and related network structures may have resulted from different mechanisms, with potential possibilities including release after sensory loss, spreading cortical depression in migraine, electrical activation in epilepsy, and neurochemical anomalies with psychiatric disorders. Hearing loss is the most common disorder associated with MHs. It is likely that diminished input to the primary auditory cortex disinhibits-or "releases"-the auditory association cortex, leading to pathological activation. Why musical hallucinations are so commonly produced as opposed to simple frequencies, voices, or other auditory phenomena remains uncertain. Since music is a human universal, ³⁷ present in all cultures, its recognition and production may be a hardwired neural element activated during MHs.

The limitations of this review include a somewhat small number of cases that were heterogeneous in terms of imaging techniques, timing of the functional neuroimaging studies (e.g., while patients experienced MHs or not, and time after onset of symptoms), and variability of the etiology of MHs in the reported cases. Nonetheless, a point of strength of the study is that the networks of cortical and subcortical structures that emerged from the single studies tell us that the temporofrontal cortices involved in auditory and music perception are also involved during music hallucinations.

The present study reviewed the functional and chemical neuroimaging studies published on patients with MHs. From our review, we found that MHs involve a localized network of cortical areas, with the superior temporal sulcus appearing as the most common site and activation as the most common mechanism. Furthermore, our findings show that MHs are associated with mostly bilateral functional changes (60%), with a small preference to the right (25%), which is consistent with previous studies^{2,38} but in contrast with the largest case series of MHs to date.³⁹ However, cross-sectional population-based studies would be useful to clarify the pathophysiology of MHs. Further prospective studies following patients with MHs compared to age-matched controls with a standardized neuroimaging assessment would be helpful to better understand the phenomenon of MHs. Furthermore, given the lack of a method to experimentally manipulate the intensity of hallucinations, the use of a residual inhibition paradigm (i.e., a transient suppression of a phantom percept after the offset of a masking stimulus) could be empirically tested in future studies of subjects with MHs to better understand this phenomenon.⁶

Study	Age (years), gender	Prior disorder	Clinical features of MHs	Functional neuroimaging performed exam(s)	Findings
Erkwoh <i>et al.</i> , 1993 ⁷	55, M	Depression	Unknown	PET performed during MHs	Bilaterally increased metabolism in the superior temporal cortex, parasagittal occipital cortex, thalamus, and bilateral basal ganglia
Kasai <i>et al.</i> , 1999 ⁸	88, F	No psychiatric, neurological conditions. No hearing impairment	Onset abrupt. Hears various tunes of familiar favorites	Magnetometry and SPECT both performed during MHs and in their absence	Magnetometry: specific functional changes in the right auditory association cortex during MHs SPECT: Adjusted RCBF was greater in the right superior temporal and the right inferior frontal gyri during MHs
Terao & Matsunaga, 1999 ²⁰	75, F	Moderate bilateral hearing loss	Abrupt onset of continuous MHs of old Japanese songs, associated with palinacousis	SPECT	Slight hypoperfusion in the bilateral thalamus and basal ganglia
Griffiths, 2000 ⁹	73, M	5 years symptomatic hearing loss	Abrupt onset of continuous MHs in the form of multiple persons singing familiar melodies with indistinguish-able lyrics	12 PET scans performed at different times; for each scan, the patient was asked to rate the severity of MHs during the scan	Group analysis of the PET results was carried out for the four subjects showing similar experiences during scanning, age, handedness, and musicality. There was no correlation between MH strength and activation of Heschl's gyrus on either side in the group analysis. There was significant activation with MHs in both planum temporale, right basal ganglia, and right frontal operculum, the posterior temporal lobes (mainly right), both cerebellar lobes, the left deep Sylvian cortex, and the left frontal lobe
Griffiths, 2000 ⁹	71, M	40 years symptomatic hearing loss	Abrupt onset of continuous MHs of light opera pieces and popular songs		
Griffiths, 2000 ⁹	78, F	40 years symptomatic hearing loss	Abrupt onset of almost continuous MHs of organ or piano music sometimes accompanied by singers; if accompanied by singers, the lyrics were distinguishable		
Griffiths, 2000 ⁹	58, F	23 years symptomatic hearing loss	Gradual onset of almost continuous MHs of individual notes with the quality of a buzzy pitch		
Griffiths, 2000 ⁹	65, M	40 years progressive deafness	Continuous MHs of 3 or 4 males singing familiar songs with musical instruments; onset followed shortly after a head injury, and was accompanied by hearing a localized noise behind his head and experiencing a hot feeling that rose up the back of his head on two occasions only		This subject was excluded from the analysis because of a lack of variability in MH severity
Griffiths, 2000 ⁹	82, F	15 years of progressive deafness	Continuous MHs of one or more singers and accom-panying piano or band; onset coincident with an episode of visual loss, disorientation, perplexion, slurring of speech, unsteadiness of body; this is likely to have been a posterior circulation vascular event; she also experienced environmental sound illusions and verbal hallucinations		This subject was excluded from the analysis because of markedly abnormal brain structure (large arachnoid cyst in the right occipital lobe)

TABLE 1. Continued					
Study	Age (years), gender	Prior disorder	Clinical features of MHs	Functional neuroimaging performed exam(s)	Findings
Tanriverdi <i>et al.</i> , 2001 ¹⁰	38, F	Past history of grand mal seizures; untreated depression lasting over a year	Abrupt hearing loss and MHs in the form of popular songs after an i.m. injection of gentamicin	SPECT (performed after the initiation of moclobemide therapy)	Hypoperfusion of the left lateral temporal lobe
lzumi <i>et al.</i> , 2002 ¹⁷	51, M	Bilateral hearing impairment	Verbal and MHs (popular songs)	Three SPECTs were performed with the patient in different conditions (baseline without hallucinations, MHs, and verbal hallucinations)	Increased RCBF in both lower frontal areas and both basal ganglia during MHs
Shinosaki <i>et al.</i> , 2003 ¹⁸	78, F	Progressive hearing impairment; depression	Abrupt onset of almost continuous MHs in the form of familiar melodies with accompanying musical instruments; at the time of the MEG study, the MHs were replaced by simple rhythmic sounds	Eight MEGs performed in the patient and in four healthy controls.	Desynchronization in the right auditory cortex, including Heschl's gyrus planum temporale and supramarginal gyrus, during MHs
Kopeček <i>et al.</i> , 2005 ¹⁹	60, F	Epilepsy, anteromesio-basal resection of the right temporal lobe and hypoacusis	MHs started at age 56 and later developed obsessive-compulsive disorder	¹⁸ FDG PET	Right anterior temporal hypometabolism (reflecting prior resection) and increased metabolism in the orbitofrontal cortex, middle/inferior frontal gyrus bilaterally, and left nucleus putamen; auditory cortices were normal
Mori <i>et al.</i> , 2006 ¹¹	73, F	AD	MHs of familiar songs began after starting donepezil (5 mg/day)	SPECT performed during MHs and in nine sex-, age-, and cognitive function-matched AD patients without delusions and hallucinations	
Umene <i>et al.</i> , 2008 ²¹	83, M	Major depressive disorder with psychotic features	MHs of old popular Japanese songs at the beginning of his depressive state	SPECT	Areas of hypoperfusion in the bilateral temporal lobe and basal ganglia
Shoyama <i>et al.</i> , 2010 ¹⁴	52, F	Persistent lower abdominal pain and depression after lithotripsy for a right ureteral calculus	MHs of old familiar nursery rhymes with accompanying musical instruments or only the melodies (sung by an uniden-tified but familiar voice) often occurred during the quiet of the night developed after a treatment with amitriptyline (85 mg/day); MHs decreased gradually and completely disappeared at 30 days after beginning carbamazepine treatment	SPECT performed before and 43 days after starting carbamazepine treatment	Following treatment, as compared to the initial scan, RCBF was decreased in the lenticular nucleus, thalamus, and hippocampus, and increased throughout most of the neocortical and cerebellum over both hemispheres; the increase was maximal in the left angular region, while the maximum decrease was in the right thalamus
Cosentino <i>et al.</i> , 2010 ²²	63, M	Cranial trauma and right temporal injury in a patient with progressive bilateral deafness that started at least 20 years earlier	Continuous MHs in the form of popular Italian songs appeared a few days after a road accident, causing cranial trauma and right temporal injury; the sound volume of MHs was initially low and then became progressively louder; MHs changed in severity over the course of the day	PET	A brain MRI performed after the trauma revealed an area of increased signal intensity on T2-weighted images indicating a contusion of the right temporal pole PET scans of the brain showed a hypoactive area corresponding to the temporal lesion evidenced on the MRI scan, while increased focal FDG uptake was detected in the right posterior temporal lobe

Bleich-Cohen <i>et al.</i> , 2011 ¹⁵	35, M	Schizo-phrenia	Auditory hallucinations, musical in content and obsessive in form	fMRI (while the patient experienced MHs)	Increased activation of inferior and middle frontal gyri bilaterally, left dorsolateral prefrontal cortex, right orbitofrontal cortex, and right middle temporal gyrus. In particular, an increased activation of the right auditory associated cortex and striatal regions, primarily the left caudate head
Calabrò <i>et al.</i> , 2012 ¹⁶	82, F	Right temporal infarction	Complex MHs of popular Italian songs increasingly in intensity during the time	fMRI performed in the patient and in five normal controls	Activation involving the primary auditory cortex and temporal associative areas bilaterally in the patient and in five normal controls, a significant increased activation in temporal planum, mostly of the right temporal cortex (in the ischemic area) in the patient
Vitorovic & Biller, 2013 ²³	60, F	Bilateral sensory-neural hearing loss for a few years	Suddenly developed MHs in the form of recognizable and unrecognizable songs	PET	Unremarkable
Giermanski <i>et al.</i> , 2013 ²⁴	30, M	Intracranial hemorrhage secondary to pineal chorio- carcinoma	Childhood onset of MHs two years after intracranial hemorrhage in the form of repeating loops of familiar song frag-ments; the onset of MHs could be spon-taneous or triggered by a true auditory musical perception	SPECT	Unremarkable
Kumar <i>et al.</i> , 2014 ⁶	66, F	20 years hearing loss	MHs of piano melodies without vocals	MEG during different states	Four left brain regions showed increased oscillatory activity during higher MH intensity compared to low MH intensity; significant power changes, after whole-brain correction, in theta/alpha, beta, and gamma bands, but not the delta or high gamma bands; increased gamma band maximal in the left anterior superior temporal gyrus; increased beta band maximal in left motor, posterior cingulate, precuneus and retrosplenial cortices; in a combined theta and alpha band, power increased maximal in the left lateral orbitofrontal cortex
Futamura <i>et al.</i> , 2014 ²⁵	83, M	Three years symptomatic sensorineural bilateral hearing loss; epilepsy	Suddenly developed MHs in the form of children, folk, military songs and the Japanese national anthem	SPECT	Late phase brain SPECT showed decreased accumulation in the right temporal lobe compared to the early phase

AD = Alzheimer's disease; 18 FDG = 18-fluoro-D-glucose; fMRI = functional magnetic resonance imaging; MEG = magnetoencephalography; MHs = musical hallucinations; PET = positron emission tomography; RCBF = regional cerebral blood flow; SPECT = single-photon emission computed tomography.

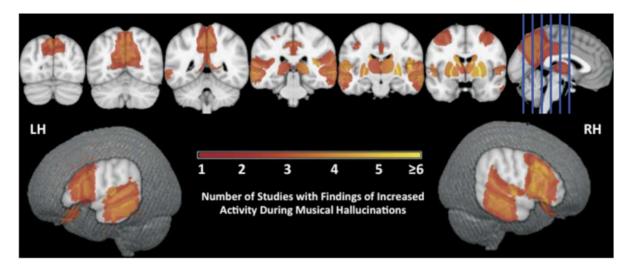


FIGURE 1. Schematic display of overlapping results from all studies reviewed. Binary masks were created for each region that showed increased activation in association with musical hallucinations from each study. Masks were created in standard MNI 1-mm template space using the Harvard—Oxford Cortical and Subcortical Structural Atlases and Juelich Histological Atlas, as available from the FMRIB Software Library (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Binary masks were summed to create an overlap map that depicts the number of studies showing positive findings at any given voxel. Red represents at least one report of positive activation at that voxel, whereas yellow represents positive findings in at least six studies.

Disclosures

Francesco Bernardini, Karen Blackmon, Luigi Attademo, and Orrin Devinsky hereby state that they have no conflicts of interest to disclose.

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