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Musical anhedonia after focal brain damage

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ABSTRACT

People listen to music because it is pleasurable. However, there are individual differences in the reward value of music. At the extreme low end of this continuum, individuals who derive no pleasure from music are said to have 'musical anhedonia.' Cases of acquired musical anhedonia following focal brain damage are rare, with only a handful having been reported in the scientific literature. Here, we surveyed a large sample of patients with focal brain damage to identify the frequency, specificity, and neural correlates of acquired musical anhedonia. Participants completed the Musical anhedonia Questionnaire and the Barcelona Music Reward Questionnaire (Mas-Herrero et al., 2013) to assess changes in musical enjoyment and reward following brain injury. Neuroanatomical data were analyzed with a proportional MAP-3 method to create voxelwise lesion proportion difference maps. No clear or consistent neuroanatomical correlates of musical anhedonia were identified. One patient with damage to the right-hemisphere putamen and internal capsule displayed specific and severe acquired musical anhedonia. These findings indicate that acquired musical anhedonia is very uncommon, a result which is consistent with the fact that only a small number of such cases have been reported in the literature. This rarity could have positive implications for the therapeutic potentialities of music in patients with severe neurological disorders.

1. Introduction

Many people listen to music because it is pleasurable. However, there are significant individual differences in the reward value of music; some individuals find music more pleasing than others (Mas-Herrero et al., 2013). These individual differences extend to both ends of the spectrum, where on one end are individuals who find abnormal pleasure in music ("musicophilia"), and on the other are individuals who derive no pleasure from music ("musical anhedonia"). The latter comes in two basic forms: 'congenital' musical anhedonia, which refers to a subset of the general population who displays a lifelong pattern of no pleasure from music; and 'acquired' musical anhedonia, which refers to individuals who previously enjoyed music but developed anhedonia for music after focal brain damage.

Congenital musical anhedonia has been shown to occur in approximately 5% of healthy adults (Mas-Herrero et al., 2013, 2014). These individuals show a lack of pleasure from music, both in self-reported ratings and physiological responses (Mas-Herrero et al., 2014). Individuals classified as musically anhedonic (using the Barcelona Music Reward Questionnaire; Mas-Herrero et al., 2013) show impaired physiological responses, and differences in neural activity, when listening to music, as compared to individuals with average and high musical hedonism (Martínez-Molina et al., 2016; Mas-Herrero et al., 2014). However, individuals with musical anhedonia display normal physiological responsiveness to monetary rewards, illustrating that their anhedonia for music does not necessarily generalize to other rewarding stimuli.

Acquired anhedonia for specific behaviors has been reported in rare patients with neurological damage (for example, anhedonia for smoking: Naqvi et al., 2007). *Music*-specific anhedonia appears to be especially rare, though, and only three published case-study reports have described individuals with a specific anhedonia for music (Griffiths et al., 2004; Mazzoni et al., 1993; Satoh et al., 2011). These case reports depict patients with similar behavioral phenotypes, all exhibiting a marked loss in emotional response and desire to listen to music following acquired brain damage.

The earliest case (Mazzoni et al., 1993) was a patient with a lesion to the right temporo-parietal area. Prior to his brain injury, this patient was an amateur guitar player. After his brain injury he showed no cognitive deficits, but complained of a lack of appreciation of music, saying that it sounded unemotional and detached. However, he performed normally on tasks that assessed perception of musical

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structure. The second case study was a patient with lesions to the left insula and amygdala (Griffiths et al., 2004). Prior to his injury, this individual was a radio announcer. He would frequently feel intense emotional "transformations," similar to musical "chills," when listening to certain Rachmaninoff preludes. After his injury, he no longer felt these transformations and had a general loss of pleasurable responses to music. He did not lose musical perceptual abilities and did not show signs of anhedonia for any other activities. The third case was a patient with damage to the right inferior parietal lobule. After his injury, he was "unable to have an emotional experience at any time when listening to music; he could not elicit interest in any music, even his favorite music or artists" (Satoh et al., 2011). He still found pleasure in any other activities, such as eating food, viewing works of art, and spending time with his family.

The lesion locations of these three reported cases of acquired musical anhedonia are varied, leaving it unclear what specific lesion(s) may be involved in causing musical anhedonia. Previous experience with music may be a factor, as each of the individuals in the reported cases showed a substantial dedication to music prior to their injuries. However, it may simply be that these cases were reported in part because music played a substantial role in the patients' lives before their brain injury, so the loss of musical enjoyment was more noticeable after their brain injury. There may be more subtle manifestations of musical anhedonia in people for whom music is not a central or substantial part of their lives.

In the present study, we sought to systematically investigate the neural correlates of acquired musical anhedonia by surveying a large sample of patients with focal brain damage. Specifically, we aimed to identify 1) The frequency with which patients with focal brain damage exhibit acquired musical anhedonia, 2) Consistent regions of brain damage associated with acquired musical anhedonia, 3) Whether acquired musical anhedonia is specific for music, and 4) Whether musical training is associated with acquired musical anhedonia. Given that acquired musical anhedonia appears to be relatively rare, we sought to capitalize on a sizeable population of patients with focal brain damage to directly address these questions.

2. Methods

2.1. Participants

Participants were patients with focal brain damage selected from the Patient Registry of the Division of Behavioral Neurology and Cognitive Neuroscience in the Department of Neurology at the University of Iowa. All brain-damaged participants have been extensively characterized neuropsychologically and neuroanatomically in the chronic epoch (at least three months post lesion onset) as part of their inclusion in the Registry. For inclusion in the Patient Registry individuals must have 1) no premorbid neurological or psychiatric dysfunction, 2) no history of alcohol or drug abuse, 3) focal brain damage due to stroke, surgical resection, herpes simplex encephalitis, head trauma with focal contusion, or hypoxia/anoxia. Additional inclusion criteria for the present experiments include: 1) lesion onset after age 18, and 2) no visual or hearing impairments not fully corrected. Neuropsychological and neuroanatomical characterization followed protocols of the Benton Neuropsychology Laboratory (Tranel, 2009) and the Laboratory of Brain Imaging and Cognitive Neuroscience (H. Damasio and Damasio, 1989; Frank et al., 1997).

Patients were recruited as extensively as possible for the present study, with the caveats of excluding patients who could not give valid data (i.e., we excluded participants who were unable to read or who had severe amnesia or aphasia that prevented them from completing the questionnaires). We sought to sample extensively to get as broad of coverage across the brain as possible. While this is a less targeted approach that is likely to result in a heterogeneous sample in terms of lesion location and etiology, our intent was to maximize chances of finding patients who show acquired musical anhedonia, and hence the heterogeneity of the sample was seen as a potential advantage. Participants were recruited via a phone call. Of the 136 individuals initially contacted by phone, 22 declined to participate. An additional 36 participants agreed to participate but did not complete the experimental protocol. This left a total of 78 (37 M, 41 F; mean age=59.2 ± 11.0) participants. Etiologies for the patients are as follows: stroke (n=31), resection for medically intractable epilepsy (n=20), benign tumor resection (n=17), anoxia (n=5), head trauma with focal contusion (n=4), and herpes simplex encephalitis (n=1). Demographic information is listed in Table 1 and lesion overlap maps for these participants are depicted in Fig. 1.

Table 1
Demographic and attribute information.

Age	Education	Sex	Handedness	Chronicity	Laterality	Musical training
59.24 (11-.07)	14.51 (2.4)	37 M, 41 F	4 L, 65 R, 9 M	16.5 (11.2)	36 L, 26 R, 16 B	3.80 (5.24)

Note. Sex, handedness, and laterality values are counts. Age, education, chronicity, and musical training values are mean years (SD). Abbreviations: Sex: M, Male; F, Female; Handedness: L, Left handed; R, Right handed; M, Mixed handed; Laterality: L, Left hemisphere; R, Right hemisphere; B, Bilateral.

2.2. Materials

Materials consisted of three questionnaires to assess musical anhedonia: the Musical anhedonia Questionnaire (MAQ), the Musical anhedonia Questionnaire – Collateral (MAQ-C) and the Barcelona Music Reward Questionnaire (BMRQ; Mas-Herrero et al., 2013). Additionally, we administered a questionnaire to assess anhedonia for other behaviors: the Snaith-Hamilton Pleasure Scale (Snaith et al., 1995). Additionally, patients who were able completed the Montreal Battery of Evaluation of Amusia (MBEA), which is a test to assess music perceptual abilities in six realms: scale, contour, interval, rhythm, meter, and memory (Peretz et al., 2003).

The MAQ was developed specifically for this study to assess changes in musical behaviors after brain injury. The questionnaire surveyed 14 various aspects of musical behavior. Following a format developed for other behaviors that can change after the onset of brain damage (e.g., the Iowa Scales of Personality Change; Barrash et al., 2011), questions on the MAQ are first asked with regard to how the patient was (behaved, felt, etc.) before their brain injury, and the same questions are asked with regard to how the patient was (behaved, felt, etc.) after their brain injury.

On the MAQ, participants first report their preferred musical genres and artists. The next two questions deal with frequency of music listening. First, patients rate frequency of **active listening**, or listening intently to music without participating in other activities. Next, patients rate the frequency of **passive listening**. This includes having music on in the background while doing another task (e.g., reading, driving, etc.). For these two questions, participants rate their frequency on a scale ranging from 1 to 3 times per month to more than 2 h per day. Next, for each type of music indicated in the first question, participants rate their **enjoyment** of this music and their **desire/urge** to listen to the music on a 7-point Likert scale from "did not enjoy/feel the urge at all" to "very much enjoyed/felt the urge." Next, they list their most disliked genre of music and rate how much they **dislike this music** on a 7-point Likert scale.

If participants ever played a musical instrument, they responded to a second section of the questionnaire. In this portion, participants list each instrument they played and rate on a 7-point scale how much they **enjoyed playing** this instrument, form "Did not enjoy at all" to "very

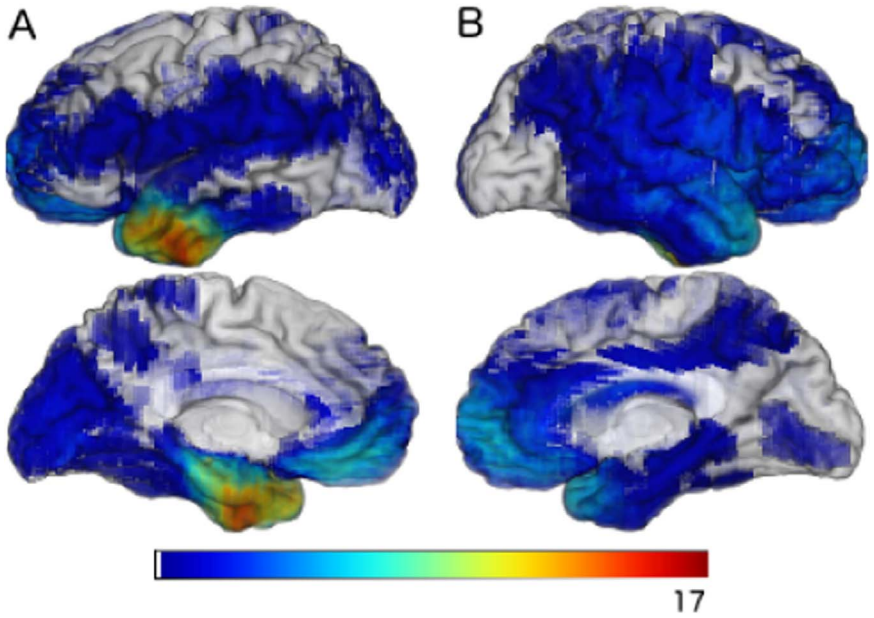

Fig. 1. Lesion overlap map for the 78 participants included in our study. Depicted here are left (A) and right (B) hemisphere views. The color bar codes for maximal lesion overlap, with "hotter" colors representing higher numbers of overlap.

much enjoyed." Next, they rate **how often they played the instrument**, ranging from 1 to 3 times per month to more than 2 h per day. They also indicate their years of formal musical training on each instrument.

Next, participants rate how often they **purchase new music** and how often they **seek out new music** (e.g., listen to unfamiliar music, ask friends for music recommendations). Next, they rate their frequency of **attending musical events**. Next, they rate how common it was for them to feel the compulsion to **interact with music** that they would hear – for example, to tap their foot or move their body to the beat of music. Next, they rate their frequency of experiencing **musical chills**. Next, participants are asked how common it was for them to engage in **unstructured musical behaviors** – for example, humming, singing, or whistling. Lastly, patients are asked to rate their **overall enjoyment** of music. All responses in this section are reported on a 7-point Likert scale ranging from "not at all" to "very much." See Appendix for a list of questions included on the MAQ.

All of these same questions are then repeated and asked with regards to *after* the patient's brain injury. A final, open-ended question asks participants to describe any changes they have noticed in their musical preferences or behaviors after their brain injury. See Fig. 2 for distributions of responses on individual items of the MAQ.

The MAQ-C is given to a collateral, such as a close friend or family member of the patient. The collateral was chosen by the participant to be someone who knew the participant well, before and after the onset of brain injury. These patients and collaterals have participated extensively in our research program and are highly motivated to cooperate with our procedures. The collateral is asked to report changes observed in the patient since his or her brain injury in the following areas: time spent listening to music, enjoyment of music, spontaneous music making, and musical tastes. Finally, collaterals are asked an open-ended question to which they can respond with any other changes they have observed in the patient's musical behavior.

The Barcelona Music Reward Questionnaire (BMRQ) is a questionnaire that was developed to assess individual differences in musical reward in healthy adults (Mas-Herrero et al., 2013). This questionnaire was used in the current experiment as another index of musical reward experiences. While it does not address change, which is the central goal of the present study, the BMRQ is an established tool for assessing musical reward. Its inclusion here is to provide a second assessment of musical reward, even though it only assesses this in the present moment. (We should note that the BMRQ is self-report, whereas the MAQ is other-report, and this is another important difference between the two instruments.) The BMRQ questions cover five facets of musical experiences: emotional evocation, sensory-motor, mood regulation, musical seeking, and social reward. The BMRQ contains 20 questions, four in each of the five facets (Factors). Each question is a statement (e.g., "Music often makes me dance") to which participants respond by rating their agreement on a 5-point scale ranging from "completely disagree" to "completely agree."

An important component of the present study is assessing the specificity of musical anhedonia. To this end, we included the Snaith-Hamilton Pleasure Scale to assess anhedonia for other pleasurable activities, such as spending time with family, watching television, or eating one's favorite foods (Snaith et al., 1995). This questionnaire contains 14 questions covering many types of rewarding experiences. Participants read each statement (e.g., "I would enjoy my favorite television or radio program") and respond with their agreement on a 4-point scale ranging from "strongly disagree" to "strongly agree."

2.3. Procedure

Participants were recruited via a phone call. During this phone call, the researcher explained the study to the potential participant. They were told their participation would consist of filling out paper questionnaires related to their musical behaviors. If the participant consented to participate, they were mailed a packet containing the questionnaires and asked to mail it back within two weeks. If the experimenter did not receive the questionnaires within two weeks from the date they were sent to the participant, the participant was called once more to see if they were still interested in participating. This was the final contact made to the participants. Of the 136 individuals initially contacted, 22 declined to participate over the phone. An additional 36 participants agreed to participate but did not mail the questionnaires back. This left a total of 78 participants who returned at least a portion of the questionnaires. While there was a relatively large proportion of participants who declined to participate, there is no indication that this group systematically differed in a meaningful way from those who participated.

Patients who completed the questionnaires were then asked to visit

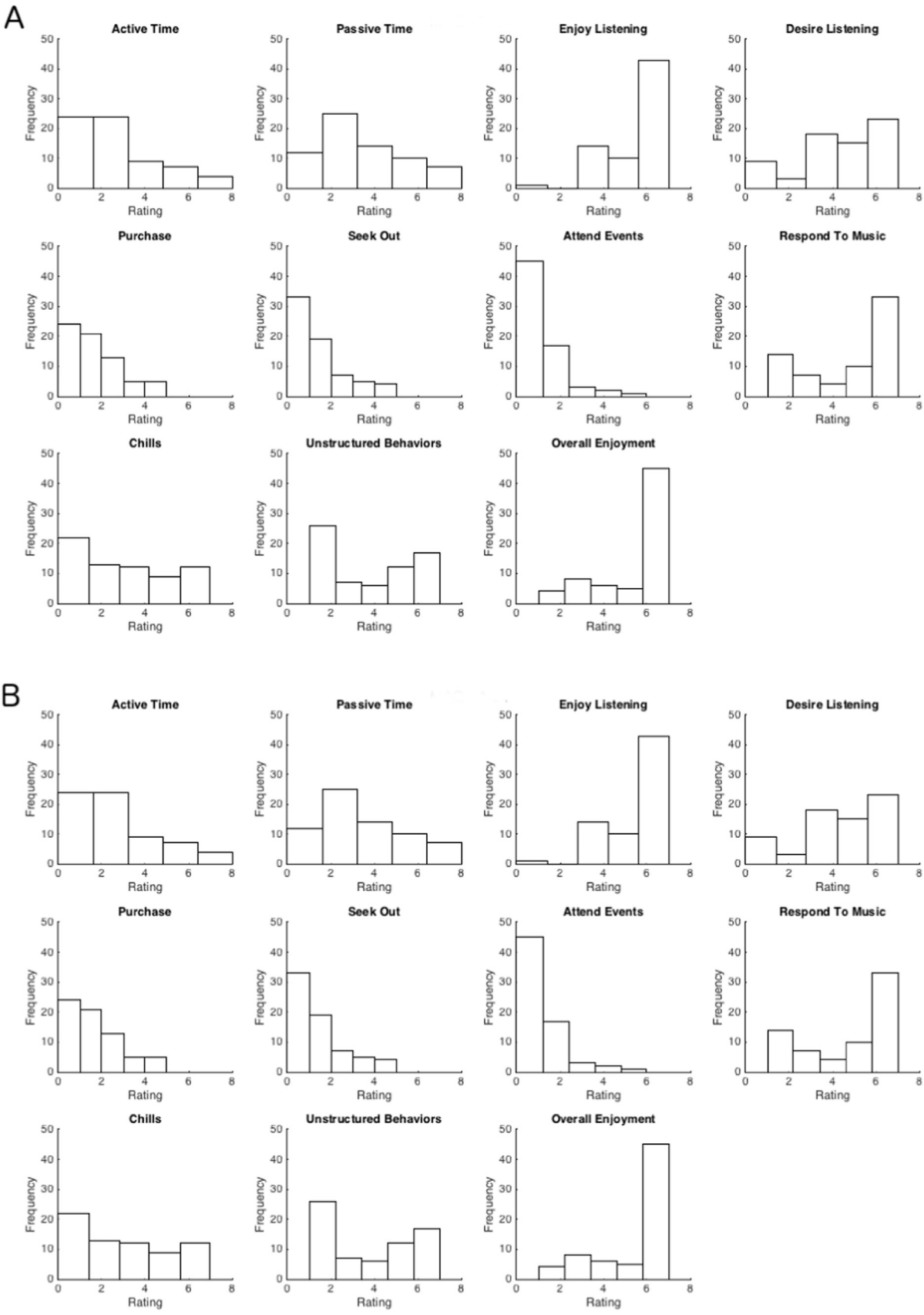

Fig. 2. Histograms depicting distribution of responses on individual items of the MAQ Before (A) and After (B).

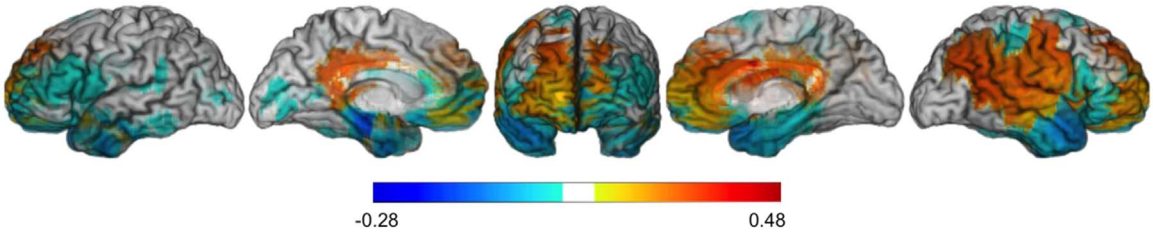

Fig. 3. Subtraction map comparing 'impaired' (N=9) and 'unimpaired' (N=69) patients based on scores from both the MAQ and BMRQ questionnaires. Hotter colors depict regions associated with impairments.

the lab in person to complete the MBEA. As this was completed in the lab, separately from the questionnaires, only subset of the patients (n=15) was able to complete this set of tasks. All procedures were approved by the University of Iowa Institutional Review Board and participants gave informed consent in accordance with the requirements of the Human Subjects Committee.

2.4. Behavioral and neuroanatomical data analysis

Change scores were calculated from the MAQ data. These scores were calculated by subtracting the ratings on the 'before brain injury' portion from the ratings on the 'after brain injury' portion of the MAQ.

2.4.1. Lesion analysis

First, voxel-based lesion-symptom mapping (VLSM) was performed to assess statistically regions that are associated with musical anhedonia. VLSM does not require identifying participants as either 'impaired' or 'unimpaired,' but allows for analysis of continuous behavioral data. Comparisons between voxels were performed using the Brunner-Munzel test (Brunner and Munzel, 2000) in MRIcron using the "Nonparametric Mapping" function (Rorden et al., 2007). For each voxel, this compares the scores of participants with and without a lesion. Significant voxels are those in which patients with damage at that voxel scored significantly lower than individuals without damage at that voxel.

Next, the proportional MAP-3 (PM3) method was used to create voxelwise lesion proportion difference maps comparing participants who showed musical anhedonia and those who did not (Rudrauf et al., 2008). PM3 expresses, for every voxel, the proportion of individuals whose lesion includes the voxel and who have a deficit (N_{LD}) relative to the total number of individuals with a deficit (N_D), minus the proportion of individuals with a lesion at the voxel and no deficit (N_{LnD}) relative to the total number of individuals with no deficit (N_{nD}). The formula can be expressed with the equation Prob (L | D) − Prob (L | nD), the conditional probability of a lesion (L) given a deficit (D) minus the conditional probability of a lesion given no deficit (nD). Therefore, PM3 accounts for differences in sample sizes between groups. In particular, for the present study, we would not expect equal group sizes since musical anhedonia is expected to be relatively rare. This same approach has been used many times in our research program to create proportional lesion-deficit maps for groups with unequal sizes, as typically there are fewer 'impaired' (compared to 'unimpaired') individuals (Belfi et al., 2016a; Kemmerer et al., 2012; Philippi et al., 2009, 2015; Sutterer et al., 2016; Tranel et al., 2009). An extended description of the PM3 method can be found in Rudrauf et al. (2008). It should be noted that the PM3 maps that we present are maps of descriptive, as opposed to inferential, statistics.

2.4.2. Correlation analyses

To assess the relationship between the MAQ and BMRQ, we correlated scores on the MAQ "After" scale with the BMRQ Factors. To assess accuracy of the participants' self-reported musical anhedonia (using the collateral report as the ground truth, and acknowledging that this is also subject to some variability), we computed intraclass correlation coefficients between the patients' and collaterals' ratings. To assess the relationship between musical anhedonia and musical experience, we correlated scores from the BMRQ and MAQ with participants' total years of formal musical training (as reported on the MAQ). Finally, to assess the relationship between music perception and musical anhedonia, we correlated scores on the MAQ and BMRQ with scores on the MBEA.

3. Results

3.1. Lesion analysis

Two separate VLSM analyses were performed, one for each questionnaire. There were no statistically significant results from these analyses. To perform the PM3 lesion-deficit analysis, participants were categorized into "impaired" and "unimpaired" groups based on their scores on the MAQ and BMRQ, separately. Participants were considered "impaired" if their score fell further than 1.5 standard deviations below the mean (see below). For the BMRQ, five participants were classified as impaired using this criterion. For the MAQ, there were five participants classified as impaired, one of whom had also been classified as impaired on the BMRQ. Due to the relatively small number of impaired participants, all participants who were considered impaired on either of the two questionnaires were classified as "impaired" for the purpose of the PM3 analysis. This resulted in a total of 9 participants in the impaired group and 69 participants in the unimpaired group. The PM3 subtraction map is depicted in Fig. 3. Areas associated with musical anhedonia include regions in left posterior cingulate gyrus, right superior frontal gyrus, posterior parietal cortex, and dorsal medial prefrontal cortex. Areas associated with unimpaired scores on the musical anhedonia factors include right and left anterior temporal lobes.

We purposefully chose a somewhat liberal cutoff of 1.5 SD to maximize inclusion of all patients with even minor signs or manifestations of musical anhedonia, so as to not miss potential 'borderline' cases. We would note that the most common cutoffs in similar work are around the level of 2 SD below the mean (Peretz et al., 2007, 2003). With this in mind, we re-classified our patients as 'impaired' or 'unimpaired' based on a 2 SD cutoff. Using this more conservative cutoff, only five patients were classified as 'impaired,' (four on MAQ, two on BMRQ, with one patient impaired on both) which is not a sufficient number for an additional PM3 analysis. The lesion locations for these patients were varied, and included: ventromedial prefrontal cortex, posterior cingulate cortex, left temporal pole, and striatum.

3.2. Relationship to general anhedonia

Seven patients in the current sample scored above the cutoff for anhedonia as measured by the Snaith-Hamilton Pleasure Scale (SHPS), i.e., had "anhedonia" as defined by the SHPS. These patients had brain damage to a variety of regions, including: left inferior parietal lobe, left anterior temporal lobe, and right ventromedial prefrontal cortex. Of these, none were included in our 'impaired' group (on either the MAQ or BMRQ). Thus, none of our patients who showed signs of musical

anhedonia had signs of general anhedonia. There were no significant correlations between scores on the SHPS and scores on the BMRQ (R=−0.04, p=0.72) or MAQ (R=−0.04, p=0.70).

3.3. Correlation analyses

3.3.1. Relationship to musical experience

One outlier was removed from the analysis of years of musical experience (this individual had 30 years of musical experience, which was greater than 2 SD above the mean of 3.8 years (5.24 SD) for the remainder of the sample). With this outlier removed, there were no significant correlations between years of musical experience and scores on the MAQ (R=−0.07, p=0.57) or BMRQ (R=0.06, p=0.62).

3.3.2. Relationship to music perception

Fifteen patients in the current sample completed the Montreal Battery for the Evaluation of Amusia (MBEA). We performed correlations between MBEA average scores and scores on the two anhedonia questionnaires. There were no significant correlations between the MBEA and the BMRQ (R=0.25, p=0.36) or between the MBEA and MAQ (R=0.17 p=0.53) scores. For each patient who completed the MBEA, we have reported their MBEA, BMRQ, and MAQ scores in Table 2.

3.3.3. Relationship to lesion size

To assess the potential influence of lesion size, we correlated lesion size and scores on the two anhedonia questionnaires. Lesion size did not correlate significantly with scores on the BMRQ (R=−0.04, p=0.73) or MAQ (R=0.02, p=0.84).

3.3.4. Relationship between BMRQ and MAQ items

We investigated the relationship between the MAQ and BMRQ items. Overall and not surprisingly, items on the MAQ were somewhat correlated with BMRQ factors (see Table 3). In particular, some specific items on the MAQ correlated fairly highly with related factors on the BMRQ, in ways that made sense. For example, “Frequency of purchasing new music” on the MAQ correlated highly with the “Music Seeking” factor on the BMRQ.

3.3.5. Agreement between self and collateral ratings

Intraclass correlation was performed to assess agreement between self and collateral ratings on the MAQ and MAQ-C. Data were available on both self and collateral ratings for 50 patient-collateral pairs. Z-Scores were created of scores on the MAQ-C in order to correspond with scores on the MAQ. Intraclass correlations were performed between each item on the MAQ-C that has a corresponding item on the MAQ. This resulted in three comparison scores: time spent listening to music, enjoyment of music, and spontaneous music making. Using a one-way random effects model, the intraclass correlation coefficient for time spent listening to music was 0.44, for enjoyment of music was 0.72, and for spontaneous music making was 0.61. These values indicate moderate to strong agreement for these variables.

Table 2
Scores on MBEA, BMRQ, and MAQ for participants who completed the MBEA.

Subject #	MBEA	BMRQ	MAQ
318	20	48	−0.27
1971	21	69	−1.85
2328	21	64	−0.31
2391	26	80	−0.20
2492	23	71	0.27
2589	26	72	−2.09
2710	24	50	−0.36
3124	23	56	−0.09
3533	23	86	0.24
3534	28	78	1.13
3575	26	57	0.20
3636	29	52	−0.27
3652	27	78	−1.05
3672	28	84	−0.15
3765	23	77	−0.33

Note: MBEA values are the overall average, BMRQ is the overall composite score, and MAQ is the average change score.

Table 3
Correlations between the BMRQ Factors and items on the MAQ ‘After’ scale.

MAQ items	BMRQ factors					
	Overall	Music Seeking	Emotion Evocation	Mood Regulation	Sensori-motor	Social
Active Time	0.23	0.22	0.15	0.23	0.17	0.07
Passive Time	0.23	0.33*	0.03	0.29*	0.13	0.16
Enjoy Listening	0.30*	0.29*	0.21	0.24	0.19	0.25*
Desire Listening	0.40**	0.48**	0.17	0.24	0.40**	0.28*
Purchase	0.36*	0.42**	0.22	0.20	0.29*	0.24*
Seek Out	0.36*	0.38*	0.17	0.15	0.29*	0.27*
Attend Events	0.30*	0.19	0.27*	0.15	0.32*	0.33*
Respond to Music	0.38*	0.32*	0.33*	0.16	0.30*	0.35*
Chills	0.44**	0.32*	0.44**	0.19	0.33*	0.36**
Unstructured Behaviors	0.37*	0.21	0.24	0.21	0.33*	0.32*
Overall Enjoyment	0.41**	0.32*	0.24	0.33*	0.44**	0.40**

Note:
* $p < 0.05$;
** $p < 0.001$

3.4. Additional analysis of BMRQ data

We conducted a secondary analysis investigating other cutoffs previously used to classify BMRQ scores (as ‘impaired’ vs. ‘unimpaired’). For example, previous research has used the BMRQ to classify individuals into three groups: ‘anhedonic,’ ‘hedonic,’ or ‘highly hedonic’ (Mas-Herrero et al., 2014). Individuals scoring in the lowest 10th percentile of respondents were classified as ‘anhedonic,’ and individuals scoring in the top 10th percentile were classified as ‘highly hedonic’ (Mas-Herrero et al., 2014). When the cutoff values associated with these 10th percentiles were applied to the data from our study, this resulted in 31 ‘anhedonic’ patients, 36 ‘hedonic,’ and four ‘highly hedonic.’ This is a much larger proportion of anhedonic individuals (~40%) than has been identified in previous work. The cutoff scores from Mas-Herrero and colleagues were calculated based on scores from a much younger sample than in the current study. This suggests that the BMRQ cutoffs determined by a college-age sample may overestimate the proportion of anhedonic individuals when used in older and/or neurological samples. It may be more appropriate to calculate cutoff scores separately for diverse populations.

Accordingly, we classified our patients as anhedonic based on the top and bottom 10% of our current sample. This resulted in seven patients classified as ‘anhedonic.’ Five of these seven patients are included in the previously defined ‘impaired’ group (using the 1.5 SD cutoff for the BMRQ scores). The other two patients have varied lesion locations, one with damage to the left posterior parietal cortex, the other with damage to left ventromedial prefrontal cortex.

3.5. Within-etiology analysis

While the goal of the present study was to sample as widely as possible with regard to lesion location and etiology, we conducted a

follow-up analysis to look within etiology groups as another approach to identifying individuals with possible musical anhedonia. Some etiology groups were too small for meaningful analysis; therefore, we conducted analyses separately for three groups: benign tumor resection (n=17), temporal lobectomy (n=20), and stroke (n=31). We identified 'impaired' patients on the BMRQ and MAQ separately, by categorizing those whose scores fell more than 1.5 SD below the mean as 'impaired' (as described in the whole group analysis above).

Within the benign tumor resection group, two patients were impaired on the MAQ and one was impaired on the BMRQ (3 total). Within the temporal lobectomy group, two patients were impaired on the BMRQ and two were impaired on the MAQ (4 total). Within the stroke group, three patients were impaired on the BMRQ and three were impaired on the MAQ (five total; one stroke patient was impaired on both questionnaires and no patients were impaired on both questionnaires in the other two etiology groups). Overall, 7 of these 12 patients were included in the "impaired" group as defined by the whole group analysis. Two patients were included in the impaired whole group analysis but were not identified as impaired within-etiology; one of these patients had an etiology of anoxia, and this group was too small to conduct a meaningful analysis here; a second patient just missed the cutoff within the stroke group, but was below the cutoff for the entire group. Of the five patients who were included as 'impaired' in the within-etiology analysis but were unimpaired in the whole group analysis, three were temporal lobectomy cases (all left hemisphere) and two were benign tumor resections, one right hemisphere lateral frontal and one bilateral orbitofrontal.

4. Discussion

Overall, from a relatively large group of neurological patients with focal, stable lesions, we identified only a small number of individuals with possible signs of musical anhedonia. This suggests that musical pleasure may be highly resistant to focal brain damage. Indeed, musical pleasure seems persist in a wide variety of neurological disorders. For example, music can still bring pleasure to individuals with Alzheimer's disease (Sung et al., 2010), Parkinson's disease (Pacchetti et al., 2000), and frontotemporal dementia (Fletcher et al., 2013). Taken together, these findings suggest that musical reward may be fairly resistant to brain damage. This may follow from the fact that music can induce emotions through multiple, non-musically-exclusive mechanisms, such as emotion contagion and episodic memory (Juslin, 2013; Juslin and Västfjäll, 2008). For example, in the case of emotion contagion, a listener may perceive the emotional valence of the music as if the music is another individual expressing these emotions; this emotional valence then is imitated in the listener. In the case of episodic memory, music may evoke a personal autobiographical memory that then conjures a strong emotional response (Belfi et al., 2016b). These various mechanisms may work by recruiting varied (and still functional) neural regions, potentially explaining why patients with even severe brain damage can still derive pleasure from music.

Given the present findings, there is no obvious or single lesion location associated with musical anhedonia. It is possible that individual differences could explain the variability in lesion locations of individuals with musical anhedonia – e.g., personality attributes, particular preferences for rewarding stimuli, learned behaviors for music practice and consumption. As we noted in the Introduction, the three previous case studies of musical anhedonia either were musicians or took a strong interest in music (Griffiths et al., 2004; Mazzoni et al., 1993; Satoh et al., 2011). In our study, years of musical experience was not significantly correlated with outcomes on the musical anhedonia scales, suggesting that experience and/or formal training per se would not explain musical anhedonia following acquired brain damage.

We also investigated the potential relationship between music perception and musical anhedonia. There was no significant relationship between scores on the Montreal Battery for the Evaluation of Amusia (MBEA, which includes measures of music perception) and scores on the MAQ or BMRQ "musical anhedonia" scales. While it would certainly not be surprising that major deficits in music perception could contribute to musical anhedonia, a double dissociation between music perception and emotional responses to music has been found in previous work. In fact, the three prior cases of acquired musical anhedonia showed normal perceptual abilities (Mazzoni et al., 1993; Griffiths et al., 2004; Satoh et al., 2011); conversely, individuals with major music perceptual deficits can show normal emotional responses to music (Peretz et al., 2003, 1998). Additionally, previous work on musical anhedonia in healthy populations found no significant relationship between MBEA scores and musical anhedonia scores on the BMRQ. Specifically, there were no differences between musically hedonic, highly hedonic, and anhedonic groups on the MBEA (Mas-Herrero et al., 2014). This suggests that deficits in music perception are not directly tied to deficits in musical pleasure. More generally, this conclusion is akin to the relation between "perception" and "recognition" in the classic literature on agnosia, where it has been firmly established that patients can have severe perceptual deficits without losing their ability to recognize, and vice versa (A.Damasio et al., 1990).

There are no real "gold standard" criteria for evaluating musical anhedonia in patient samples. We used multiple criteria to assess anhedonia. Our first criterion was selecting any patient who scored less than 1.5 SD below the mean on the BMRQ or MAQ scales (or both). This resulted in nine patients classified as 'anhedonic' (see Fig. 3). When using a stricter cutoff of 2.0 SD (for either questionnaire), we identified five patients as 'anhedonic' (~6% of our sample). An additional criterion was set as the bottom 10% of scores on the BMRQ average score (from our overall sample), which resulted in six 'anhedonic' patients. It is important to note that the BMRQ does not capture information about change, which is assessed in the MAQ. This could explain the differences between the two 'anhedonic' groups as assessed by the MAQ and BMRQ scores, as well as the fairly modest correlations between the two measures.

It is also interesting to consider the variability of patients classified as 'anhedonic' using different criteria, in light of the apparent rarity of full-blown musical anhedonia. In fact, in our study only one patient was classified as 'anhedonic' across all classification criteria. This patient had focal damage to the right striatum and showed a marked musical anhedonia following brain injury. This lesion coincides with previous neuroimaging research indicating that structures in the dopamine reward network, such as the striatum, are involved in musical pleasure (Blood and Zatorre, 2001; Martínez-Molina et al., 2016; Salimpoor et al., 2011, 2014). Additionally, this is consistent with previous work that has identified that gray matter loss in right-hemisphere regions, including the putamen, is associated with changes in auditory hedonic symptoms in patients with dementia (Fletcher et al., 2015). However, these regions are not only involved in musical reward, but also have been shown to be important for music perception more generally (Sihvonen et al., 2016). Moreover, there were other cases of striatal damage (both right and left hemisphere) in our sample that did not develop full-blown musical anhedonia, so the specificity and reliability of this brain-behavior relation would not appear to be very high.

There is a large variability between healthy individuals in their music reward value, from extremely hedonic to virtually anhedonic. It is worth briefly noting here that individuals with brain damage can also exhibit extreme hedonic responses to music, or an "abnormal craving for music" which has been termed "musicophilia" (Fletcher et al., 2015, 2013). A recent study indicated that musicophilia seems to be associated with frontotemporal lobar degeneration. The authors suggest that musicophilia reflects a shift towards enjoyment of abstract activities due to impairments in social behaviors (Fletcher et al., 2013). In the present study, we did not assess 'musicophilia' directly, although few participants reported substantial positive changes (e.g., one patient scored 1.5 SD *above* the mean on the BMRQ, and one patient scored

1.5 SD above the mean on the MAQ) in their musical reward.

The current study has several limitations. While the sample size was relatively large, a larger sample might allow for more coverage of varied brain regions and would potentially allow for a better ability to detect consistent relationships between lesion location and musical anhedonia. In addition, our current sample was fairly heterogeneous in terms of lesion location and etiology; further research could aim to characterize acquired musical anhedonia in more homogenous sub-populations of neurological patients with focal lesions. Also, since previous research has indicated changes in musical reward following other neurological disorders, expanding the present study to patients with neurodegenerative diseases may help to clarify situations in which acquired musical anhedonia occurs. Additionally, the psychometric properties of the new questionnaire we developed, the MAQ, have not been established fully (this is obviously beyond the scope of the present experiment, but would be important for future work).

Previous research has had some success in identifying neuroanatomical correlates for musical perception (Särkämö et al., 2009) and emotion recognition from music (Gosselin et al., 2007), but it remains the case that there does not appear to be a consistent neural correlate associated with musical reward. The present study addressed this issue in detail, but overall, the results did not point to a clear brain region (or regions) whose damage was strongly associated with musical anhedonia. These findings may indicate that individual differences play an important role in a loss of musical reward or that musical reward is strikingly resistant to focal brain damage.

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Appendix. List of questions on the MAQ

The following questions are asked both regards to *before* and *after* brain injury.

1. (Before/After) your brain injury, how often would you **actively** listen to music? For example, active listening includes turning on music and listening to it. That is, when music is the focus of your attention.
2. (Before/After) your brain injury, how often would you **passively** listen to music? For example, passively listening to music includes having music on in the background while doing another task, such as working on a computer, reading, exercising, driving, etc.
3. (Before/After) your brain injury, how much did you **enjoy** listening to music?
4. (Before/After) your brain injury, how much did you **desire/feel the urge to listen** to music?
5. (Before/After) your brain injury, how strongly did you **dislike** your most disliked type of music?
6. If you have ever played a musical instrument: (Before/After) your brain injury, how much did you **enjoy** playing this instrument?
7. If you have ever played a musical instrument: (Before/After) your brain injury, how **often** would you play this instrument?
8. (Before/After) your brain injury, how often would you **purchase** new music? For example, how often would you buy or download new albums or songs?
9. (Before/After) your brain injury, how often would you **seek out** new music? For example, how often would you look for new music in magazines, borrow albums from friends, or use online music players to find new artists?
10. (Before/After) your brain injury, how often would you **attend musical events**? For example, how often would you go to see a symphony, a musical theater production, or a concert?
11. (Before/After) your brain injury, was it common for you to **feel the compulsion** to respond to music? For example, how common was it for you to move to music, dance, tap your foot, or hum along with music?
12. (Before/After) your brain injury, how often would you **experience musical "chills?"** Musical chills occur when you feel 'shivers-down-the-spine' when listening to music.
13. (Before/After) your brain injury, how common was it for you to **engage in unstructured musical behaviors**? For example, to hum, sing, or whistle when you were not listening to music?
14. (Before/After) your brain injury, pleas rate your **overall enjoyment** of music, in general. How much did you enjoy listening, playing, and participating in music?

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