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Focal brain lesions causing acquired amusia map to a common brain network

Abbreviated title: Localizing amusia and aphasia

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Abstract

Music is a universal human attribute. The study of amusia, a neurologic music processing deficit, has increasingly elaborated our view on the neural organization of the musical brain. However, lesions causing amusia occur in multiple brain locations and often also cause aphasia, leaving the distinct neural circuits for amusia unclear. Here, we utilized lesion network mapping to identify these circuits. A systematic literature search was carried out to identify all published case reports of lesion-induced amusia. The reproducibility and specificity of the identified amusia network were then tested in an independent prospective cohort of 97 stroke patients (46 female and 51 male) with repeated structural brain imaging, specifically assessed for both music perception and language abilities. Lesion locations in the case reports were heterogenous, but connected to common brain regions, including bilateral temporoparietal and insular cortices, precentral gyrus, and cingulum. In the prospective cohort, lesions causing amusia mapped to a common brain network, centering on the right superior temporal cortex and clearly distinct from the network causally associated with aphasia. Lesion-induced longitudinal structural effects in the amusia circuit were confirmed as reduction of both grey and white matter volume, which correlated with the severity of amusia. We demonstrate that despite the heterogeneity of lesion locations disrupting music processing, there is a common brain network, that is distinct from the language network. These results provide evidence for the distinct neural substrate of music processing, differentiating music-related functions from language, providing a testable target for non-invasive brain stimulation to treat amusia.

Significance Statement

Perspectives on the neural organization of language and music have been elaborated by studying the respective brain lesion induced deficits, aphasia and amusia, but without leading to an agreement regarding their shared and distinct neural circuitries. This study demonstrates that lesions disrupting music processing map to a common brain network, which is distinct from speech processing networks in the brain. Importantly, our data confirms, the lesion-induced longitudinal structural effects in the central nodes of the amusia network, resulting in both grey and white matter atrophy. The results lend insight into the neural substrate of music processing, add neural evidence for the differentiability of music-related functions from language, and provide first testable targets for non-invasive brain stimulation to treat amusia.

Introduction

Neuroimaging studies have indicated that both language (Hickok and Poeppel, 2007) and music (Alluri et al., 2012) processing are primarily subserved by frontotemporal networks, and perspectives on their neural organization have been elaborated by studying the respective brain lesion-induced deficits, aphasia and amusia. Lesion studies (Alyahya et al., 2020) have confirmed the classical typology of aphasia and language organization according to dual-stream models (Hickok and Poeppel, 2007) associating lesions in the left inferior frontal and precentral areas with speech production deficits and damage to the left temporoparietal cortex with deficits in speech comprehension. However, the evidence for lesions giving rise to amusia, a neurological deficit affecting music processing, has remained incoherent. Although lesions affecting certain brain regions, such as the left and right inferior frontal cortex, right basal ganglia and superior temporal regions, have been shown to be associated with development of amusia, lesions causing amusia have been reported in highly heterogeneous locations with no consensus on the key structures involved. (Stewart et al., 2006; Sihvonen et al., 2019)

To further complicate symptom localization in acquired amusia, a single focal lesion can give rise to both aphasia and amusia, resulting in considerable post-stroke comorbidity ranging between 41−55% (Schuppert et al., 2000; Sihvonen et al., 2016, 2017a, 2019). Moreover, severe amusia that shows poor recovery has been associated with bilateral progressive white matter (WM) degeneration, including language-related tracts (Sihvonen et al., 2017b), arguing that amusia is a network disorder resulting from dysfunction of multiple brain regions, that is, spatially distributed lesions disrupting a functionally connected network can result in amusia. However, the key nodes of the music network, and how they are distinct to those of the language network, have yet to be identified.

A relatively recently developed technique, termed lesion network mapping allows linking causal lesions in different locations to brain networks using the human connectome (Boes et al., 2015; Fox, 2018). Lesion network mapping leverages the concept of diaschisis, i.e. the remote effects of the lesion to brain regions that were connected to the lesion location, to explain and predict how damage to heterogeneous regions can give rise to a common symptom. This method has lent valuable insight in refining our understanding of the underlying neural substrates of a growing number of neurological and psychiatric symptoms (Fox, 2018) (for a comprehensive review of published lesion network mapping studies see (Joutsa et al., 2022a)). Findings obtained by this approach demonstrate that this principle can be generalized to other deficits in which multiple aetiologies cause the same symptom and reveal potentially effective therapeutic targets (Joutsa et al., 2018b, 2022b). This is also relevant for amusia, since loss of music processing can have negative impact on life and music-based interventions have recently emerged as promising stroke rehabilitation strategies (Sihvonen et al., 2017c), included also in the current American Heart Association stroke rehabilitation guideline (Winstein et al., 2016).

Here, we apply lesion network mapping approach to lesions causing amusia with and without co-occurring aphasia to identify the brain networks causally and specifically linked with amusia, while controlling for the presence of aphasia.

Methods and materials

Patient Cases from the Literature

Cases of lesions causing amusia were identified from a systematic search of Pubmed using the combination of the following terms: "amusia" or "tone deafness" and "MRI," "CT," "lesion," or "case" from inception to the end of 2022. Inclusion criteria were: brain imaging performed in patients with amusia interpreted to be caused by focal lesions, a case report written in English, and the full text was accessible. Cases were excluded if: the lesions were not focal or, a figure showing the lesion(s) was not included.

Lesion network mapping

Lesion network mapping was conducted as described in detail previously (Joutsa et al., 2022b). Lesion locations of individual patient cases from the literature search were drawn on the standard brain (T1-weighted MNI template). All lesions shown in the published figures were combined into a single lesion mask for each case. It should be noted that this approach results in 2D approximations of the true lesions. Previous work has demonstrated that the connectivity profiles derived from 2D approximations of the lesions match well with connectivity profiles derived from full 3D lesions (Boes et al., 2015). Whole brain connectivity profile for each case was computed using a resting state functional connectivity MRI (rs-fcMRI) dataset with 1,000 subjects (Holmes et al., 2015). Full details of the dataset and functional connectivity analyses have been published earlier (Joutsa et al., 2022b). The resulting connectivity maps were thresholded to $|t| \geq 7$ to create lesion networks representing brain regions connected to lesion locations, as in prior work (Joutsa et al., 2018a). Finally, the lesion networks of the cases were overlapped to identify brain regions connected to lesion locations causing amusia. However, it should be noted that as lesions causing amusia also often cause other neurological symptoms, the regions connected to these lesion locations may not be specific for amusia.

Prospective lesion cohort

The prospective lesion cohort was used to investigate reproducibility and specificity of the identified network to amusia. Ninety-seven participants (46 female and 51 male) were enrolled in two cohort studies in Helsinki and Turku, Finland. Forty-nine participants were recruited during 2004–2006 from the Department of Neurology of the Helsinki University Hospital (HUS) and 48 participants during 2013–2014 from the Department of Neurology of the Turku University Hospital. All patients had an MRI-verified acute ischemic stroke or intracerebral haemorrhage in the left or right hemisphere, had cognitive or motor deficits, and were right-handed. All patients had normal hearing and were able to cooperate to ensure reliable behavioural assessment and MRI data acquisition. Patients with prior neurological or psychiatric disease or substance abuse were excluded. Studies were approved by the Ethics Committees of the Hospital District of Helsinki and Uusimaa (434/E9/03) and of the Hospital

District of Southwest Finland (85/180/2022) and performed in conformance with the Declaration of Helsinki. All participants signed an informed consent and received standard stroke care.

Out of the 97 patients, 15 received thrombolytic treatment in the hyperacute setting. However, the presence of amusia and aphasia did not significantly differ between the patients who received thrombolysis and those who did not ($p=0.770$ and $p=0.374$, respectively). Moreover, the amount of cognitive rehabilitation received by the patients between acute and 6 months post-stroke stage was comparable between the groups of patients with amusia and without amusia (speech therapy $p=0.843$; neuropsychological therapy, $p=0.586$). In turn, as expected, patients with aphasia and no aphasia significantly differed in the amount of received speech therapy ($p<0.001$), but not in the amount of received neuropsychological therapy ($p=0.242$). None of the patients were professional musicians and only 6 patients out of 97 had had any formal music training.

Behavioural assessment

All participants underwent a behavioural assessment within 3 weeks of the stroke where music perception was assessed with a shortened version (Särkämö et al., 2009) of the Montreal Battery of Evaluation of Amusia (MBEA) (Peretz et al., 2003). While MBEA is the gold standard assessment for amusia, shortened version (approx. 45 minutes) was specifically selected because including the full-length MBEA (approx. 90 minutes) as a part of the larger neuropsychological test battery would not have been possible in the acute clinical stroke setting. Participants' musical pitch and rhythm perception were evaluated using the MBEA Scale and Rhythm subtests, respectively. Both subtests comprise 14 pairs of short piano melodies, half of which are identical and half containing a musically altered tone in the second melody. Patients were asked to judge on each trial whether the two melodies sounded identical or not. In the Scale subtest, the altered tones have an out-of-scale pitch change. In the Rhythm subtest, the alteration is a change in the duration values of two adjacent tones in the melody. The average percentage score in both MBEA Scale and Rhythm subtests was calculated to represent an overall index of music perception (Särkämö et al., 2009). There was no missing data.

To control the specificity of the lesion patterns to amusia, aphasia was also assessed using the Aphasia Severity Rating Scale (ASRS) from the Boston Diagnostic Aphasia Examination (BDAE) (Goodglass and Kaplan, 1983). In addition to clinical assessment of communication based on face-to-face interview with psychologist, the performance of the patients in three language tests was used to derive the clinical ASRS estimate: Verbal Fluency Test (Lezak et al., 2012), shortened Token Test (De Renzi and Faglioni, 1978), and shortened Boston Naming test (Laine et al., 1993).

MRI data acquisition and preprocessing

Structural MRI imaging data was acquired from all participants within 3 weeks of stroke onset as well as 6 months post-stroke. Participants from Helsinki were scanned with a 1.5T Siemens Vision scanner of the HUCH Department of Radiology to obtain high-resolution T1 images (flip angle=15°; TR=1900ms; TE=3.68ms; isotropic voxel size=1.0mm^3). Patients from Turku were scanned using a 3T Siemens Verio scanner of the Medical Imaging Centre of Southwest Finland. The structural MRI was a T1-weighted MPRAGE image (flip angle=9°; TR=2300ms; TE=2.98ms; isotropic voxel size=1.0mm^3). There was no missing data.

MRI data preprocessing was conducted as previously described (Sihvonen et al., 2020). To achieve optimal normalization with no post-registration lesion shrinkage or out-of-brain distortion, cost function masking (CFM) was applied (Brett et al., 2001). To define the cost function masks, A.J.S. and T.S. created binary masks of the lesioned areas by manually depicting, on a slice-by-slice basis, the precise boundaries of the lesion directly into the T1 images (Ripollés et al., 2012). MRIcron (https://www.nitrc.org/projects/mricron) was used to do the aforementioned lesion tracing (Rorden and Brett, 2000). Then, T1 images and binary lesion masks were preprocessed using a previously reported pipeline (Sihvonen et al., 2016, 2017a) using Statistical Parametric Mapping (SPM8) under MATLAB v8.4.0. Unified Segmentation with medium regularization and CFM was applied to T1 images, segmenting them precisely into grey matter, white matter, and cerebrospinal fluid probability maps. This technique has been widely used with stroke patients (Ripollés et al., 2012; Sihvonen et al., 2016, 2017a). The segmented grey and white matter images were then modulated to preserve the original signal strength, smoothed using an isotropic spatial filter (FWHM, 8 mm) to reduce residual interindividual variability, and then normalized to the MNI space. Lastly, the binary lesion masks were registered to MNI space for lesion network mapping using the normalization parameters obtained during the segmentation process.

Lesion network mapping

First, to assess which parts of the identified network are specific for amusia, the resulting connectivity r maps were z-transformed and compared between lesion locations causing and not causing amusia using general linear model and permutation-based correction for multiple comparisons implemented in FSL randomise function (Winkler et al., 2014). To ensure that the findings were not confounded by age, sex or lesion size, the analysis was repeated using these variables as covariates. To verify that the amusia network is independent of aphasia, this analysis was repeated controlling for aphasia, excluding patients with aphasia, and identifying regions specific for aphasia rather than amusia. Second, as music perception and aphasia can both be viewed a continuum rather than dichotomous, we next computed the connectivity profiles specific for amusia and aphasia as continuous variables (MBEA and BDAE, respectively). The analyses were run across the whole brain to identify all brain regions associated with, and to investigate the differences between music perception and language. In all analyses, permutation-based threshold free cluster enhancement (TFCE) corrected $P<0.05$ for family-wise error (FWE) were considered significant.

Longitudinal structural effects

To verify the association between amusia and morphological changes in the identified regions connected to lesion locations causing amusia, the mean grey matter (GM) volumes within the identified common significant cluster (see Results and Figure 3) was extracted for all patients at acute and 6 months post-stroke stages. Then, using Human Connectome Project template (HCP1065) under DSI Studio (http://dsi-studio.labsolver.org, version Apr 2021), structural connectivity from the identified common significant cluster was calculated using a region-of-interest-based fiber tracking with 5000 seeds (step size=random, angular threshold=random, length=0−300mm, topology-informed pruning iterations=16) using the previously created mask. The resulting fiber tracking was then transformed into a region-of-interest mask to obtain WM volume estimates from within the WM region-of-interest at acute and 6 months post-stroke. Longitudinal (6 months−acute) GM and WM volume changes were then i) correlated with acute stage MBEA scores using two-tailed Pearson correlations (Bonferroni-corrected) and ii) compared between amusic and non-amusic patients using a *t*-test.

Data Availability

Anonymized data reported in this manuscript are available from the corresponding author upon reasonable request and subject to approval by the appropriate regulatory committees and officials.

Results

Patient Cases from the Literature

Our literature search identified 24 cases of lesion-induced amusia (Table 1). Lesion locations were heterogeneous, including left and right frontal, parietal, temporal and insular cortices (Figure 1A; see Figure 1-1 for all lesions). Connectivity between each lesion location and the rest of the brain was computed, and commonalities across the 24 lesions were identified using lesion network mapping (Figure 1A).

Lesion locations causing amusia were functionally connected to a common set of brain regions, including bilaterally the middle and superior temporal gyrus, insula, supramarginal gyrus, postcentral and precentral gyrus, and cingulum as well as the right inferior frontal gyrus (Figure 1A). In turn, these lesion locations were negatively connected to the cerebellum and superior frontal and inferior occipital gyrus bilaterally as well as to the left caudate (Figure 1A). However, as lesions in the included cases also caused many other symptoms, including aphasia (n=10/24, 42%) (Table 1), some of the identified connections could be linked to these other symptoms rather than amusia.

Prospective lesion cohort

According to the established cut-off values of the MBEA(Peretz et al., 2003) (average MBEA score<75%), 63 participants were amusic at baseline, and out of them 18 had comorbid aphasia and the remaining 45 had pure amusia (i.e., without aphasia). 15 patients had pure aphasia without amusia, and 19 patients did not show signs of either amusia or aphasia.

To test reproducibility and specificity of the brain regions for amusia identified based on the published cases, we compared connectivity from the lesion locations causing amusia (n=63) to that of locations not causing amusia (n=34) within the case mask. The demographic data are presented in Table 2. Lesion locations causing amusia were significantly more positively connected to the right middle and superior temporal gyrus, and insula ($P_{FWE}<0.05$; Figure 1B). To verify that the results were not driven or confounded by aphasia, the results were confirmed by controlling for aphasia (Figure 1B) and excluding patients with aphasia (n=45 vs. n=19) ($P_{FWE}<0.05$; Figure 1B). Voxels in the right superior temporal gyrus and middle temporal gyrus survived all analyses and were considered specific for amusia (cluster 1: peak MNI coordinates=52,-42,18, size=339mm^3; cluster 2: peak MNI coordinates 40,-18,-2, size=696mm^3). None of the negatively connected regions were specific for amusia. Lesion locations causing aphasia (adjusted for amusia) were functionally connected to regions in the opposite side of the brain but were not reproducible across all analyses within the amusia network (Figure 1-2).

The analyses were repeated using parametric analyses of MBEA and BDAE scores, further controlling for the confounding effects of BDAE and MBEA scores (respectively), sex, age, and lesion size. The main results remained the same (Figure 2, see Extended Data and Figure 2-1).

Longitudinal structural effects

The GM and WM volume within the amusia circuit showed significantly greater longitudinal atrophy (6 months−acute) for amusic than non-amusic patients ($p=0.014$, $p=0.006$, respectively) (Figure 3). The WM volume reductions in the identified circuitry comprised the right inferior fronto-occipital and longitudinal fasciculi, and the tapetum. There were no baseline differences in GM ($p=0.168$) or WM ($p=0.440$) volume in this circuit between amusic and non-amusic patients. The longitudinal change in the GM and WM volume correlated with amusia severity, as reflected by the MBEA scores ($r=0.439$, $p<0.001$, and $r=0.465$, $p<0.001$) (Figure 3). In contrast, the longitudinal change in the GM and WM volume did not correlate with acute stage verbal memory performance, language skills, attention and executive functions, mood or depression (see Extended Data), suggesting that the observed structural atrophy is specific to amusia.

Discussion

There are three important findings in the present study. First, although lesions causing amusia are spatially heterogenous, they are part of a common neural network, defined by connectivity to specific regions in the right superior temporal gyrus. Second, this network is independent of the network disrupted in aphasia, which localizes to the left superior temporal gyrus and supramarginal gyrus. Finally, lesions causing amusia lead to GM and WM atrophy in the central nodes of the amusia network, correlating with the severity of amusia.

There is a long-standing discrepancy between the evidence derived from lesion-based studies and functional neuroimaging studies of healthy subjects regarding the shared and distinct neural substrates of music and language. While studies on patients with focal brain lesions have reported selective impairment in music and language (Piccirilli et al., 2000; Peretz and Coltheart, 2003), functional neuroimaging studies on healthy subjects have shown considerable neuroanatomical overlap in responses to music and speech (Maess et al., 2001; Rogalsky et al., 2011). The results of the present study provide direct evidence for the dissociation of language and music processing in the brain, suggesting recruitment of different neural circuits for each respective cognitive domain (Piccirilli et al., 2000; Peretz and Coltheart, 2003). Given that we show a common cluster between the published case studies and our own prospective dataset, disruption of the connectivity to right superior temporal cortex could be considered as a probable condition for a lesion to cause amusia. Our findings align with previous lesion-symptom mapping (Sihvonen et al., 2016, 2017a), GM voxel-based morphometry (Sihvonen et al., 2016, 2017a) and functional neuroimaging (Särkämö et al., 2010; Sihvonen et al., 2017d) studies, which have implicated right superior temporal cortex in amusia adding confidence into our findings. However, our findings help to zero in on the causal substrates of amusia as the prior studies also highlighted multiple other brain regions (Stewart et al., 2006; Sihvonen et al., 2019, 2021), including right frontoinsular regions and basal ganglia, and even left hemispheric structures. However, it should be noted that this finding does not infer that damage to this network alone is sufficient to cause acquired amusia, given that there may be additional factors that are required to precipitate the symptom.

We also revealed longitudinal reductions of both GM and WM volume in the identified amusia circuit correlating with the severity of amusia at the acute stage. Previous studies have highlighted GM (Sihvonen et al., 2016, 2017a) and WM (Sihvonen et al., 2017a, 2017b) atrophy in amusia, but in multiple regions comprising not only the right hemisphere but also the left hemisphere. The present results show that lesions causing amusia lead to longitudinal WM volume reduction in the identified amusia circuit localizing largely in the right ventral stream, and, therefore, suggest this circuitry as the neural substrate of amusia (Sihvonen et al., 2017b, 2021). These morphometric changes may reflect diaschisis, which is one of the possible mechanisms of stroke lesion network effects, as described earlier. (Cheng et al., 2020)

Our findings align with two recent connectome-based studies on aphasia in which left temporoparietal disconnections were associated with deficits in both word and sentence comprehension (Matchin et al., 2022) as well as repetition, auditory comprehension, and both afferent and efferent syntactic processing (Billot et al., 2022). Taken together, these results highlight temporoparietal disconnections in aphasia, and the role of this region as the critical node in the language network supporting sensory-motor integration for speech (Hickok and Poeppel, 2007).

There are several limitations in the present study to be considered when interpreting the results. First, the clinical characterization of acquired amusia was not consistent in the published case reports. To address this limitation, we included the prospective lesion dataset and were able to control for nonspecific connectivity and to ensure that the findings were not confounded by concurrent aphasia. Second, we used a large normative dataset based on healthy subjects to approximate individual connectivity patterns for each patient at the time of the lesion, to reflect connectivity prior to the onset of amusia. While these normative data do not account for individual differences in age, gender, or co-morbidities, which can impact connectivity, prior work suggests that age-matched or disease-matched connectomes have little impact on lesion network mapping results and that the individual differences are small in relation to the overall connectivity pattern (Boes et al., 2015). Third, here we consider amusia as a music perception deficit based on the average score of MBEA Scale and Rhythm subtests rather than focused on selective impairments in pitch and rhythm processing. Furthermore, the patients were not assessed for music production deficits. Therefore, future lesion network mapping studies are needed to evaluate more fine-grained substrates of the amusia circuitry. Fourth, compared to the lesion tracing on the prospective dataset, it must be noted that there is some inherent error in lesion tracing based on a published image in a case report onto an anatomical template. However, this error is unlikely to drive the current results, since (i) lesion networks derived from 2D representations of 3D lesions are nearly identical to lesion networks derived from the actual 3D lesions (Boes et al., 2015), (ii) the findings were replicated in large scale 3D lesion dataset, and (iii) any error in tracing a lesion of a case study should bias the results against the current findings of a common network underlying amusia. Fifth, this study focused on stroke lesions, which occur predominantly in regions supplied by the medial cerebral artery that could be reflected in the findings of the present study. However, lesion network mapping investigates connectivity across the whole brain, and the identified network was specific for lesions causing amusia compared to similar lesions that did not, making false positives unlikely. Yet, it is still possible that our approach was better powered to identify regions in the medial cerebral artery area, encouraging replication of the findings in other lesion aetiologies in future studies. Lastly, premorbid music processing deficits, that is, congenital amusia, were not assessed. However, the current results are unlikely to be biased by patients with congenital amusia as it affects only 1.5% of the population and possible a couple cases of congenital amusia in our cohort would only add noise into our data reducing statistical power but not lead to systematic bias(Peretz, 2016). Similarly, the current results are unlikely to be biased by people with congenital amusia in the generic normative connectome of 1,000 healthy subjects.

The clinical significance of amusia can be understood as impeding positive effects of music on brain health and psychological well-being, individual development and rehabilitation (Sihvonen et al., 2017c; Matziorinis and Koelsch, 2022; McCrary et al., 2022). Music has numerous beneficial emotional, social, cognitive, linguistic and motor effects throughout the life cycle in supporting healthy development as well as in the treatment and rehabilitation of brain diseases (Fancourt and Finn, 2019). A wealthy body of evidence has accumulated on the rehabilitative and therapeutic use of music in brain diseases (Sihvonen et al., 2017c). As amusia is a common post-stroke deficit with prevalence of 35−69% (Schuppert et al., 2000; Särkämö et al., 2009; Sihvonen et al., 2016, 2017a), these patients are especially at risk in missing out on the well-documented beneficial effects of music-based therapies on cognition, motor function, mood, behavioural and psychosocial disturbances and quality of life, especially singing-based interventions in aphasia, apt to reduce patients' quality of life by affecting social interaction and psychological well-being (Sihvonen et al., 2017c). Therapeutic interventions for amusia may therefore have potential in reducing adverse effects of brain disorders and facilitating rehabilitation.

In conclusion, our results suggest that amusia originates from a circuit defined by connectivity to specific regions in the right superior temporal cortex (peak MNI coordinates: 52,-42,18 and 40,-18,-2), and thus offer testable targets for amusia treatment, for example by using non-invasive brain stimulation, which has shown promise in boosting neural plasticity in the recovery of post-stroke aphasia (Harvey and Hamilton, 2022).

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Figures

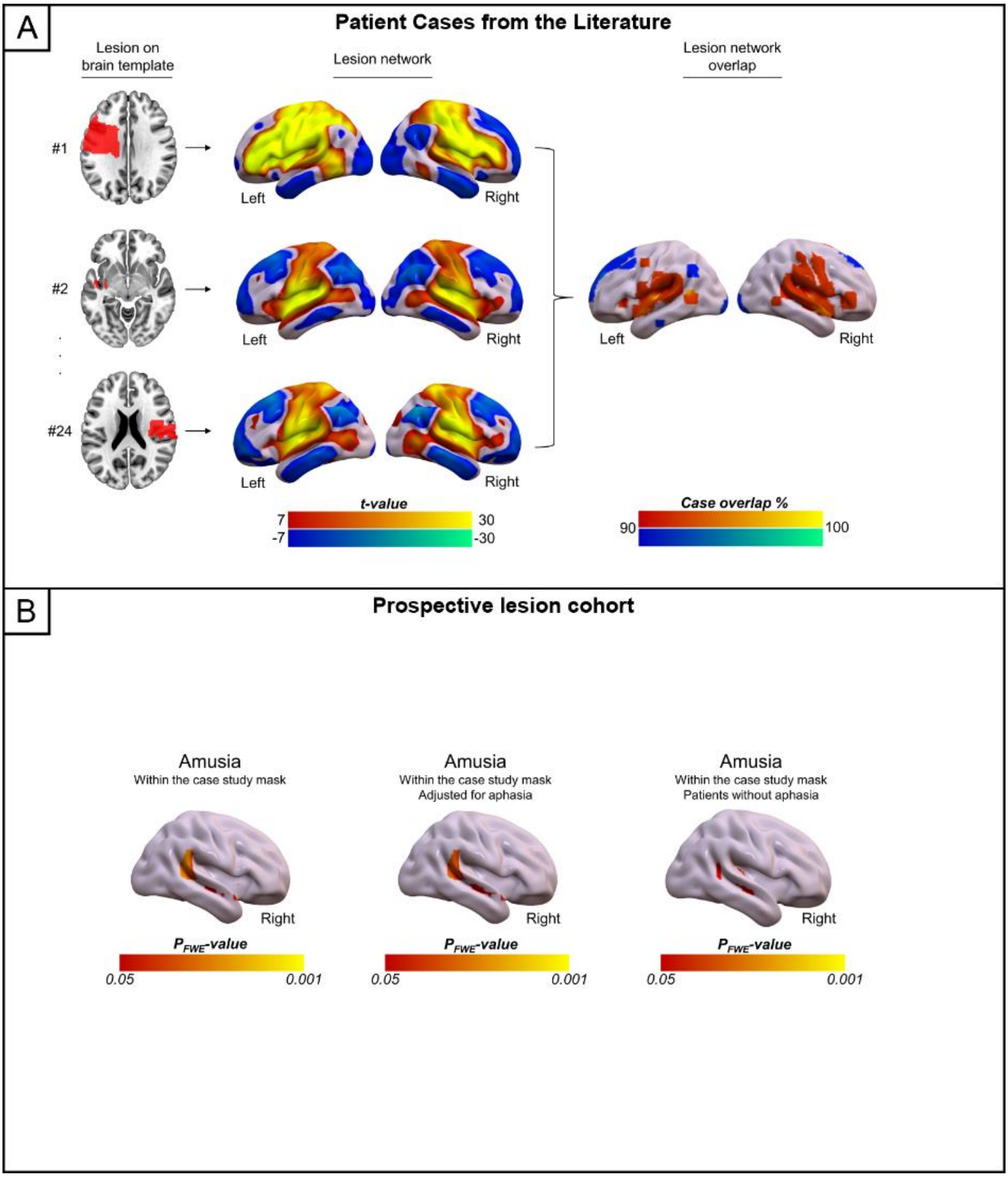

Figure 1. Lesion network mapping results of amusia. (A) Lesion network mapping of amusia case studies. Left, three representative lesions causing amusia (selected from n=24). See Figure 1-1 for all lesions. Middle, lesion network mapping method. Lesions from the literature are

traced onto a standard brain atlas. The set of voxels functionally connected to each lesion location are identified (“lesion networks”). Warm colours represent positive functional connectivity with the lesion location; cool colours represent negative functional connectivity with the lesion location. Right, regions of network overlap across all amusia-causing lesions. Functional connectivity for each lesion network thresholded at $|t| \geq 7$. (B) Amusia circuitry derived from prospective lesion cohort. Left, amusia vs. no amusia within the case study mask (n=97), Middle, amusia vs. no amusia adjusted for aphasia within the case study mask (n=97). Right, amusia vs. no amusia excluding patients with aphasia (i.e., purely amusic vs. non-amusic/non-aphasic patients; n=64). See Figure 1-2 for details on the aphasia circuitry derived from prospective lesion cohort.

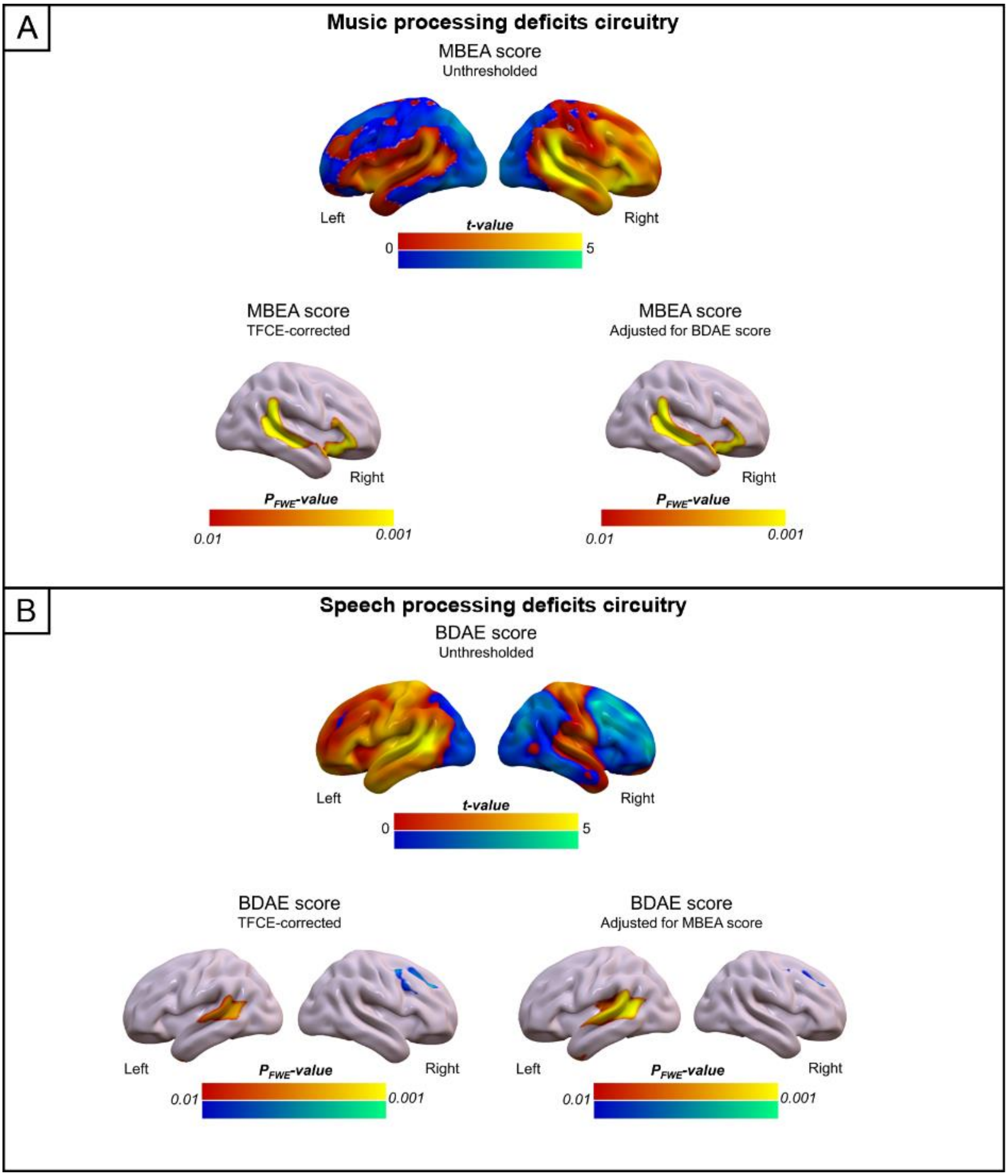

Figure 2. Music and speech processing deficits circuitries derived from prospective lesion cohort. (A) Parametric analysis of MBEA score (n=97) showing affected network associated with poor music processing performance and analysis adjusted for speech processing deficits (i.e., BDAE score). (B) Parametric analysis of BDAE score (n=97) showing affected network

associated with poor language outcomes and analysis adjusted for music processing deficits (i.e., MBEA score). See Figure 2-1 for more details. BDAE=Boston Diagnostic Aphasia Examination, FWE=Familywise error rate, MBEA=Montreal Battery of Evaluation of Amusia, TFCE=Threshold Free Cluster Enhancement.

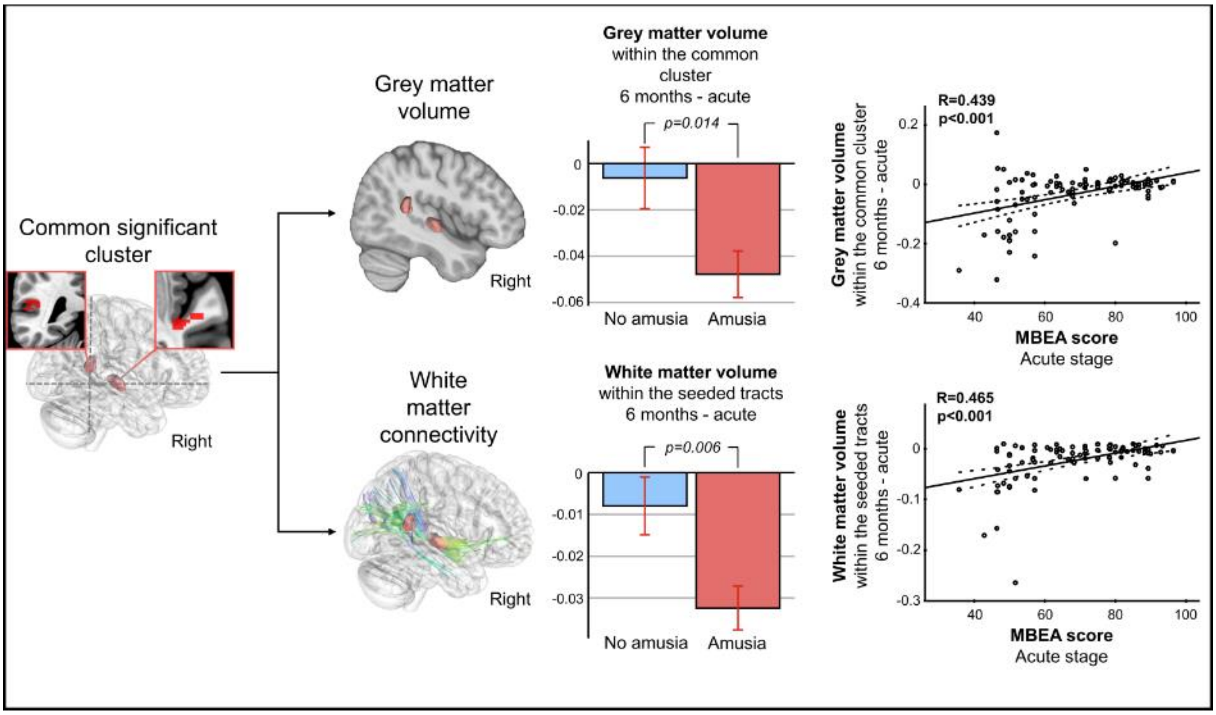

Figure 3. Common significant cluster and the longitudinal (acute to 6 months) structural effects within the identified network. Longitudinal grey and white matter atrophy within the identified amusia circuit are shown in bar plots for amusic vs. non-amusic patients (mean + standard error of mean). The scatter plots present correlations of the longitudinal grey and white matter volume change with the initial severity of amusia, as reflected by the MBEA scores. MBEA=Montreal Battery of Evaluation of Amusia.

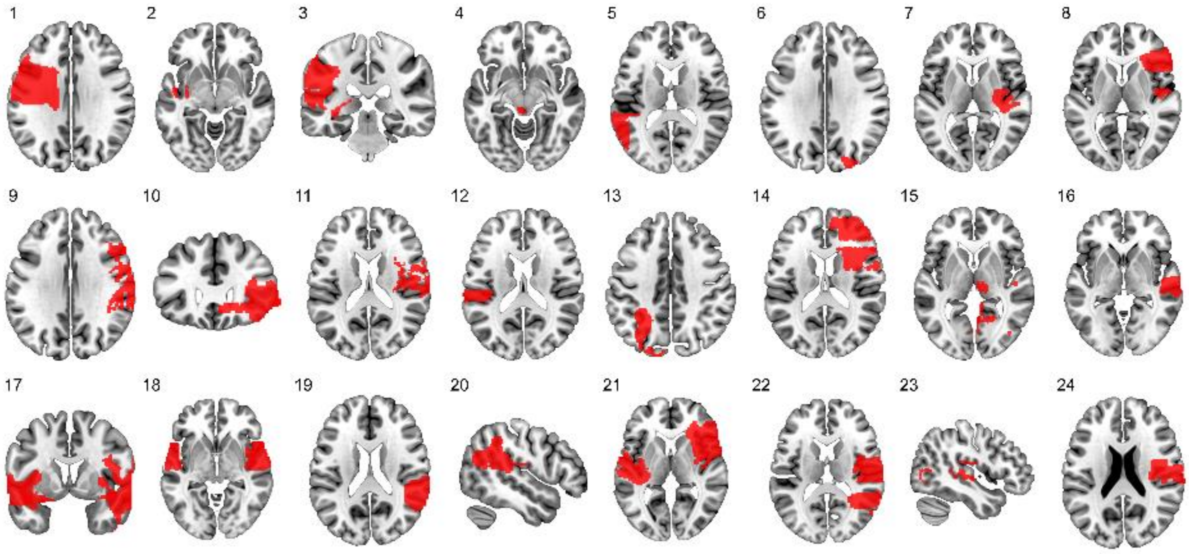

Figure 1-1. All lesions from the identified patient cases from the literature (n=24) traced onto a standard brain atlas.

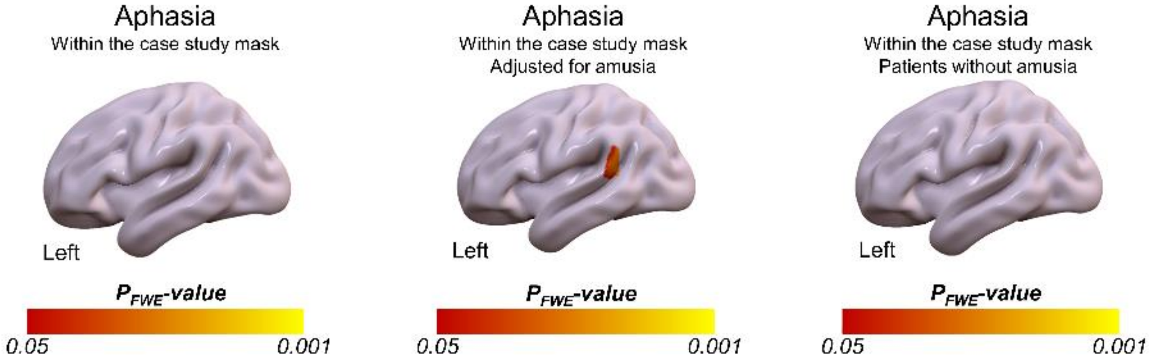

Figure 1-2. Aphasia circuitry derived from prospective lesion cohort. (A) Aphasia vs. no aphasia within the case study mask (n=97), (B) aphasia vs. no aphasia adjusted for amusia within the case study mask (n=97), and (C) aphasia vs. no aphasia excluding patients with amusia (i.e., purely aphasic vs. non-amusic/non-aphasic patients; n=34). FWE=Familywise error rate.

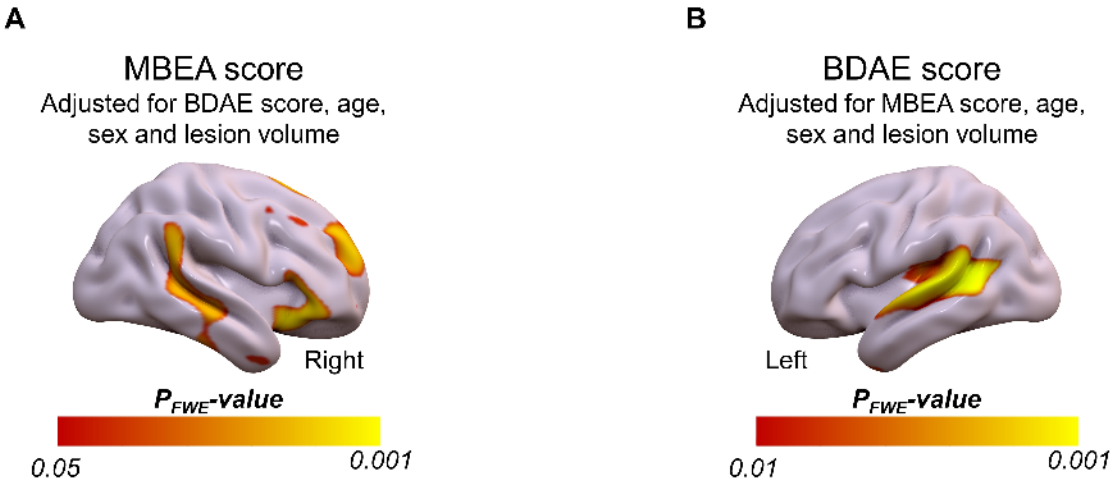

Figure 2-1. Music and language processing deficits circuitry derived from prospective lesion cohort. Parametric analysis of (A) MBEA score (n=97) showing affected network associated with poor music processing performance adjusted for BDAE score, age, sex and lesion volume, and (B) BDAE score (n=97) showing affected network associated with poor language outcomes adjusted for MBEA score, age, sex and lesion volume. BDAE=Boston Diagnostic Aphasia Examination, FWE=Familywise error rate, MBEA=Montreal Battery of Evaluation of Amusia.

Tables

Table 1. Amusia case studies.

References for acquired amusia case studies meeting inclusion criteria	Age	Sex	Lesion type and laterality	Clinical description	Music perception assessment	Extra patient details	Language deficits
Baird, A. D., Walker, D. G., Biggs, V., & Robinson, G. A. (2014). Selective preservation of the beat in apperceptive music agnosia: A case study. *Cortex*, *53*, 27–33.	18	M	Tumour resection, right hemisphere	Receptive, rhythm amusia	MBEA	Right-handed, amateur musician	No
Cope, T. E., Baguley, D. M., & Griffiths, T. D. (2015). The functional anatomy of central auditory processing. *Practical Neurology, 15*, 302–308.	48	M	Haemorrhage, right hemisphere	Receptive, pitch amusia	MBEA	Right-handed	No
Di Pietro, M., Laganaro, M., Leemann, B., & Schnider, A. (2004). Receptive amusia: temporal auditory processing deficit in a professional musician following a left temporo-parietal lesion. *Neuropsychologia*, *42*(7), 868–877.	48	M	Ischemic stroke, left hemisphere	Expressive, receptive, rhythm amusia	Discrimination of timbre, intensity, pitch, length, interval and identification of musical instruments and musical pieces	Right-handed, professional musician	Yes

Griffiths, T. D., Rees, A., Witton, C., Cross, P. M., Shakir, R. A., & Green, G. G. (1997). Spatial and temporal auditory processing deficits following right hemisphere infarction. A psychophysical study. *Brain, 120 (Pt 5),* 785–794.	75	M	Ischemic stroke, right hemisphere	Receptive amusia	Tune, lyric and environmental recognition tests	Right-handed, amateur musician	No
Hochman, M. S., & Abrams, K. J. (2014). Amusia for pitch caused by right middle cerebral artery infarct. *Journal of Stroke and Cerebrovascular Diseases, 23*(1), 164-165.	61	M	Haemorrhage, right hemisphere	Expressive, pitch amusia	NA	Right-handed	No
Jain, S. V., & Morton, L. D. (2008). Ischemic stroke and excellent recovery after administration of intravenous tissue plasminogen activator. *Pediatric Neurology, 38*, 126–129.	15	F	Ischemic stroke, right hemisphere	Expressive amusia	NA	Right-handed	-
Klarendić, M., Gorišek, V. R., Granda, G., Avsenik, J., Zgonc, V., & Kojović, M. (2021). Auditory agnosia with anosognosia. *Cortex, 137*, 255-270.	66	F	Ischemic stroke, right hemisphere	Expressive, receptive amusia	Recognition and repetition of melodies with and without lyrics	Right-handed	Yes

Mazzucchi, A., Marchini, C., Budai, R., & Parma, M. (1982). A case of receptive amusia with prominent timbre perception defect. *Journal of Neurology, Neurosurgery & Psychiatry, 45*(7), 644-647.	58	M	Ischemic stroke, right hemisphere	Receptive amusia	Recognition of musical sounds, musical instruments, tonal pairs	Right-handed, amateur musician	-
McChesney-Atkins, S., Davies, K. G., Montouris, G. D., Silver, J. T., & Menkes, D. L. (2003). Amusia after right frontal resection for epilepsy with singing seizures: case report and review of the literature. *Epilepsy & Behavior, 4*(3), 343-347.	31	M	Frontal resection, right hemisphere	Expressive, rhythm amusia	According to Wertheim and Botez (1961, Brain).	Right-handed, amateur musician	Yes
McFarland, H. R., & Fortin, D. (1982). Amusia due to right temporoparietal infarct. *Archives of Neurology*, *39*(11), 725–727.	78	M	Ischemic stroke, right hemisphere	Expressive, receptive, rhythm amusia	Dorgeuille test battery	Right-handed, professional musician	No
Mendez, M. F., & Geehan, G. R. J. (1988). Cortical auditory disorders: Clinical and psychoacoustic features. *Journal of Neurology,*	23	M	Ischemic stroke, right hemisphere	Receptive amusia	Melody discrimination test	Ambidextrous	Yes

Neurosurgery & Psychiatry, 51, 1–9.							
Midorikawa, A., & Kawamura, M. (2000). A case of musical agraphia. *Neuroreport, 11*, 3053–3057.	53	F	Tumour scar, left hemisphere	Musical agraphia, difficulties in rhythm	Pitch discrimination, recognition of well-known tunes, cadence counting, and Révész rhythm test	Right-handed, professional musician	No
Murayama, J., Kashiwagi, T., Kashiwagi, A., & Mimura, M. (2004). Impaired pitch production and preserved rhythm production in a right brain-damaged patient with amusia. *Brain and Cognition*, *56*(1), 36–42.	62	F	Ischemic stroke, right hemisphere	Expressive, pitch amusia	NA	Right-handed, amateur musician	No
Piccirilli, M., Sciarma, T., & Luzzi, S. (2000). Modularity of music: evidence from a case of pure amusia. *Journal of Neurology, Neurosurgery & Psychiatry*, *69*(4), 541–545	20	M	Hematoma, tumour, left hemisphere	Expressive, receptive amusia	Recognition of familiar melodies and musical characteristics, Bentley's test	Left-handed, amateur musician	Yes
Ponzetto, E., Vinetti, M., Grandin, C., Duprez, T., van Pesch, V., Deggouj, N., Lhommel, R., & Hantson, P. (2013). Partly reversible central	55	F	Haemorrhage, right hemipshere		NA	Right-handed	Yes

auditory dysfunction induced by cerebral vasospasm after subarachnoid hemorrhage. *Journal of Neurosurgery*, *119*(5), 1125–1128.							
Russell, S. M., & Golfinos, J. G. (2003). Amusia following resection of a Heschl gyrus glioma: case report. *Journal of Neurosurgery, 98*(5), 1109-1112.	28	F	Resection, right hemisphere	Expressive, receptive amusia	NA	Right-handed, professional musician	No
Satoh, M., Takeda, K., & Kuzuhara, S. (2007). A case of auditory agnosia with impairment of perception and expression of music: Cognitive processing of tonality. *European Neurology, 58*, 70-77.	68	M	Ischemic stroke, bilateral	Expressive, receptive, pitch amusia	Pitch, rhythm and chord discrimination, discrimination and recognition of familiar songs, Seashore's measures of musical talents	Right-handed	Yes
Satoh, M., Takeda, K., Murakami, Y., Onouchi, K., Inoue, K., & Kuzuhara, S. (2005). A case of amusia caused by the infarction of anterior portion of bilateral	53	F	Ischemic stroke, bilateral	Receptive amusia	Pitch, rhythm and chord discrimination, discrimination and recognition of familiar songs,	Right-handed	Yes

temporal lobes. *Cortex, 41*(1), 77-83.					Seashore's measures of musical talents		
Tanaka, Y., Yamadori, A., & Mori, E. (1987). Pure word deafness following bilateral lesions. A psychophysical analysis*. Brain, 110 (Pt 2)*, 381–403.	26	F	Ischemic stroke, bilateral	Expressive, pitch, rhythm amusia	NA	Right-handed, amateur musician	Yes
Terao, Y., Mizuno, T., Shindoh, M., Sakurai, Y., Ugawa, Y., Kobayashi, S., ... & Tsuji, S. (2006). Vocal amusia in a professional tango singer due to a right superior temporal cortex infarction. *Neuropsychologia, 44*(3), 479-488.	62	F	Ischemic stroke, right hemisphere	Expressive, receptive, pitch amusia	Pitch discrimination and reproduction, the Seashore test	Right-handed, professional musician	No
Tillmann, B., Peretz, I., Bigand, E., & Gosselin, N. (2007). Harmonic priming in an amusic patient: The power of implicit tasks. *Cognitive Neuropsychology, 24*, 603–622.	48	F	Aneurysmal, bilateral	Receptive amusia	MBEA	Right-handed	No
Uetsuki, S., Kinoshita, H., Takahashi, R., Obata, S., Kakigi, T., Wada, Y., & Yokoyama, K. (2016). A case of	53	F	Haemorrhage, left hemisphere	Expressive, pitch amusia	Pitch discrimination, MBEA, singing tasks	Right-handed	No

expressive-vocal amusia in a right-handed patient with left hemispheric cerebral infarction. *Brain and Cognition, 103*, 23-29.							
Wilson, S. J., Pressing, J. L., & Wales, R. J. (2002). Modelling rhythmic function in a musician post-stroke. *Neuropsychologia, 40*, 1494–1505.	67	M	Ischemic stroke, right hemisphere	Expressive, pitch, rhythm amusia	Pitch, melodic and chord discrimination, pitch working memory, familiar tune identification, tonal and sound identification, rhythmic timing, classification and reproduction	Right-handed, amateur musician	No
Yoo, H. J., Moon, H. I., & Pyun, S. B. (2016). Amusia After Right Temporoparietal Lobe Infarction: A Case Report. *Annals of rehabilitation medicine*, *40*(5), 933–937.	36	M	Ischemic stroke, right hemisphere	Expressive, receptive, rhythm amusia	MBEA	Right-handed, amateur musician	Yes

F=female, M=Male, MBEA=Montreal Battery of Evaluation of Amusia, NA=non-available.

Table 2. Baseline demographic and clinical characteristics of the prospective lesion cohort patients.

Demographic information	
Age (years)	58.2 (11.4)
Sex (female/male)	46/51
Education (years)	12.2 (4.0)
Clinical information	
Stroke type (ischaemic/hemorrhage)	88/9
Thrombolysis (yes/no)	15/82
Lesion size (dl)	0.5 (0.5)
Lesion laterality (left/right)	46/51
BDAE-ASRS score	4.4 (1.0)
Musical information	
MBEA score	67.9 (15.4)

Data are mean (SD) unless otherwise stated. BDAE-ASRS=Boston Diagnostic Aphasia Examination / Aphasia Severity Rating Scale, MBEA=Montreal Battery of Evaluation of Amusia