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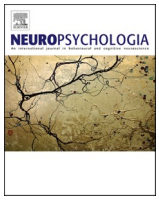

Music perception in acquired prosopagnosia

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ABSTRACT

Background: Acquired prosopagnosia is often associated with other deficits such as dyschromatopsia and topographagnosia, from damage to adjacent perceptual networks. A recent study showed that some subjects with developmental prosopagnosia also have congenital amusia, but problems with music perception have not been described with the acquired variant.
Objective: Our goal was to determine if music perception was also impaired in subjects with acquired prosopagnosia, and if so, its anatomic correlate.
Method: We studied eight subjects with acquired prosopagnosia, all of whom had extensive neuropsychological and neuroimaging testing. They performed a battery of tests evaluating pitch and rhythm processing, including the Montréal Battery for the Evaluation of Amusia.
Results: At the group level, subjects with anterior temporal lesions were impaired in pitch perception relative to the control group, but not those with occipitotemporal lesions. Three of eight subjects with acquired prosopagnosia had impaired musical pitch perception while rhythm perception was spared. Two of the three also showed reduced musical memory. These three reported alterations in their emotional experience of music: one reported music anhedonia and aversion, while the remaining two had changes consistent with musicophilia. The lesions of these three subjects affected the right or bilateral temporal poles as well as the right amygdala and insula. None of the three prosopagnosic subjects with lesions limited to the inferior occipitotemporal cortex exhibited impaired pitch perception or musical memory, or reported changes in music appreciation.
Conclusion: Together with the results of our previous studies of voice recognition, these findings indicate an anterior ventral syndrome that can include the amnestic variant of prosopagnosia, phonagnosia, and various alterations in music perception, including acquired amusia, reduced musical memory, and subjective reports of altered emotional experience of music.

1. Introduction

Acquired prosopagnosia is the loss of familiarity for faces after a brain lesion (Corrow et al., 2016a, 2016b), a relatively selective problem that cannot be attributed to more general impairments in vision and memory. It is not a single disorder, but has functional and anatomic variants (Barton, 2008a,b; Damasio et al., 1990; Davies-Thompson et al., 2014; De Renzi, Faglioni, Grossi and Nichelli, 1991). The lesions that are associated with acquired prosopagnosia range from occipitotemporal lesions, often involving the fusiform gyrus, to anterior temporal lesions, and are usually either bilateral or right-sided (Davies-Thompson et al., 2014), with rare subjects having only left-sided damage (Barton, 2008a, 2008b).

As with all pathologic lesions, the structural damage in these subjects is often large and frequently encompasses regions outside of the face network. The consequence is that prosopagnosia is often associated with other impairments from damage to adjacent processing circuits. Prosopagnosia from occipitotemporal lesions is often part of a ventral visual syndrome, with cerebral dyschromatopsia (Moroz et al., 2016) and topographic disorientation, the inability to orient in familiar

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surroundings (Corrow et al., 2016a, 2016b). Prosopagnosia with bilateral anterior temporal lesions can be associated with phonagnosia, the inability to recognize voices (Liu et al., 2016), consistent with other evidence that the right anterior temporal lobe is involved in person recognition from multiple modalities (Gainotti and Marra, 2011).

Prosopagnosia can also be developmental. Subjects with this variant do not have visible structural lesions by definition. These subjects tend to have normal colour perception (Moroz et al., 2016), though some also have problems with topographic orientation or voice recognition (Corrow et al., 2016a, 2016b; Ran R Liu, Corrow, Pancaroglu, Duchaine, & Barton, 2015). Recently, we discovered that some subjects with developmental prosopagnosia also have congenital amusia, or tone-deafness (Corrow et al., 2019), and conversely, that subjects with congenital tone-deafness can have face processing impairments (Paquette et al., 2018), an observation since replicated by others (Tao et al., 2019). Since amusia is neither a visual disorder nor a problem of person recognition, its co-occurrence with developmental prosopagnosia is unexpected. The basis of the association is unknown. As with the other perceptual deficits in acquired prosopagnosia, it could reflect anatomic proximity of face and music processing networks, so that they have a shared structural vulnerability to some focal disturbance. On the other hand, it may indicate that the responsible developmental failure has widespread effects on many disparate perceptual networks in vision, audition, and possibly other modalities.

If the first explanation were correct, this would predict that some subjects with acquired prosopagnosia would also have acquired amusia. The clustering of additional perceptual deficits with acquired prosopagnosia almost always reflects the close physical relationship between different perceptual networks within ventral occipitotemporal cortex. Although neurodegenerative pathology is somewhat diffuse, a supportive observation is one report of impaired familiarity for both faces and melodies in frontotemporal dementia (Hsieh et al., 2011).

In this study, we examined eight subjects with acquired prosopagnosia with tests of the perception of pitch, rhythm and musical memory. Our goal was to determine if any showed music impairments, and if so, what type of impairment. We then reviewed their neuroimaging to determine whether acquired impairments of music perception were associated with a specific anatomic variant of prosopagnosia.

2. Methods

2.1. Subjects

All prosopagnosic and control subjects could hear well enough to converse comfortably with the experimenter and none reported a hearing impairment. All subjects were fluent in English, had lived in Canada or the United States for a minimum of 10 years, most of them having spent the majority of their lives in Canada. The institutional review boards of the University of British Columbia and Vancouver Hospital approved the protocol, and all subjects gave informed consent in accordance with the principles of the Declaration of Helsinki.

Eight subjects with acquired prosopagnosia were recruited from the website www.faceblind.org or from a local neuro-ophthalmologic clinic (Table 1). These were 2 female and 6 male subjects with a mean age of 40.87 years (s.d. 16.5, range 18–62 years). These subjects were part of a cohort that has been studied extensively, whose details are also given in other recent reports (Corrow et al., 2016a, 2016b; Hills et al., 2015; Liu et al., 2016; Moroz et al., 2016). All subjects had a neuro-ophthalmological history and examination, including Goldmann perimetry. All had corrected Snellen visual acuity of at least 20/30 in the better eye. All complained of impaired face recognition in daily life and none had complaints of mistaking one type of object for another.

Subjects underwent a battery of neuropsychological tests for handedness, general intelligence, executive function, memory, attention, visual perception and language skills (Table 2). The diagnosis of prosopagnosia was supported by performance on face recognition tests (Table 3). Subjects were impaired on at least one of two tests of familiarity for recently viewed faces, the Cambridge Face Memory Test (Duchaine and Nakayama, 2006) or the face component of the Warrington Recognition Memory Test (E. Warrington, 1984), while performing normally on the word component of the latter. Face recognition was evaluated with a Famous Faces Test (J. Barton, Cherkasova and O'Connor, 2001). Although not part of the diagnostic criteria for prosopagnosia, subjects were also assessed for perceptual discrimination of faces with the Benton Face Recognition Test (Benton and Van Allen, 1972), the Cambridge Face Perception Test (Duchaine et al., 2007), and a face imagery test (J. Barton and Cherkasova, 2003). Six of these subjects (Table 3) had also participated in a prior study of discrimination and short-term familiarity for voices (R. R. Liu et al., 2016).

All prosopagnosic subjects had structural magnetic resonance imaging (Fig. 1) as described in recent reports about this cohort (Hills et al., 2015; Liu et al., 2016; Pancaroglu et al., 2016). The nomenclature for our prosopagnosic subjects follows primarily the tissue loss or hypointensity on T1-weighted images. Those with right-only lesions are designated 'R', whereas those with bilateral lesions are designated 'B'. Lesions mainly anterior to the anterior tip of the middle fusiform sulcus (Weiner et al., 2014) were designated as anterior temporal (AT) and those posterior to it as inferior occipitotemporal (IOT). B-OTAT3 had a more complex lesion, with extensive right-sided lesions from the occipitotemporal to anterior temporal and parietal regions, with FLAIR sequences also showing white matter hyperintensity in the left anterior temporal and occipito-temporo-parietal regions.

Tests of music perception were also performed by 25 control subjects (16 female, mean age 44.76 years, range 24–70). These were the same controls in our prior report on music perception in developmental prosopanosia (Corrow et al., 2019). Subjects were excluded if they reported a history of a neurologic disorder or had best-corrected visual acuity of worse than 20/60 in their best eye. To be considered, control subjects had to affirm that they did not believe that they had any trouble recognizing faces. To guard against undiagnosed developmental prosopagnosia in our initial sample of 27 control subjects, we excluded two subjects for having a score on the Cambridge Face Memory Test of less than 44.

Table 1
Patient data.

subject	age at testing	age at onset	gender	cause	visual fields
R-IOT1	56	37	M	hemorrhage, AV malformation	left upper quadrantanopia
R-IOT4	62	61	M	infarction	left upper quadrantanopia
B-IOT2	60	26	M	subdural hematoma	bilateral hemifield defects
R-AT1	35	23	F	epilepsy surgery	full
R-AT3	37	30	M	HSV encephalitis	full
R-AT2	34	25	F	HSV encephalitis	full
B-AT1	25	21	M	HSV encephalitis	full
B-ATOT3	18	10	M	HSV encephalitis	left hemifield defects

M = male, F = female, HSV = herpes simplex virus, Initialisms: R = right, B = bilateral, IOT = inferior occipitotemporal, AT = anterior temporal, OT = occipitotemporal.

Table 2
Neuropsychologic test results.

Test	Max	R-IOT1	R-IOT4	B-IOT2	R-AT1	R-AT3	R-AT2	B-AT1	B-ATOT3
Attention									
Trails A	-	39	48#	**80**	33	22	21	18	41
Trails B	-	61	102#	**142**	**59**	37	44	25	**114**
Star Cancellation	**54**	54	54	53	54	54	54	54	53
Visual Search	**60**	54	n/a	56	59	59	59	59	56
Memory									
Digit span-forward	**16**	12	8	14	10	16	13	12	10
Spatial span-forward	**16**	9	10	8	8	12	9	10	8
Word list, immediate recall	**48**	28	37	35	37	31	35	**27**	29
Visuo-perceptual									
Hooper Visual Organization	**30**	27	22	22.5	25	27.5	28	20	6.5
Benton Judgment of Line Orientation	**30**	29	24	29	29	30	28	28	26
Visual Object and Spatial Perception									
Object:Screening	**20**	20	18	20	19	20	20	20	19
Incomplete Letters	**20**	19	19	19	19	19	20	19	17
Silhouettes	**30**	21	18	**12**	19	22	18	**10**	2
Object Decision	**20**	16	19	14	17	17	20	16	8
Progressive Silhouettes	**20**	9	13	15	14	11	10	**17**	**20**
Spatial:Dot Counting	**10**	10	9	10	10	10	10	10	9
Position Discrimination	**20**	20	19	19	18	19	20	19	14
Number Location	**10**	10	10	10	10	10	9	10	6
Cube Analysis	**10**	10	10	10	10	10	10	10	–
Imagery									
Mental Rotation	**10**	10	10	10	9	10	9	10	10

Bold underlined text denotes impaired, # denotes borderline performance, (–) no data.

Table 3
Results for face and voice processing.

	R-IOT1	R-IOT4	B-IOT2	R-AT1	R-AT3	R-AT2	B-AT1	B-ATOT3
FACES								
Face Perception								
BFRT (/54)	45	46	**38**	41	**38**	47	45	**28**
CFPT (/72)^	**62**	**76**	**70**	7.25	48	40	52	**92**
Familiarity								
famous faces d'	**1.96**	**1.29**	**1.31**	**0.97**	**0.90**	**0.65**	**0.36**	**–0.80**
Face Memory								
WRMT face (/50)	**33**	39	**21**	**17**	**31**	**27**	**27**	**26**
WRMT word (/50)	41	50	42	41	47	47	45	48
CFMT (/72)	44	**27**	**24**	**19**	**31**	**33**	**30**	**28**
Face imagery	82	84	86	**73**	**49**	**73**	a	**60**
VOICES								
Voice discrimination (/40)	35	32	33	(–)	37	31	30	(–)
Voice familiarity (/42)	32	30	26	(–)	26	28	**25**	(–)

BFRT - Benton face recognition test, WRMT - Warrington Recognition Memory Test, CFMT - Cambridge face memory test, bold underlined text indicates an abnormal result, (–) not tested, ^On this test, high scores indicate poor performance.
[a] B-AT1 did not recognize enough celebrity names to perform the imagery test.

2.2. Music assessments

We administered several tests of pitch and rhythm perception to confirm that any abnormality was consistent across different methods of testing. All tests were hosted online, and detailed instructions were emailed to subjects. Subjects were instructed to adjust their headphone volume to a comfortable level during practice stimuli before completing the test battery.

The *Montréal Battery for Evaluation of Amusia* (Peretz et al., 2003) is the current "gold standard" for assessing deficits in music perception (Wilcox et al., 2015) and is the most frequently used test for diagnosing congenital amusia (Pfeifer and Hamann, 2015; Vuvan et al., 2015). We administered all six sub-tests, each evaluating different aspects of music perception, including scale, contour, interval, rhythm, meter, and incidental musical memory recognition. Each test began with written instructions and examples. The first three tests evaluated scale, contour, and interval components of pitch perception. In each, subjects heard two melodies sequentially and indicated if the two musical phrases were the same or different by clicking a circle next to the words 'same' or 'different.' In the fourth test, the two phrases differed only in rhythm, not pitch. The fifth test, of meter, presented a single melody and subjects indicated if the melody was a waltz or a march. Participants clicked a circle next to the words 'waltz' or 'march' to indicate their response. Finally, the sixth test examined short-term incidental memory for music: half the trials were musical phrases that had been heard in the first five tests, while half were new phrases, and subjects responded whether or not they had heard the phrases before. Participants again indicated their response with the click of a mouse. The scale, contour, interval, and rhythm tests contained 30 trials each, plus one catch trial in each test, which was subsequently removed. The meter and memory tests contained 30 trials. For each test, all trials appeared on a single page and the participant clicked an on-screen button with their mouse to initiate the audio for a given trial. Scores for each test were calculated as the number correct out of 30. As in previous studies (Nathalie Gosselin, Paquette, & Peretz, 2015; Peretz et al., 2009), we calculated a subject's composite melodic score as the average of their scores for the first three subtests (scale, contour, and interval) with pitch components. Occasionally, a participant failed to provide an answer for a trial because they either accidently scrolled past a trial without realizing it, or they clicked slightly outside of the response circle provided. This occurred on a total

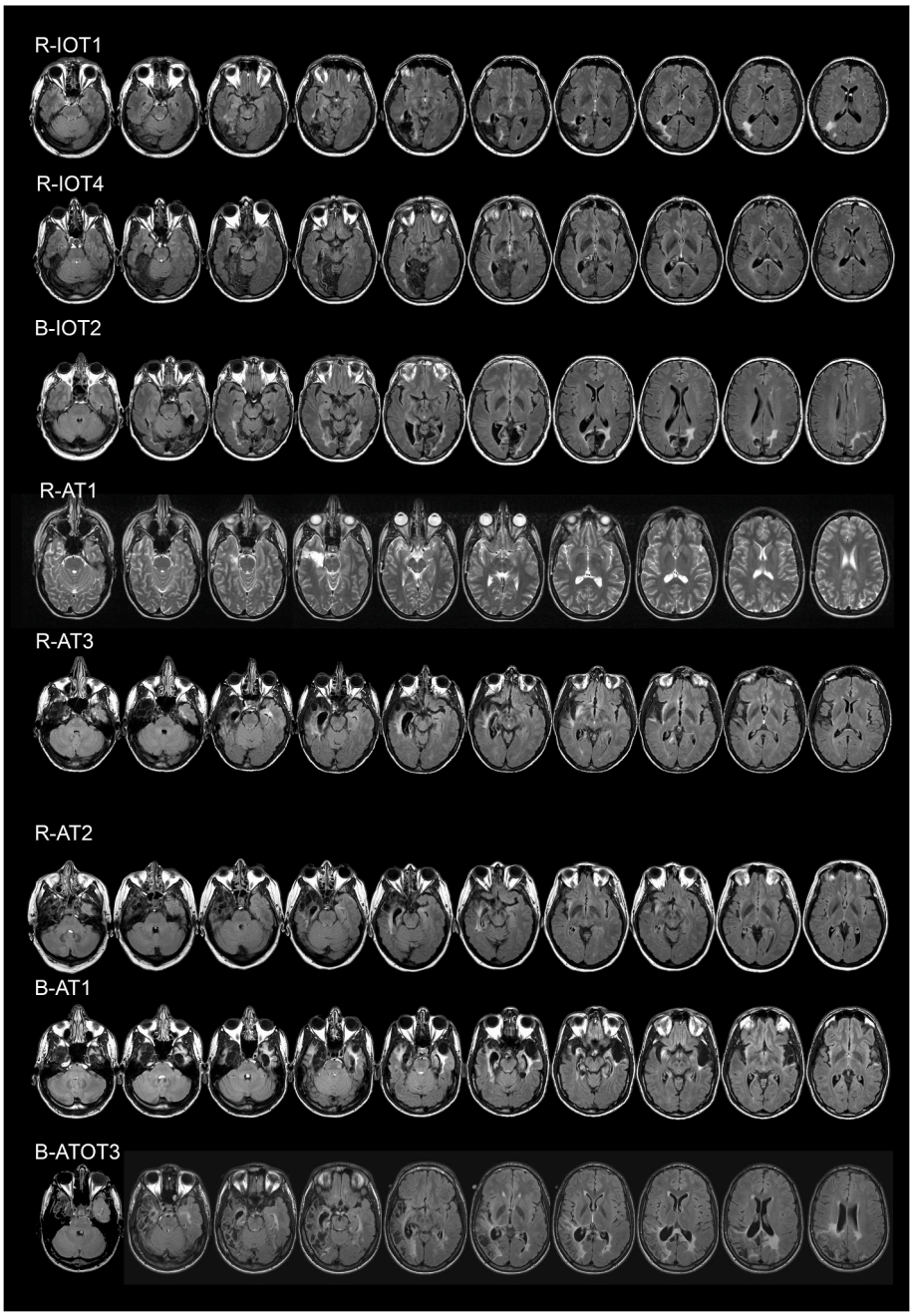

Fig. 1. Axial MRI scans for the eight subjects with acquired prosopagnosia. FLAIR images are shown for all except for the T2-weighted image for R-AT1.

of 7 trials for the control group, and 3 trials for the prosopagnosic group. In all, no more than one trial was missing for a test. To provide a conservative estimate of performance in these cases, missing trials were counted as correct. None of the participants included in the final analysis missed the catch trials.

The *Distorted Tunes Test* was originally described by Kalmus and Fry (1980) and later updated and made available online (https://www.nidcd.nih.gov/tunestest/take-distorted-tunes-test) (Drayna et al., 2001). Twenty-six melodies of well-known North American tunes were played on a piano. Nine were correctly played but seventeen contained a wrong note, off by up to two semi-tones of the correct note, but still following the contour of the original melody. Subjects clicked a button with their mouse to begin each melody and responded whether the melody was played correctly by clicking one of two circles next to the words 'yes' or 'no.' Scores were calculated as the number correct out of 26.

The *Pitch Discrimination Test* (Loui et al., 2009) presented two tones sequentially, and subjects indicated if the second tone was higher or lower in pitch than the first by clicking one of two buttons labeled 'higher' and 'lower'. This test used a staircase design, and subjects continued the task until they had completed six reversals in the staircase: the average of the values at these 6 reversals determined their pitch discrimination threshold, expressed in Hz. Subjects completed the task twice, and their final threshold estimate was the average of the two. This test complemented the prior two tests by evaluating fine pitch discrimination outside of a musical context, with less demands on attention and memory. However, this task did involve pitch direction identification as the participants were required to state if the second tone was higher or lower than the first, rather than simply indicate if the two tones were the same or different. For the sake of consistency with prior literature (Corrow et al., 2019; Loui et al., 2009), we refer to it as a

pitch discrimination task.

The *Harvard Beat Assessment Test* (Fujii & Schlaug, 2013) complemented the two subtests for rhythm and meter in the Montréal Battery of Evaluation of Amusia, as those subtests are useful but not infallible measures of temporal aspects of music perception, since alternative strategies can be used by participants with rhythm processing deficits (e.g. pattern of durations can be compared in the rhythm task and acoustic accents can be compared in the meter task) (Tranchant and Vuvan, 2015). This task used a computerized version of the Beat Finding and Interval Test described in Fujii and Schlaug (2013). It had two components; one for beat perception and one for beat production, each using a staircase design. Both components had a repeating rhythm tapped out on a woodblock. This rhythm consisted of one quarter-note, two eighth-notes, one dotted-quarter-note, and one eighth-note (Fig. 2).

Each trial began with a pure tone, followed by 27 woodblock tones corresponding to 21 quarter note beats. The task followed a temporal-change rule that resulted in the inter-beat interval either slowing down or speeding up. The change in inter-beat interval started from 20 ms. For example, on a slower trial, the first four inter-beat intervals started at 500, 520, 540, and 560 ms. The task began with either a slower or faster trial, chosen randomly. If the participant correctly characterized the change as slower or faster for two consecutive trials, the inter-beat interval was halved. In all other cases it doubled. Therefore the staircase followed a two-down, one-up paradigm. All turnaround points in the staircase were recorded and the task continued until 6 turnaround points had occurred. The average of the 6 turnaround points was recorded as a threshold. See Fujii and Schlaug (2013) for further details.

In the beat perception component, subjects indicated with a mouse click or key press whether the beat was accelerating or decelerating across its repetitions. In the beat production component, subjects listened to this woodblock rhythm and tapped the space bar to the "beat" of the rhythm in quarter-notes. The rhythm accelerated or decelerated, and the test determined if subjects made a corresponding increase or decrease in tapping frequency.

Several months after completion of testing, we asked our prosopagnosic subjects two simple written questions by email, first whether they were aware of any problems with music perception or tone-deafness prior to the lesion causing prosopagnosia, and second if their music perception had changed after the onset of prosopagnosia.

2.3. Analysis

We first checked to ensure that there was no statistically significant difference in the ages of our acquired prosopagnosic and control subjects. Then, because our subjects spanned a wide age range, and there is evidence of age-related declines in music perception and performance on tests such as the Montréal Battery for Evaluation of Amusia (Moreno-Gomez et al., 2017), we determined if performance correlated with age, particularly focusing on pitch-related tasks.

To evaluate potential pitch perception deficits, we calculated composite scores of the Montreal Battery which includes the sum of the scale, contour, and interval subsets. To incorporate scores across pitch tasks and model the analysis completed in Corrow et al. (2019), we next derived for each subject a global score for pitch perception, by averaging the z-scores across relevant tasks from the different tests. This included the Pitch discrimination test, the Scale, Contour, and Interval subtests of the Montréal Battery for Evaluation of Amusia, and the Distorted Tunes Test.

We performed a small group-level analysis to determine if the occipitotemporal or anterior temporal lesion groups were impaired in pitch perception relative to the control group on this global pitch perception score, after controlling for age, which was included as a covariate.

For single subjects we determined if any subject met a standard published criterion for amusia (Chen et al., 2015; Marin et al., 2015; Pfeifer and Hamann, 2015), namely a summed score of 65 or less on the 3 melodic subtests – i.e., scale, contour and interval – of the Montréal Battery of Evaluation of Amusia, which equals the sum of the cut-off scores reported in Peretz et al. (2003). To determine how many subjects with prosopagnosia had impaired global pitch perception scores, we calculated 95% prediction intervals from the control data (Whitmore, 1986) and classified each subject as normal or impaired by this criterion.

Similarly, we obtained a global score for rhythm perception, including the results from the Rhythm and Meter subtests of the Montréal Battery of Evaluation of Amusia, and the two tests of the Harvard Beat Assessment Test. This was motivated by two reasons. First, reports state that subjects with congenital (Hyde and Peretz, 2004) and acquired amusia (Murayama et al., 2004) often have intact rhythm perception despite impaired pitch perception. Second, many of the subjects with developmental prosopagnosia in our prior report similarly had selective deficits in pitch but not rhythm perception. Therefore we again performed an analysis for a dissociation between pitch and rhythm processing in a sample with acquired prosopagnosia. We conducted a group level analysis to examine potential deficits in rhythm perception, after controlling for age, and calculated 95% prediction intervals for classification of the performance of individual subjects.

Finally, in the control group, global pitch and global rhythm scores were highly correlated ($r = 0.68$, $p < .001$). To determine if any prosopagnosic subject had a deficit greater for pitch than for rhythm perception, we regressed out the variance related to rhythm perception and used the residual variance to calculate 95% prediction intervals appropriate for single-subject comparisons for the relationship between pitch and rhythm scores. This allowed us to see if, as with previous reports, subjects were more affected in their pitch processing than in rhythm, meeting criteria for a putative classical dissociation (Gerlach et al., 2018).

Third, we reviewed the test assessing short-term incidental memory for music. This was the sixth test of the Montréal Battery for the Evaluation of Amusia. Because of the small number of trials, we compared the results to published normative criteria from large samples of 100 or more subjects (Cuddy et al., 2005; Nan et al., 2010; Peretz et al., 2003), which indicate that a score of 21 or less is abnormal.

3. Results

The age of the acquired prosopagnosia ($M = 40.87$, $sd = 16.5$) and control subjects ($M = 44.76$, $sd = 14.8$) did not significantly differ ($t(31) = 0.079$, $p = .93$, Cohen's $d = 0.03$), making it unlikely that any group level differences in performance could be attributed to age differences. Furthermore, in this sample of healthy subjects, we did not find an age-related decline of either the global pitch score ($r(23) = 0.28$, $p = .17$) or the global rhythm score ($r(23) = 0.15$, $p = .94$). The correlation of age with the total score for the Montréal Battery for Evaluation of Amusia also did not reach significance ($r(23) = 0.22$, $p = .3$). Looking at specific pitch-related scores, we found an age-related decline in the pitch discrimination test ($r(23) = 0.42$, $p = .037$) but not for the Distorted Tunes Test ($r(23) = 0.009$, $p = 097$) or the summed score for the scale, contour and interval subtests Montréal Battery for Evaluation of Amusia

Fig. 2. Score notation for the woodblock pattern repeated in the Harvard Beat Assessment Test.

(r (23) = 0.23, p = .28).

3.1. Pitch perception

i. Group level. We asked if the two acquired prosopagnosic groups were impaired in pitch processing, relative to the control group, after controlling for age. We performed an ANCOVA with group (*anterior temporal*, *occipitotemporal*, and control) as a between-subjects factor, global pitch scores as the dependent variable, and age as a covariate. Evaluations of the assumptions of ANCOVA revealed a violation of Levene's test for homogeneity of variances, so we used a "reflect and log" transformation (Statistics, 2017) of the global pitch scores. After this transformation, standardized residuals for the interventions were normally distributed, as assessed by Shapiro-Wilk's test (p > .05). There was homoscedasticity, as assessed by visual inspection of the standardized residuals plotted against the predicted values. There was homogeneity of variances, as assessed by Levene's test of homogeneity of variance (p = .178). There were no outliers in the data, i.e., cases with standardized residuals greater than ±3 standard deviations. Unadjusted means are presented, unless otherwise stated. The mean of global pitch scores for the control group was 0.0 (sd = 0.7). This was expected given that global pitch scores represent an average of z-scores for each test. The *anterior temporal* group had more extreme (worse) z-scores (M = −2.41, sd = 2.56) than the *occipitotemporal* group (M = −1.15, sd = 0.73). After adjustment for age as a covariate, there was a statistically significant difference between groups (*anterior temporal*, *occipitotemporal*, control - F (2, 29) = 8.18, p = .002, partial η2 = 0.361). Using a Sidak correction, adjusted global pitch scores were significantly lower in the *anterior temporal* group (M = 0.595, SE = 0.085) than the control group (M = 0.27, SE = 0.03), a mean difference of 0.325, 95% CI (0.095, 0.555), p = .004. There was no significant difference between the *occipitotemporal* group (M = 0.49, SE = 0.085) and controls, with a mean difference of 0.208, 95% CI (−0.023, 0.439), p = .088.

ii. Single-subject level. For global pitch scores, three subjects with prosopagnosia fell outside of the prediction limit for controls. This included BATOT3 (−2.06), BAT1 (−2.69), and RAT2 (−5.89) (see supplementary table for individual z-scores on each test). Four of the eight prosopagnosic subjects met a standard criterion for amusia, scoring 65 or less for the sum of the performances on the scale, contour and interval subtests of the Montréal Battery for Evaluation of Amusia (Table 4). These were R-AT2 (score of 51), R-AT3 (score of 65), B-AT1 (score of 63), and B-OTAT3 (score of 65).

3.1.1. Rhythm perception

i. Group level. We ran an ANCOVA with group (*anterior temporal*, *occipitotemporal*, and control) as a between-subjects factor, global rhythm scores as the dependent variable, with age as a covariate. Standardized residuals for the overall model were normally distributed, as assessed by Shapiro-Wilk's test (p > .05). There was homoscedasticity, as assessed by visual inspection of the standardized residuals plotted against the predicted values. There was homogeneity of variances, as assessed by Levene's test of homogeneity of variance (p = .133). There were no outliers in the data, i.e., cases with standardized residuals greater than ±3 standard deviations. Unadjusted means are presented, unless otherwise stated. The mean of global rhythm scores for the control group was 0.0 (sd = 0.67), by definition. The *anterior temporal* (M = −0.6, sd = 0.73) and *occipitotemporal* (M = −0.74, sd = 0.31) groups performed similarly to the controls. After adjustment for age, there was no significant difference in global rhythm scores between the groups, F (2, 29) = 3.12, p = .057, partial η2 = 0.18.

ii. Single-subject level. All subjects scored below the upper 95% prediction limit for the global rhythm perception score (Fig. 4).

3.1.2. Pitch versus rhythm perception

We assessed whether pitch perception was more greatly affected than rhythm perception in individual subjects. We regressed out the variance related to rhythm perception in the control group and used the residual variance to calculate 95% prediction intervals appropriate for single-subject comparisons for the relationship between pitch and rhythm scores. For all three subjects with impaired pitch perception, the global pitch score was disproportionately reduced compared to their global rhythm score (Fig. 3), falling outside of the 95% prediction limit for the relationship between pitch and rhythm perception seen in the controls, as indicated by the upper dotted line in Fig. 3.

Two subjects had borderline findings. The global pitch score of R-AT3 was well within the normal range, but his rhythm perception was very good, leading to a nearly significant difference between pitch and rhythm perception. R-IOT1 had a similar pattern, and scored in the impaired range on the distorted tunes test, and in the low range of normal for the Montréal Battery for Evaluation of Amusia. We would conclude that there is insufficient evidence of a music deficit in these two patients.

3.1.3. Music memory

For short-term incidental memory for music, only B-AT1 and R-AT2 performed below the published normative criterion of 22 on the sixth subtest of the Montréal Battery for the Evaluation of Amusia (Table 4). B-ATOT3 scored 25, and of the five subjects with intact pitch perception, all scored 26 or better, with the exception of R-AT3 again, who scored 23. The Distorted Tunes Test also evaluates pitch perception in the context of familiar tunes, and thus could be considered an indirect assessment of long-term familiarity. Indeed, the two lowest scores on this test belonged to B-AT1 and R-AT2, who also had the lowest scores on the sixth subtest of the Montréal Battery for the Evaluation of Amusia (Table 4).

3.1.4. Subjective impressions

None of our subjects had noted a problem with music perception or tone deafness before the onset of prosopagnosia. Of the four without evidence of amusia, three reported no change after the onset of face recognition problems (R-AT1, R-IOT4, and B-IOT2). R-IOT1 reported that an unrelated life-long tinnitus had worsened and reduced his enjoyment of music. R-AT3, with the borderline deficit in pitch perception, also had not noted any change.

The three subjects with definite evidence of amusia reported alterations in musical experience after the onset of prosopagnosia. B-AT1 reported that a dislike of music was among the first changes he had noted: "Beforehand, I liked music enough that I had a $3000 car stereo system with amplifiers and subwoofers. Afterwards, I went through a several-year period where I preferred silence over music … For amusia, I think it's more memory than perception". In contrast, B-ATOT3 felt that his hearing was more acute and that he could "hear rhythms, lyrics and tones better". He was teaching himself guitar and taking singing lessons, spending 20 hours a week on music. R-AT2 stated that her "love and appreciation for music became stronger … it seems to grab me more now and evoke lots more emotion."

3.1.5. Lesion review

R-AT2 has a lesion of the right temporal pole and amygdala, with hyper-intense signal in the right insula extending posteriorly in the white matter of the temporal lobe (Figs. 1 and 4). B-AT1 has bilateral lesions of the temporal pole and right amygdala, and like R-AT2 has hyper-intense signal in the right insula and temporal white matter. B-ATOT3 has extensive bilateral damage, which on the right includes the temporal pole, amygdala and superior temporal gyrus, with hyper-intensity in the white matter underlying the right posterior insula. Of note, none of the three subjects with lesions limited to the inferior occipitotemporal cortex had amusia.

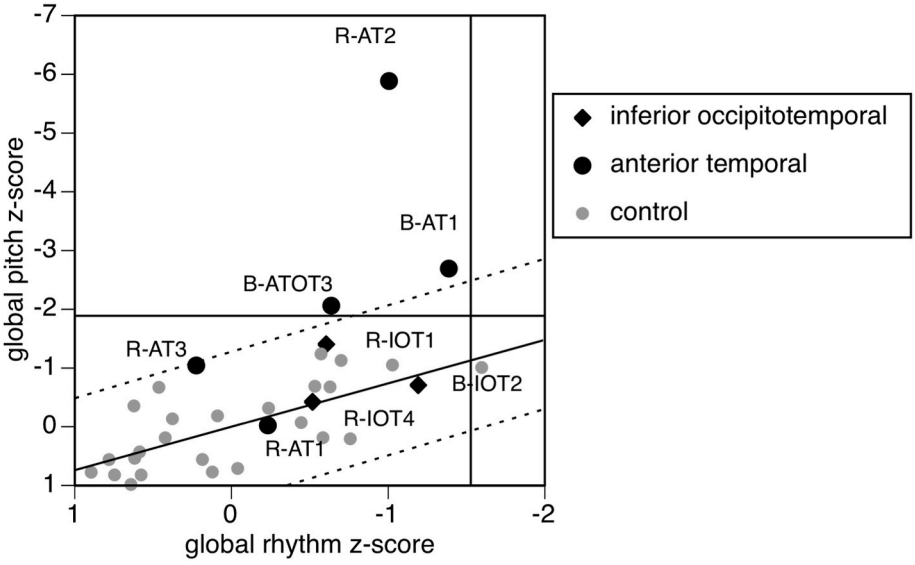

Fig. 3. Global pitch score plotted against global rhythm score for each subject. Black symbols are for prosopagnosic patients, with diamonds for those with lesions confined to occipitotemporal cortex, and discs for those whose lesions included anterior temporal cortex. The black solid diagonal line is the linear regression of global pitch against global rhythm scores for the control group, with the dotted black lines indicating 95% prediction limits for this regression. The horizontal and vertical solid lines indicate 95% prediction limits for global pitch and global rhythm scores respectively. Scores falling above the horizontal black line and the upper dotted diagonal line meet criteria for a 'putative classical dissociation'. This is the case for R-AT2, B-ATOT3 and B-AT1.

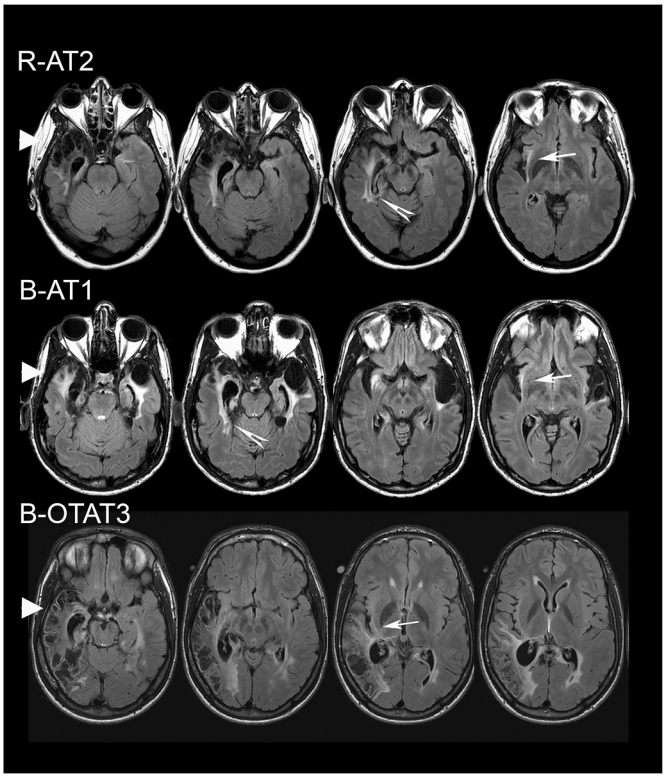

Fig. 4. Close-up views of relevant axial FLAIR MRI sections in patients with amusia. Left-most sections show the damage to the right anterior temporal poles (triangular arrowheads) and amygdalae. White arrows with tails point to the hyperintensities in the right insulae. White arrows without tails in R-AT2 and B-AT1 point to hyperintensities in the white matter of the inferior aspect of the right superior temporal gyri. B-ATOT3 has substantial damage to the right superior temporal gyrus, as seen in right three sections.

4. Discussion

At the group level, we found that prosopagnosic subjects with anterior temporal lesions were impaired in pitch processing relative to a control group, but not subjects with occipitotemporal lesions. We found no evidence of group-level impairments in the processing of rhythm.

Individually, we found consistent evidence of impaired pitch discrimination in three of eight prosopagnosic subjects, all of whom had anterior temporal lesions. None recalled pre-existing problems of music perception, but since none could be tested prior to the onset of prosopagnosia, and not all subjects with congenital amusia are aware of their deficit (Peretz and Vuvan, 2016), we cannot exclude the possibility that some may have had an coincidental congenital amusia. However, given an estimated prevalence of the latter in the general population of 1.5% (Peretz and Vuvan, 2016), the likelihood that a random sample of eight subjects would contain three individuals with congenital amusia is less than 0.0002. Furthermore, all three with impaired pitch perception had noted a change in their musical experience. Though music perception declines with age (Moreno-Gomez et al., 2017), age-related declines were not a confound. All three of our subjects with amusia as well as the subject with a borderline deficit were under 40 years of age. Furthermore, age was included as a covariate in our group-level analysis.

As in our subjects with developmental prosopagnosia (Corrow et al., 2019), impaired pitch perception was a relatively specific musical deficit, as rhythm perception was generally intact. This dissociation is consistent with the results in congenital amusia (Hyde and Peretz, 2004; Murayama et al., 2004) and most subjects with acquired amusia (Stewart et al., 2006).

We previously studied the voice recognition of six of these subjects (Liu et al., 2016). R-AT2 performed normally on voice testing, thus providing an acquired parallel to the finding of intact voice identification in congenital amusia (Julie Ayotte, Peretz and Hyde, 2002). B-AT1 had impaired short-term familiarity for voices, which indicates that bilateral anterior temporal lesions can result in a constellation of impairments in face, voice and music perception. His prior results also showed intact perceptual discrimination of faces and voices (Liu et al., 2016) indicating that his face and voice recognition deficits more likely reflect amnestic/associative rather than apperceptive types of dysfunction. In contrast, his amusia is characterized by an apperceptive deficit in pitch discrimination, as well as reduced memory for music and self-reported music anhedonia. Hence, his problems with music and voices likely have different mechanistic origins. This independence is consistent with evidence that pitch discrimination can be normal in some cases of developmental phonagnosia (Roswandowitz et al., 2014; Roswandowitz et al., 2017). Nevertheless, the co-occurrence of phonagnosia and impaired pitch perception has also been reported in two other subjects, CN and GL (Peretz et al., 1994). CN and GL had bilateral lesions involving the superior temporal gyri, temporal poles, inferior frontal gyri and insulae, similar to B-AT1.

Table 4
Results on music tests.

	Control M(sd)	Published Cutoff	R-IOT1	R-IOT4	B-IOT2	R-AT1	R-AT3	R-AT2	B-AT1	B-ATOT3
Montreal Battery for the Evaluation of Amusia (Peretz et al., 2003)										
1 scale (/30)	27 (1.8)	22	24	25	26	26	**23**	***16***	**23**	***20***
2contour (/30)	24.8 (3.25)	22	24	25	22	25	*21*	***16***	*20*	*20*
3interval (/30)	24.72 (3.3)	21	*20*	*21*	25	26	*21*	*19*	20	25
4rhythm (/30)	25.72 (3.01)	23	*22*	*23*	*22*	28	26	*21*	*20*	*20*
5 m (/30)	26.68 (3.58)	20	28	28	27	26	28	***18***	***17***	26
6 memory (/30)	26.72 (3.17)	22	28	28	28	26	23	***18***	***20***	25
MBEA subtests 1–3 (/90)	76.52 (7.26)	65[a]	68	71	73	77	*65*	***51***	*63*	*65*
Distorted tunes test (/25)	25.16 (.94)	[b]	**21**	25	25	25	24	**11**	**17**	**21**
Pitch discrimination^	5.4 (4.4)	[b]	2.2	4.4	**14.4**	4.7	3.1	**22.5**	4.0	8.1
Harvard Beat Assessment Test										
beat perception^	3.7 (4.7)	[b]	0.6	1.6	**16.7**	0.6	0.7	6.0	0.4	3.1
beat production^	4.5 (4.9)	[b]	**15.2**	14.2	8.8	**15.0**	5.4	2.2	12.5	7.3

Bold indicates scores 2sd from the control mean, Underlined indicates scores outside of the prediction limit for controls, Italicized text indicates that they scored at or below published cut-offs, if available, ^On these tests, a high score indicates poor performance.

[a] Used in Chen et al. (2015); Marin et al. (2015); Pfeifer and Hamann (2015).

[b] Normed or suggested cut-off not available.

The co-occurrence of acquired prosopagnosia and amusia suggests anatomic proximity between some components of the face and music processing networks. Neuroimaging in healthy subjects shows a right-dominant core face network in occipitotemporal regions, namely the fusiform gyrus (Kanwisher et al., 1997) and the posterior superior temporal sulcus (Haxby et al., 2000), which interacts with an extended network that includes the precuneus, inferior frontal gyrus, and anterior inferior temporal cortex (Haxby et al., 2000). For a recent review of the neural regions involved in the processing of faces, see Barton (2022). Correspondingly, the neuropsychological data show that right or bilateral lesions of either occipitotemporal or anterior temporal cortex can cause prosopagnosia (Davies-Thompson et al., 2014). Occipitotemporal lesions cause an apperceptive variant, with impaired perception of facial structure, whereas anterior temporal lesions are associated with an amnestic variant, in which subjects cannot recall the appearances of faces (Barton, 2008a,b; Damasio et al., 1990; Davies-Thompson et al., 2014).

The music processing network also shows right hemispheric predominance for some aspects, although lateralization may be modulated by experience. Music processing depends on local connections within the temporal lobe between primary, secondary and higher order association regions, as well as projections to inferior parietal and inferior frontal regions via the arcuate fasciculus (Albouy et al., 2019; Loui et al., 2009; Sihvonen et al., 2017a, 2017b; Zatorre, 2001). For a recent review of the temporal regions involved in the processing of music, see Sihvonen and Särkämö (2022). As with faces, though, music perception is multi-faceted, and the neural substrates for pitch, timbre, melody, rhythm, memory and emotional overtones have both overlapping and distinct elements (Stewart et al., 2006). Cases of impaired pitch perception often have lesions that involve at least the anterior to middle portion of the right superior temporal gyrus and insula (Ayotte et al., 2000; Hochman and Abrams, 2014; Peretz et al., 1994; Sihvonen et al., 2016; Terao et al., 2006), sometimes bilateral or extending to the temporal poles (Peretz et al., 1994). These and additional lesions to right-sided regions such as the amygdala and inferior frontal and middle tempora gyri were also implicated in acquired amusia by a study of 90 stroke patients (Sihvonen et al., 2017a, 2017b). A study using voxel-based morphometry found that interval perception was correlated with larger volumes of the bilateral amygdala, right superior temporal gyrus, and left planum polare (Li et al., 2014). Our three subjects with impaired pitch perception had large right anterior temporal lesions that encompassed parts of the superior temporal gyrus and amygdala, with subtle anomalies in the right insula.

While our testing of musical memory was limited, two of these three subjects were also impaired on the incidental memory test of the Montréal Battery for the Evaluation of Amusia, and had the lowest scores on the Distorted Tunes Test, which uses familiar songs as the context for testing pitch perception. Impaired memory for pitch is seen in congenital amusia (Gosselin et al., 2009; Tillmann, L√©v√™que, Fornoni, Albouy and Caclin, 2016). Likewise, many acquired cases with impaired musical memory also have impaired pitch perception (Stewart et al., 2006), and hence can be considered as having an apperceptive music agnosia. This is again associated with lesions of the anterior superior temporal gyrus and insula, as in our subjects. Studies of subjects with anterior temporal lobectomy have shown impaired melodic memory after right-sided lesions and impaired memory for lyrics with left-sided lesions (Samson and Zatorre, 1991, 1992).

The narratives of our patients also suggest variable effects on the emotional response to music. This not necessarily a given, as music perception and its emotional response are dissociable. Some subjects with acquired (Lechevalier et al., 1984; Peretz et al., 1998) or congenital amusia (Nathalie Gosselin et al., 2015) still report enjoyment of music, as is also true of some patients with Landau-Kleffner syndrome who have impaired music perception (Lévêque et al., 2020), while musical anhedonia can occur with intact music perception (Griffiths et al., 2004; E. Mas-Herrero et al., 2014). Among our cases with impaired pitch perception, B-AT1's report is consistent with musical anhedonia and music aversion, as previously reported in some cases of impaired pitch or timbre perception from right temporal and insular lesions (Griffiths et al., 1997; Hirel et al., 2014; Mazzucchi et al., 1982; Terao et al., 2006). In a series of 73 patients with frontotemporal dementia (Fletcher et al., 2015), 14 showed music aversion, which was associated with cortical thinning in right anterior temporal cortex, entorhinal cortex, hippocampus, amygdala and bilateral insulae.

In contrast, two of our three amusic subjects reported enhanced enjoyment of and/or participation in music, consistent with musicophilia (Fletcher et al., 2015). There are case reports of musicophilia in patients with frontotemporal dementia (Boeve and Geda, 2001; Geroldi et al., 2000; Hailstone et al., 2009). In one this evolved in concert with right amygdala and temporal atrophy (Boeve and Geda, 2001). Larger series suggest that musicophilia may be present in a quarter to a third of subjects with frontotemporal dementia (Fletcher et al., 2015; Fletcher et al., 2013). Although some authors report the impression that musicophilia is often accompanied by loss of music discrimination (Fletcher et al., 2013), music perception has rarely been evaluated in musicophilia, with the exception of a demonstration of preserved memory for famous tunes in one case (Hailstone et al., 2009). Our report provides objective evidence that musicophilia can occur with impaired pitch discrimination. However, the present study assessed changes in the emotional response to music with self-report. Future work could utilize available tools to assess changes in the emotional response to music, such as the Barcelona Music Reward Questionnaire for assessing musical

anhedonia (Ernest Mas-Herrero, Marco-Pallares, Lorenzo-Seva, Zatorre and Rodriguez-Fornells, 2012). Future work could also investigate whether there is a relationship between the emotional processing of music and the emotional processing of faces, although a recent study suggests that those with congenital amusia are not affected in emotional face processing (Lévêque et al., 2018).

The co-occurrence of acquired amusia and prosopagnosia is a novel finding. However, studies of acquired amusia generally did not include face recognition tests in their neuropsychological batteries (Baird et al., 2014; Griffiths et al., 1997; Peretz et al., 1994; Sarkamo et al., 2009a, 2009b). One amusic study even reported on the word but not the face component of the Warrington Recognition Memory Test (Baird et al., 2014). The omission of face tests reflects the fact that the focus of their testing was on general cognitive processes of memory, attention and linguistic processing, and any testing of vision was limited to basic processes probed by the Visual Object and Space Perception battery (Baird et al., 2014; Griffiths et al., 1997; Warrington and James, 1991).

While we are not aware of prior reports of patients with both acquired prosopagnosia and amusia specifically, some studies of frontotemporal dementia have reported co-existent problems with face and music perception. Although not directly relevant to our report, two studies established the multimodal nature of impaired emotion recognition in frontotemporal dementia by showing parallel deficits in emotional processing of music, faces and voices (Hsieh et al., 2012; Omar et al., 2011). However, recognition of facial emotions is dissociable from recognition of facial identity (Fox et al., 2011) and its impairment is not part of the definition of prosopagnosia. Also, the subjects of these two studies were not shown to have amusia: in fact, the subjects in one report performed well on the scale subtest of the Montréal Battery for the Evaluation of Amusia (Hsieh et al., 2012).

More relevant to our work are two other studies of frontotemporal dementia. One reported a patient with musicophilia and impaired face and object recognition, who performed poorly on a test of famous face recognition (Hailstone et al., 2009). The second studied 13 patients and found impaired familiarity for both famous faces and famous melodies (Hsieh et al., 2011). However, in both reports these impairments were part of more widespread semantic deficits, and neither evaluated music discrimination. Nevertheless, while these points reduce the parallel with our work, the voxel-based morphometric analysis of the latter study (Hsieh et al., 2011) did find overlap in the right anterior temporal lobe between regions implicated in impaired familiarity for famous tunes and that for famous faces, a finding that supports our conclusion that focal lesions in this region can impair both face and music processing.

We note some limitations of our study. First, prior studies have demonstrated that musical training can improve pitch processing ability (Micheyl et al., 2006). In the present study, we did not collect information about the number of years of musical training of our participants with acquired prosopagnosia. In our prior report with developmental prosopagnosic subjects, we found a relationship between face recognition ability and pitch processing ability that was independent of prior musical training. This study used the same set of controls. Second, prior studies have demonstrated a relationship between bilingualism and pitch processing ability in adults (Liu et al., 2022) and children (Liu and Kager, 2017). To our knowledge, none of our subjects with acquired prosopagnosia are bilingual. Finally, we were limited by the small number of patients studied; however, acquired prosopagnosia is rare and our cohort is the largest assembled in recent decades.

Our prior work with this group has shown that apperceptive prosopagnosia is associated with dyschromatopsia (Moroz et al., 2016) and impaired cognitive map formation (Corrow et al., 2016a, 2016b) as part of a ventral visual syndrome following right or bilateral lesions of inferior occipitotemporal cortex. This accords with prior reports (Bouvier and Engel, 2006) but clarifies that these associations are specific to the occipitotemporal variant. The co-occurrence of these deficits is not invariable: not all patients have all three components, which is to be expected as face, colour and topographic processing involve neighbouring rather than identical perceptual networks, and the impact of a lesion in any given patient will differ across these networks. The consistency iof selective impairments within subjects, combined with our extensive testing battery, lends support to the notion that these impairments are not due to task demands, but rather to select impairments related to their lesions. Along with our prior study of voice recognition (Liu et al., 2016), the current report points to the existence of a second syndrome, an anterior temporal agnosia syndrome, which follows right or bilateral damage and consists of the amnestic variant of prosopagnosia, phonagnosia, and various alterations of music perception, including impaired pitch discrimination, reduced musical memory, and altered emotional responses to music, such as music aversion and musicophilia. Again, not all face, voice and music deficits are present in all patients, which may reflect the degree of pre-morbid lateralization of separate processing networks as well as the anatomic extent of lesions in one or both hemispheres. Just as we report patients with prosopagnosia who have intact voice and music perception, so too there are patients with acquired phonagnosia with intact face recognition (Luzzi et al., 2018). Given the rich and complex nature of sensory processing, further studies will likely reveal other perceptual or recognition deficits in the same or other sensory modalities following anterior temporal damage.

Credit author statement

JJSB – Conceptualization; Behavioural Investigation; Neuroimaging, Formal analysis; Writing and editing. JS – Administering testing, data collation, writing first draft, editing. SP – Analyzing music data. BD – Recruitment of subjects. GS – Analzying music data, supply and design of rhythm test. SLC – Supervision, Data analysis, writing and editing.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

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