Neuropsychologia 124 (2019) 87–97

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Perception of musical pitch in developmental prosopagnosia

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ARTICLE INFO

Keywords:
Amusia
Face recognition
Music perception
Pitch perception

ABSTRACT

Studies of developmental prosopagnosia have often shown that developmental prosopagnosia differentially affects human face processing over non-face object processing. However, little consideration has been given to whether this condition is associated with perceptual or sensorimotor impairments in other modalities. Comorbidities have played a role in theories of other developmental disorders such as dyslexia, but studies of developmental prosopagnosia have often focused on the nature of the visual recognition impairment despite evidence for widespread neural anomalies that might affect other sensorimotor systems.

We studied 12 subjects with developmental prosopagnosia with a battery of auditory tests evaluating pitch and rhythm processing as well as voice perception and recognition. Overall, three subjects were impaired in fine pitch discrimination, a prevalence of 25% that is higher than the estimated 4% prevalence of congenital amusia in the general population. This was a selective deficit, as rhythm perception was unaffected in all 12 subjects. Furthermore, two of the three prosopagnosic subjects who were impaired in pitch discrimination had intact voice perception and recognition, while two of the remaining nine subjects had impaired voice recognition but intact pitch perception.

These results indicate that, in some subjects with developmental prosopagnosia, the face recognition deficit is not an isolated impairment but is associated with deficits in other domains, such as auditory perception. These deficits may form part of a broader syndrome which could be due to distributed microstructural anomalies in various brain networks, possibly with a common theme of right hemispheric predominance.

1. Introduction

Developmental prosopagnosia is a lifelong impairment in face recognition despite intact basic visual function and memory (Duchaine and Nakayama, 2006b; Susilo and Duchaine, 2013). Much research has been devoted to determining if the deficit is specific to faces or also affects other visual categories such as object recognition (Behrmann et al., 2005; Duchaine and Nakayama, 2005; Duchaine et al., 2006) and word recognition (Rubino et al., 2016). However, little consideration has been given to whether there are associated impairments in non-visual cognitive processes. To date, this has been mostly limited to exploring whether voice recognition is also impaired (R.R. Liu et al., 2015; von Kriegstein et al., 2006), with the goal of exploring if the processing deficit in developmental prosopagnosia is specific to face-specific stages in person identification, or extends to amodal stages (Gainotti, 2013).

The possibility that a congenital failure of face recognition is associated with other disorders of high-level sensory information processing is suggested by analogy with other developmental conditions. For example, some subjects with developmental dyslexia also have phonological deficits, poor frequency discrimination in audition, motion perception deficits (Skottun and Skoyles, 2008) or problems with balance and motor control, which may be linked to dyslexia in either a correlative or a causal fashion (Habib, 2000; Ramus, 2004). While the anatomic correlates of developmental prosopagnosia continue to be debated (Avidan et al., 2014; Garrido et al., 2009; Gomez et al., 2015; Song et al., 2015; Thomas et al., 2009), it may be that, as hypothesized for dyslexia (Ramus, 2004), the primary developmental failure is one that produces more widely distributed anomalies of cortex or white matter and thus affects other cognitive processes. In fact, some have

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https://doi.org/10.1016/j.neuropsychologia.2018.12.022
Received 14 November 2017; Received in revised form 19 December 2018; Accepted 29 December 2018
Available online 06 January 2019

Table 1
Bold scores indicate performance 2 sd. outside of the published normative means. NA – Not administered. Scores on the Wechsler Memory scale are age-adjusted scaled scores.

	DP014	DP035	DP044	DP032	DP024	DP016	DP008	DP033	DP039	DP202	DP201	DP029
Demographics												
Gender	M	M	F	M	F	F	F	F	M	F	F	F
Age (yrs)	43	40	36	67	36	53	62	47	50	20	53	29
Yrs Education	16	16	21	21	16	14	18	18	18	13	18	18
Yrs Music Training	1	0	5	14	15	0	7	2	9	4	2	10
WASI-Full IQ	129	116	NA	126	137	120	119	135	117	130	117	131
Face Recognition												
PI20	**91**	**84**	**95**	**86**	**75**	**87**	**72**	**84**	**85**	**86**	**94**	**79**
CFMT (/72)	**32**	**36**	**40**	**42**	**41**	**41**	**36**	**29**	**22**	**33**	**42**	**42**
Famous Faces (/60)	**8**	**9**	**26**	**39**	**14**	**37**	43	**32**	**37**	NA	**41**	**28**
Old/New (d')	**0.67**	**1.46**	2.34	**2.08**	**1.89**	**2.06**	**1.46**	**2.06**	**1.81**	**− 0.21**	3.24	**1.88**
Wechsler Memory Scale												
Word Lists I	13	13	13	17	16	8	13	16	9	8	12	NA
Word Lists II	13	13	15	15	15	11	15	15	8	9	11	NA
Digit Span	14	16	16	9	14	14	18	12	11	10	11	NA
Spatial Span	17	15	NA	14	16	14	13	12	11	9	13	NA
Object Recognition												
Silhouettes	**14**	20	22	**15**	22	20	20	21	21	22	26	25
Object Decision	19	20	**15**	18	18	17	17	17	18	16	17	18
Progressive Silhouettes	8	11	10	7	6	10	13	11	8	8	11	11

recently proposed that neurodevelopmental disorders such as dyslexia, developmental prosopagnosia, and congenital amusia (a deficit in fine pitch discrimination), may be different variants of a common underlying disorder (Peretz, 2016; Susilo and Duchaine, 2013). If these share a common cause, then these disorders should co-occur to some degree (Peretz, 2016) and, functionally, these skills may be related to one another.

In our series of studies of developmental prosopagnosia (R.R. Liu et al., 2015; Moroz et al., 2016; Rubino et al., 2016), we encountered occasional subjects who incidentally mentioned lifelong difficulties with music perception and production. This led us to ask whether congenital amusia occurred more frequently than expected by chance in developmental prosopagnosia, indicating an association between two seemingly independent deficits in different sensory modalities. Congenital amusia, also known as tone-deafness, is characterized by impaired pitch discrimination or recognition of musical melodies, with intact hearing and no gross abnormality on structural brain imaging (Ayotte et al., 2002; Peretz et al., 2002). Estimates of the prevalence of congenital amusia vary. It was originally thought to affect approximately 4% of the population (Kalmus and Fry, 1980). However, others suggest that this estimate may be inflated by the use of liberal statistical criteria (Henry and McAuley, 2010), with a more recent estimate suggesting a prevalence of 1.5% (Peretz and Vuvan, 2017). (However, see Pfeifer and Hamann, 2015). Amusia is most often diagnosed (Vuvan et al., 2017) with the Montreal Battery for the Evaluation of Amusia (Peretz et al., 2003). Just as the recognition of facial identity dissociates from the processing of other facial properties such as expression and lip-reading (Campbell et al., 1986; Fox et al., 2011), pitch discrimination dissociates from other aspects of musical processing such as rhythm perception (Hyde and Peretz, 2004; Murayama et al., 2004).

In this report, we evaluated pitch and rhythm perception in a cohort of subjects with developmental prosopagnosia. The subjects were recruited on the basis of their face recognition impairment, without any knowledge of their music perception, and compared to a carefully matched control group. Our first goal was to determine if an impairment in pitch or rhythm perception is more common in developmental prosopagnosia than in the general population. We evaluated both pitch and rhythm perception separately, to determine if there was a selective deficit in pitch discrimination, which is typical of amusia (Hyde and Peretz, 2004). Second, we evaluated the prevalence of tone deafness in the developmental prosopagnosia sample to see if it differs from that of the control group or the general population. Third, we determined if there was a systematic relationship between face recognition abilities and pitch processing, which would reinforce the inference that these two seemingly unrelated skills share a common developmental mechanism. Finally, we asked if any deficits in musical processing were associated with other auditory processing deficits, such as voice discrimination and recognition, which have been recently studied in prosopagnosic populations (Liu et al., 2014; R.R. Liu et al., 2015).

2. Methods

2.1. Subjects

2.1.1. Developmental prosopagnosia

12 subjects (8 female, mean age 44.67 years, range 20 – 67) were recruited from www.faceblind.org. Subjects were recruited on the basis of their face recognition impairment only, without inquiry about their musical or voice processing abilities. Diagnostic criteria (Barton and Corrow, 2016) were a) self-reported lifelong difficulty in face recognition as established by the 20-item Prosopagnosia Index (Shah et al., 2015) and b) confirmation of impaired face recognition on objective tests. The latter included a score at least 2 standard deviations below the previously reported control mean on the Cambridge Face Memory Test (Duchaine and Nakayama, 2006a), as well as impairment on at least one additional test of face memory with published normative data, which were either a test of famous face identification (Duchaine et al., 2007) or an old/new test of familiarity for recently viewed faces (Duchaine et al., 2003). All subjects had best corrected visual acuity of 20/60, normal visual fields, normal general memory abilities as determined by 4 subtests of the Weschler Memory Scale-III (Wechsler, 1997), and performed normally on at least 2 of 3 subtests of the Visual Object and Space Perception Battery (Warrington and James, 1991) (Table 1). To exclude autism spectrum disorders (where face recognition deficits are also common; e.g. Klin et al., 1999), all subjects scored less than 32 on the Autism Spectrum Quotient (Baron-Cohen et al., 2001). When possible, subjects had MRI with T1-weighted and FLAIR sequences to exclude lesions. MRI was contraindicated in three subjects (DP033, DP039, and DP202), and declined by two subjects (DP032 and DP029).

2.1.2. Control subjects for music perception tests

Two healthy controls were matched to each prosopagnosic subject based on age (± 5 years) and gender, for a total of 24 control subjects

(16 female, mean age 45.0 years, range 24–70). An additional control subject had originally been excluded based on Montreal Battery of Evaluation of Amusia but was added back to the sample after editorial review, resulting in a total of 25 control subjects (16 female, mean age 44.76 years, range, 24–70). To be considered, control subjects had to affirm before testing that they did not believe that they had any trouble recognizing faces. Three other subjects were excluded on the basis of the following additional criteria. All subjects were asked to report the number of years of education and number of years of formal musical training with a teacher, though they were not matched on these qualities. One control subject was excluded after testing with the Wechsler Abbreviated Scales of Intelligence for an IQ score of less than 100 (the lowest IQ score of the prosopagnosic group was 101). To guard against undiagnosed prosopagnosia or amusia, two additional control subjects were excluded for having a score on the Cambridge Face Memory Test of less than 44. After exclusions, two-tailed independent samples t-tests showed that the prosopagnosic and control groups did not differ in age (prosopagnosia: mean 44.67, s.d. 13.49; control: mean 44.76, s.d. 14.81; t(35) = -0.02, p = .985), number of years of education (prosopagnosia: mean 17.25, s.d. 2.42; control: mean 16.04, s.d. 2.82; $t_{(35)} = 1.28$, p = 0.21), number of years of musical training with a teacher (prosopagnosia: mean 5.75, s.d. 5.26; control: mean 4.84, s.d. 4.55; $t_{(35)} = 0.54$, p = 0.592), and IQ as measured by the Wechsler Abbreviated Scales of Intelligence (prosopagnosia: mean 125.18, s.d. 7.69; control: mean 121.48, s.d. 10.49; $t_{(34)} = 1.05$, p = 0.302). As expected, the prosopagnosic group performed worse than the control group on the Cambridge Face Memory Test (prosopagnosia: mean 36.33, s.d. 6.34; control: mean 58.00, s.d. 7.06; $t_{(35)} = -9.017$, $p < 0.001$).

2.1.3. Control subjects for voice perception tests

These were reported in R.R. Liu et al. (2015). Seventy-three control subjects completed the voice discrimination test (50 female, mean age 33.6 years, range 19–70), 54 of whom also completed the voice recognition test (41 females, mean age 37.2, range 19–70). Control subjects were included if they denied any trouble recognizing faces.

All prosopagnosic and control subjects could hear well enough to converse comfortably with the experimenter and no subject reported hearing problems other than DP032, who used a hearing aid due to age-related hearing loss. 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. 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. 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.

2.2. Assessments

All tasks were completed in a quiet room without distractions. *The Wechsler Abbreviated Scales of Intelligence* (WASI; Wechsler, 1999) is a standardized measure of intellectual function. Four sub-tests (vocabulary, block-design, similarities, and matrix reasoning) assess verbal and performance IQ, together creating a full-scale assessment of intellectual function. The WASI was completed at a desk across from a trained experimenter. Subjects completed all four sub-tests, and we report age-adjusted full-scale IQ scores. DP044 was ineligible to complete the WASI due to previous exposure to the test. *The Cambridge Face Memory Test* (Duchaine and Nakayama, 2006a) is a standardized test of short-term familiarity for recently viewed faces and served to index face processing skills.

2.3. Music assessments

We administered several tests of pitch and rhythm perception to confirm that any abnormality was consistent across different methods of testing. All were run on a computer equipped with Panasonic RP-HTX7 headphones, and subjects adjusted the volume to a comfortable level during practice stimuli.

Pitch Discrimination Test (Loui et al., 2009) presents two tones sequentially, and subjects indicated if the second tone was higher or lower in pitch than the first. This test used a staircase design, and subjects continued the task until they completed six reversals in the staircase: the average of the values at these 6 reversals was their pitch discrimination threshold, expressed in Hz. Subjects completed the task twice, and their final threshold estimate was the average of the two.

The *Montreal Battery of 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., 2017, 2015). We administered five tests, each evaluating different aspects of music perception, including scale, contour, interval, rhythm, and meter. Each test began with written instructions and examples. The first three tests evaluated pitch perception in different ways. In each, subjects heard two melodies sequentially and indicated if the two musical phrases were the same or different. The different phrases in the first test differed in scale, in the second test they differed in contour, and in the third test they differed in interval. The fourth subtest was identical with the exception that the two phrases differed only in rhythm, but not pitch. The fifth test, of meter, presented a single melody and subjects indicated if the melody was a waltz or a march. The scale, contour, interval, and rhythm tests contained 30 trials each, plus one catch trial in each test, which was subsequently removed. The meter test contained 30 trials. Scores for each test were calculated as the number correct out of 30. As in previous studies (Gosselin et al., 2015; Peretz et al., 2009), we calculated a subject's overall pitch score as the average of their scores for the first three subtests (scale, contour, and interval). Occasionally, a participant failed to provide an answer for a trial. This occurred in a total of 5 trials for the DP group and 7 trials for the control group. In all but one case, no more than one trial was missing for a test (for DP024, two trials were missing for the scale test). To provide a conservative estimate of performance in these cases, missing trials were counted as correct.

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 17 contained a wrong note, off by up to two semi-tones of the correct note, but still following the contour of the original melody. With a key press, subjects responded whether the melody was played correctly. Scores were recorded as the number correct out of 26.

2.3.1. Harvard Beat Assessment Test (Fujii and Schlaug, 2013)

This task used a computerized version of the Beat Finding and Interval Test of the Harvard Beat Assessment Test described in Fujii and Schlaug (2013). It had two components, one for beat perception and one for beat production, both using a staircase design. Both components have a repeating rhythm tapped out on a woodblock. This rhythm consists of one quarter-note, two eighth-notes, one dotted-quarter-note, and one eighth-note. In the beat perception component, subjects indicated by a 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. The rhythm accelerated or decelerated, and the test determined if subjects made a corresponding increase or decrease in tapping frequency. An adaptive two-alternative forced-choice discrimination paradigm was used to advance the test. A parameter was halved when the pattern of the stimulus matched with the participant's response twice consecutively, but doubled otherwise. Every time the direction of parameter change reversed from down to up or from up to

down, the parameter at which this occurred was recorded as an inflection point. One run of this task continued until six inflection points were collected. The average across these six inflection points was defined as the perception/production threshold.

2.4. Voice assessments

The stimuli and procedure were reported in R.R. Liu et al. (2015). Tests of voice processing were run on an IBM Lenovo laptop with 1280 × 800 pixels resolution and the tests were conducted with SuperLab (www.superlab.com) software. Audio clips were generated from 20 male and 20 female volunteers for the discrimination test and from 21 male and 21 female volunteers for the recognition test. Each audio clip was never used more than once as a target or a distractor.

2.4.1. Voice discrimination

Each trial began with a Target Voice, which consisted of a 10-s audio clip of a voice reading a sentence. After a 1.5 s pause, and an 875 ms auditory mask, the subject heard two sequential audio-clips of two 'Choice' voices, both reading the same sentence, different from the first. The subject selected which of the two was the same person as the target voice. The gender of the choice voices always matched that of the target voice, and the order of the choice voices was randomized. There were two blocks, one with male and one with female voices, both with 20 trials. The score was the number correct out of 40.

2.4.2. Voice recognition

This tests the ability to remember voices over a short interval. Subjects listened to the audio clips of three different voices during a learning phase, labeled as Voices A–C. Each audio clip was followed by an 875 ms auditory mask. After the learning phase, the testing phase presented 3 pairs of choice voices. In the first pair, one voice was Voice A and the other was a distractor of the same gender. Subjects identified which of the two choice voices was Voice A. This process was repeated for voices B and C. Each audio clip was followed by an 875 ms ringtone. In each block, subjects completed seven sets of this procedure, yielding 21 trials; with two blocks there were a total of 42 trials. Their score was the number correct out of 42. In the first block, target and testing voices answered two different questions for the learning and testing phase stimuli: "What was your favorite childhood activity?" and "What was your favorite vacation?". In the second block, audio clips presented the same voices reading a random passage from one short story for the learning phase and another for the testing phase.

All subjects completed the voice discrimination test first, with subjects counterbalanced to start with either male or female stimuli. There was a break of at least 10 min before starting the voice recognition component of the test.

2.5. Analysis

Our first goal was to evaluate the hypothesis that pitch perception is impaired in developmental prosopagnosia. We derived for each subject a global z-score for pitch perception, by averaging z-scores (based on the control group) across relevant tasks from the different tests. This included the Pitch discrimination test, the Scale, Contour, and Interval subtests of the Montreal Battery of Evaluation of Amusia, and the Distorted Tunes Test, for a total of 5 tests. At an individual subject level, to determine how many subjects with developmental prosopagnosia had impaired pitch discrimination, we calculated 95% prediction intervals from the control data (Whitmore, 1986) and classified prosopagnosic subjects as normal or impaired by this criterion.

To assess whether there was a dissociation between pitch and rhythm perception, we obtained a similar global z-score for rhythm perception, including the results from the Rhythm and Meter subtests of the Montreal Battery of Evaluation of Amusia, and the two tests of the Harvard Beat Assessment Test. We performed similar group and individual analyses for the rhythm tests. We then examined the difference between the global z-score for pitch and that for rhythm, to determine if any prosopagnosic subject had a greater impairment in pitch than rhythm perception, or vice versa. For those impaired in pitch perception, we compared the z-scores of each individual test to evaluate the consistency of the impairment.

Second, we compared the results of those impaired in pitch perception to diagnostic criteria established in the field. To determine if the proportion of prosopagnosic subjects with impairment was greater than that expected for prevalence estimates for the general population, we used binomial proportions.

Third, we assessed the relationship between pitch perception and face recognition ability across our entire sample. As the Cambridge Face Memory Test yields accuracy scores, to ensure that our analysis compares measures with similar metrics, we focused on tests of pitch perception that also report accuracy. Therefore we used the Pitch Average Score of the Montreal Battery of Evaluation of Amusia. This combination allows us to compare performance on a standard test for diagnosing prosopagnosia with the corresponding standard test for diagnosing amusia. We submitted these scores to a hierarchical regression analysis, examining the relationship between pitch perception and face recognition, controlling for age, number of years of musical training and intelligence as reflected by the WASI.

Finally, for the voice discrimination and recognition tasks, we calculated accuracy for each subject to see if any impairment in pitch perception extended to other auditory functions. As in R.R. Liu et al. (2015), we regressed out the variance due to age in voice control subjects and used the residual variance to calculate 95% prediction intervals appropriate for single-subject comparisons.

Table 2
Bold scores indicate performance 2 sd. outside of the control mean. Underlined scores indicate performance outside of the prediction limit for controls.

	Control M(sd)	DP008	DP014	DP016	DP024	DP029	DP032	DP033	DP035	DP039	DP044	DP201	DP202
Pitch Tests													
Pitch Discrimination	5.37(4.42)	3.32	7.38	**25.88**	3.82	3.11	2.22	**17.75**	**30**	3.38	2.91	13.38	5.13
MBEA: Scale (/30)	27(1.80)	25	28	27	26	28	24	**20**	29	26	27	**18**	28
MBEA: Contour (/30)	24.8(3.25)	22	27	22	24	24	27	19	**17**	27	23	21	22
MBEA: Interval (/30)	24.72(3.30)	20	25	27	28	26	25	**18**	19	27	27	21	24
MBEA: Pitch Avg (/30)	25.51(2.42)	22.33	26.67	25.33	26	26	25.33	**19**	21.67	26.67	25.67	**20**	24.67
Distorted Tunes (/26)	25.16(0.94)	26	25	24	26	26	26	**22**	**16**	25	26	**21**	**23**
Global Pitch	0(0.70)	− 0.41	0.08	− 1.33	0.3	0.43	0.15	**− 3.08**	**− 4.42**	0.16	0.33	**− 3.09**	− 0.78
Rhythm Tests													
Harvard Beat: Percep.	3.66(4.73)	3.44	0.57	6.25	1.17	1.09	5.31	1.33	4.38	1.56	1.69	3.54	4.38
Harvard Beat: Prod.	4.51(4.88)	5.94	2.29	**15.83**	0.39	3.85	7.5	8.75	12.5	6.04	2.19	2.19	2.5
MBEA: Rhythm (/30)	25.72(3.00)	26	29	27	28	28	24	24	24	26	27	26	25
MBEA: Meter (/30)	26.68(3.358)	29	26	26	30	28	29	**15**	21	**19**	26	27	24
Global Rhythm	0(0.67)	0.05	0.47	− 0.79	0.75	0.41	− 0.32	− 1.22	− 1.15	− 0.66	0.23	0.12	− 0.26

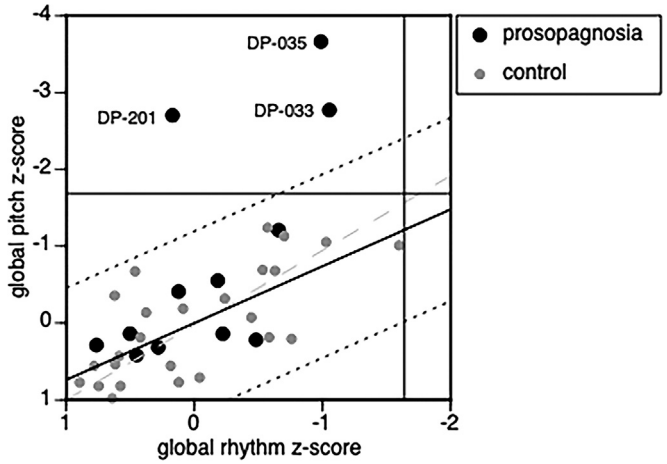

Fig. 1. Global rhythm score plotted against global pitch score for each subject. The light grey dashed line indicates identity, where the global pitch score equals the global rhythm score. The black solid diagonal line is the linear regression of global pitch against global rhythm scores for the control 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. DP201, DP033, and DP035 fall above the limit for global pitch but below the limit for global rhythm perception. In addition, their data lie beyond the upper limit for the relationship between pitch and rhythm perception. Thus, on both grounds, they have a selective deficit in pitch perception, with intact rhythm perception.

3. Results

The scores for each music assessment are reported in Table 2. A correlation matrix for all tasks is reported in the Supplementary materials along with reliability estimates for each measure, when available.

Analyzing the global pitch score, the prosopagnosic group had larger variance than the control group (Levene's $F(1, 35) = 10.733$, $p = .002$) and the data for the developmental prosopagnosia group was negatively skewed (Shaprio Wilk's $S\text{-}W(12) = .8$, $p = .009$). Therefore, we report bias-corrected and accelerated 95% confidence intervals, which are resistant to violations of normality. On average, subjects with developmental prosopagnosia ($M = -0.82$, $SE = 0.40$) had lower global pitch scores than control subjects ($M = 0$, $SE = 0.14$). The bias corrected and accelerated 95% bootstrapped confidence interval $[-1.63, -0.07]$ suggested a non-zero difference between the groups but was shy of significance, $p = .084$, with a large effect size, $d = 0.72$. At the individual level, three of 12 prosopagnosic subjects had global pitch scores below the lower prediction limit for controls (DP035, DP033, and DP201) (Fig. 1).

Analyzing the global rhythm score, the two groups had similar variance ($F_{(1, 35)} = 0.513$, $p = 0.479$) and were normally distributed according to Shaprio Wilk's test ($p > .05$). We additionally report bias-corrected and accelerated 95% confidence intervals for comparison with the global pitch scores. On average, subjects with developmental prosopagnosia ($M = -0.11$, $SE = 0.17$) had slightly lower global rhythm scores than control subjects ($M = 0$, $SE = 0.13$). However, this difference was not significant, $t(35) = -0.47$, $p = .639$, despite a large effect size $d = 1.70$. Furthermore the bias corrected and accelerated 95% CI – 0.52, 0.33], crosses the zero-boundary, suggesting no differences between groups ($p = .654$). At the individual level, no prosopagnosic subject was impaired (Fig. 1).

In the control group, global pitch and global rhythm scores were highly correlated ($r = 0.70$, $p < 0.001$). To further confirm that the three prosopagnosic subjects with impaired pitch perception had a deficit greater for pitch than for rhythm perception, we regressed out

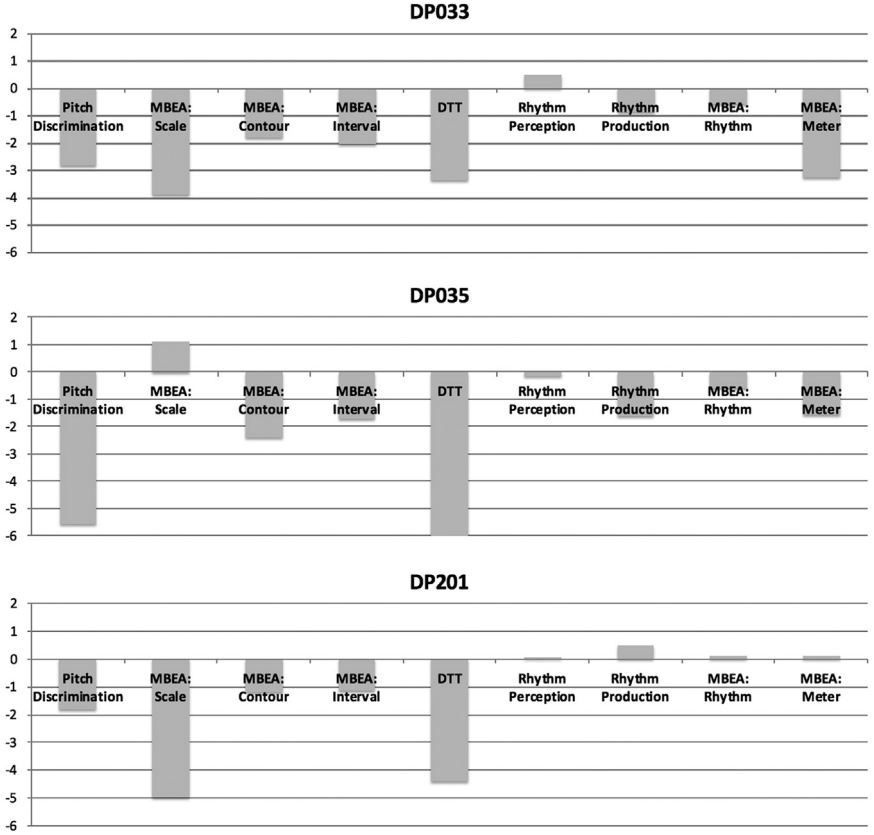

Fig. 2. Z-scores across musical tasks for each of the three subjects with impaired global pitch scores. The first 5 tasks reported are measures of pitch perception and the last 4 tasks reported are measures of rhythm perception. DTT = Distorted Tunes Task. Z-scores were cut-off at −6 for the DTT test for DP035 and DP201.

the variance related to rhythm perception to isolate the variance unique to pitch perception. We then used this residual variance to calculate 95% prediction intervals (Whitmore, 1986) appropriate for single-subject comparisons for the regression of pitch scores against rhythm scores. In other words, we plotted a regression line representing the relationship between global rhythm and global pitch scores with prediction intervals representing the variance in pitch processing at each level of rhythm processing. This analysis allows us to examine impairment in pitch processing relative to that of rhythm processing. This showed that the impaired global pitch scores of these three prosopagnosic subjects were beyond that predicted by their global rhythm score (Fig. 1).

To examine the consistency of the results in the three prosopagnosic subjects impaired in pitch perception, we plotted their z-scores for the different tests (Fig. 2). DP033 was more than 2 standard deviations from the mean of controls on four out of five pitch tasks, and marginally impaired on the contour test, while on tests of rhythm she showed a deficit only for the meter subtest of the Montreal Battery of Evaluation of Amusia. DP035 was impaired on three of five pitch tasks, and borderline impaired on another, but performed in the low normal range on rhythm tests. DP201 performed two standard deviations below in the mean on the scale and distorted tunes tests and at least one standard deviation below the control mean on all other pitch tasks, but at or slightly above the control mean on all tasks of rhythm perception. In contrast, eight of the 12 subjects were not impaired in a single task of pitch perception.

Overall, these data provide clear evidence of impaired pitch perception in three of 12 subjects (25%) with developmental prosopagnosia. These findings raise the question of whether the prevalence of impaired pitch perception differs between the prosopagnosic and control groups. The three prosopagnosic subjects with impaired pitch perception all meet criteria commonly used for the diagnosis of congenital amusia, namely, a summed score of 65 or less on the three melodic subtests of the Montreal Battery of Evaluation of Amusia (Chen et al., 2015; Marin et al., 2015; Pfeifer and Hamann, 2015). However, a recent paper (Vuvan et al., 2018) using the original data from Peretz et al. (2003) combined with additional unpublished data reported a 2 standard deviation cutoff of 21.36 for the average of the melodic subtests. Two of our prosopagnosic subjects met this cutoff, while the third was just beyond with a melodic average of 21.6. In contrast, only one subject in the 25-person control group (4%) met the either criteria. Fisher's exact test examining the difference in binomial proportions between these two samples was not significant (p = .098). However, the sample sizes are small and Fisher's exact is a conservative test. A 4% prevalence rate of amusia in the control sample is consistent with a prevalence rate of 4% in the general population (Henry and McAuley, 2010; Kalmus and Fry, 1980), suggesting that our control group is similar to previously published data. Furthermore, a binomial test indicated that a prevalence rate of 25% exceeds this liberal estimate of the prevalence of amusia in the general population of 4% (p = .001, one-tailed).

The entire group of subjects (developmental prosopagnosia and control) produced a wide-ranging continuous distribution of face recognition scores on the Cambridge Face Memory Test (Fig. 3), providing the opportunity to examine whether musical ability systematically varies with face recognition ability in the entire sample of subjects. This allows for the possibility that controls on the lower end of the face processing distribution may also have poorer pitch discrimination than those with higher face recognition scores.

We used hierarchical multiple regression to assess the ability of Cambridge Face Memory Test scores to predict the Average Pitch score on the Montreal Battery of Evaluation of Amusia, after controlling for age, years of musical training, and intelligence. Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity, and homoscedasticity. Age, years of musical training, and WASI scores were entered at step 1, explaining 12.0% of

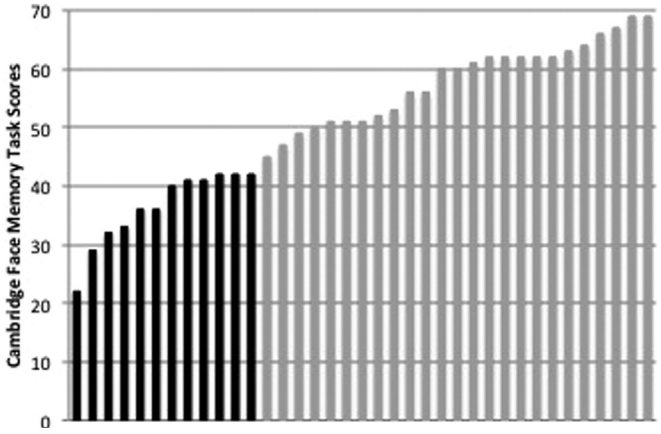

Fig. 3. Cambridge Face Memory Test scores for each individual subject. Black bars indicate those with developmental prosopagnosia and grey bars indicate each of the 25 control subjects. The distribution of scores on the Cambridge Face Memory Test provided a continuous distribution of scores, allowing for the examination of the systematic relationship between face recognition and pitch processing across the entire sample.

the variance in pitch perception scores. After entry of the Cambridge Face Memory Test scores at step 2, the total variance explained by the model was 26.9%, $F_{(4, 31)} = 2.85$, p = .04. Thus, the Cambridge Face Memory Test scores explained an additional 14.9% of the variance in pitch perception scores after controlling for age, years of musical training, and intelligence scores (R^2 change = 14.9, F change $_{(1, 30)}$ = 6.32, p = .017). In the final model, only performance on the Cambridge Face Memory Test was a significant predictor of the Average Pitch score of the Montreal Battery of Evaluation of Amusia (*beta* = 0.40, p = .017).

Finally, we assessed if these subjects also exhibited impairment in voice discrimination or recognition. The regression analysis showed that DP035 was borderline impaired in voice discrimination and low-average in voice recognition (Fig. 4) DP033 and DP201 were not impaired in either voice discrimination or recognition: thus their auditory

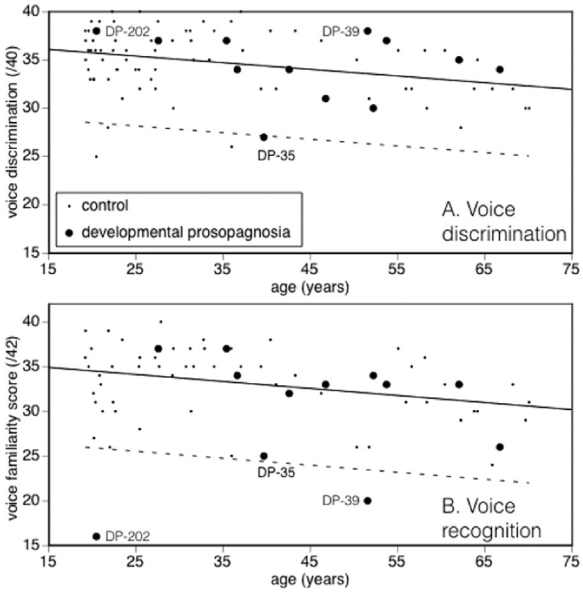

Fig. 4. Voice scores plotted as a function of age. A. Voice discrimination, B. Voice recognition. Control subjects are depicted by the small dots. The solid line represents the mean of the linear regression and the dotted line shows the age-adjusted lower 95% prediction limit. Subject DP035 was impaired on voice discrimination and borderline in voice recognition. Subjects DP033 and DP039 have poor voice recognition, despite their normal performance on pitch tasks.

deficit is more selective for pitch perception. Conversely, DP202 and DP039 were not impaired in pitch perception but had poor voice recognition, completing the double dissociation.

4. Discussion

In this rather modest sample, we found initial evidence that the incidence of tone deafness may be higher in a prosopagnosic sample than in a non-prosopagnosic sample. Three subjects were impaired in the perception of pitch, a prevalence of 25% that is higher than predicted from a liberal 4% estimate of the prevalence of congenital amusia in the general population (Henry and McAuley, 2010; Kalmus and Fry, 1980), and certainly far higher than a more recent prevalence estimate of 1.5% (Peretz and Vuvan, 2017). This was a selective deficit, in that rhythm perception was less affected in all three subjects, similar to dissociations reported for subjects with congenital amusia (Hyde and Peretz, 2004) and acquired amusia (Murayama et al., 2004). On the other hand, we also found that most subjects with developmental prosopagnosia have normal pitch processing: eight of the 12 subjects (66%) were not impaired on any task of pitch perception. Nevertheless, the higher prevalence of amusia in this prosopagnosic sample is consistent with suggestions that a number of neurodevelopmental disorders such as dyslexia, prosopagnosia, and amusia may be variants of a common underlying disorder (Peretz, 2016). Furthermore, across the entire sample (n = 37), scores on the Cambridge Face Memory Test were a significant predictor of global pitch scores even after controlling for age, years of musical training, and IQ score, further supporting the relationship between face and pitch processing.

Is there an alternative explanation for poor pitch processing in those three subjects? At the group level, the developmental prosopagnosia and control groups were matched for gender and age, and if anything, the prosopagnosic group had slightly more years of education, years of formal musical training, and higher intelligence scores. Of the three subjects impaired in pitch perception (DP033, DP035, and DP201), all were college educated; two with master's degrees and all three had full-IQ scores ranging between 116 and 135. However, the number of years of musical training was low for these subjects (DP033 = 2, DP035 = 0, and DP201 = 2). While one might claim that this accounts for their impaired pitch perception, it is also possible that they obtained fewer years of musical training *because* of their difficulty with pitch perception. Furthermore, two other prosopagnosic subjects who also had little musical training (DP014 had 1 year, DP016 had 0 years) were not impaired in their global pitch score, and 10 of the 24 control subjects had two or fewer years of formal musical training, and none of these were impaired in their global pitch score. Indeed, studies show that even sophisticated musical processing is not dependent on formal training but is acquired by non-musicians through normal exposure in daily life (Bigand and Poulin-Charronnat, 2006; Tillmann et al., 2015). For these reasons it seems unlikely that lack of formal musical training explains the results of DP033, DP035, and DP201.

None of our subjects complained of auditory problems in everyday life outside of amusia, with the exception of DP032, who wore a hearing aid for age-related hearing loss but still performed normally on our music perception tests. All prosopagnosic subjects also demonstrated normal auditory rhythm perception. For voice processing, DP035 showed a borderline impairment in voice discrimination and DP039 and DP202 showed impairment in voice recognition. Hence, in the auditory domain, DP033 and DP201 have a selective deficit for pitch perception, with intact rhythm perception and intact voice recognition. This is consistent with other reports that subjects with congenital amusia can have preserved rhythm perception (Hyde and Peretz, 2004) and voice identification (Ayotte et al., 2002). Furthermore, our results complete the double dissociation between voice and pitch processing, as DP039 and DP202 showed impaired voice recognition but intact pitch discrimination.

Is it possible that these subjects are not actually impaired, but rather, we are over-classifying amusia? A recent report by (Pfeifer and Hamann, 2015) correctly points out that the reported prevalence rate of congenital amusia largely depends on the statistical criterion used as a cut-off and that different studies have reported varying prevalence rates depending on how they chose to diagnose amusia. Indeed, when they use the cutoff suggested by Peretz et al. (2003) in their own sample, they find an amusia prevalence rate of 13.5%. The issue of determining an appropriate diagnostic cut-off is not specific to research on amusia. In fact, it is an issue that is also discussed in studies of developmental prosopagnosia (Barton and Corrow, 2016; Dalrymple and Palermo, 2016). One approach that has been taken in the field of prosopagnosia research is to require impairment on at least two tests of face memory (S.L. Corrow et al., 2016). This approach, while still somewhat arbitrary, at minimum ensures that individuals classified as impaired show some consistency in their low scores. Using this approach, Pfeifer and Hamann (2015) report that only 5 of 111 (4.5%) subjects tested scored below their control-based cutoff on at least 2 tests of pitch processing, similar to previous estimates. In our study, all three subjects classified as having amusia scored more than 2 standard deviations below the mean on at least two tests of pitch processing while none of the control subjects met this criterion (Fisher's Exact, $p = .03$). This suggests that our method has not overclassified the prevalence of pitch processing impairment in our prosopagnosic sample. Using the global pitch score, which is an average, the prevalence rate of amusia in our control group was 4%, which is similar to a previous estimate of prevalence (Kalmus and Fry, 1980), (although with a small sample was not significantly different than the 25% prevalence rate in the prosopagnosic group). If we had used overly liberal criteria, an inflated prevalence rate should have been observed in the control group as well. Therefore, while our sample size of prosopagnosic subjects is modest, it is unlikely that the inflated prevalence rate in the developmental prosopagnosia sample is a mere reflection of cut-off used to determine impairment.

How might congenital amusia, an non-visual disorder, be related to developmental prosopagnosia? One possibility draws on an analogy with theories about developmental dyslexia that postulate that anomalies of cell migration create not only perisylvian ectopias that may be responsible for a reading impairment (Galaburda et al., 1985), but also more widely distributed cortical anomalies, possibly emphasizing the left hemisphere (Pernet et al., 2009; Robichon et al., 2000). Indeed, there are candidate genes for dyslexia that are shown to affect neuronal migration (Kere, 2011). These kinds of neuronal migration disorders may cause subtle abnormalities in language, visual, and sensory domains, as well as producing other developmental disorders (Ramus, 2004). Similarly, it may be that congenital amusia and developmental prosopagnosia stem from a migration disorder with a capacity for multiple dysfunctions of right hemispheric sensory processing. Likewise, if the pathogenetic abnormality is not one of cortical migration but of white matter connectivity, these results may point to a pathology with potential for more widespread disconnection than within a single sensory network. Deficits in white matter connectivity have been observed in the perceptual networks of those with developmental prosopagnosia (Gomez et al., 2015; Song et al., 2015; Thomas et al., 2009), congenital amusia (Hyde et al., 2006; Loui et al., 2009) (but see (Chen et al., 2015)), and developmental dyslexia (Carter et al., 2009; Odegard et al., 2009; Rimrodt et al., 2010).

The possibility then is that, in at least some cases, developmental prosopagnosia may be one manifestation of a more widespread dysfunction in perceptual networks, and associated with other deficits like congenital amusia in a non-causal fashion. Similarly, a range of other impairments has been reported in those with congenital amusia and developmental dyslexia. Amusia has been associated with deficits in perception of lexical tones (Jiang et al., 2012; Nan et al., 2010; Patel et al., 2008), emotional prosody (Thompson et al., 2012), speech comprehension (F. Liu et al., 2015), phonological processing (Jones et al., 2009), and mental rotation (Douglas and Bilkey, 2007). In developmental dyslexia there is greater prevalence of impairments in

verbal language (McArthur et al., 2000), mathematical ability (Landerl and Moll, 2010), voice recognition (Perrachione et al., 2011), pitch discrimination (Ahissar et al., 2006; France et al., 2002; see Ahissar et al., 2006 for an alternative theory; Mengler et al., 2005), motion perception (Menghini et al., 2010), visuo-spatial attention (Buchholz and Davies, 2007; Facoetti et al., 2008; Menghini et al., 2010), and motor control (Fawcett et al., 1996; Rochelle and Talcott, 2006). It seems unlikely that all of these problems can be linked to a single cognitive dysfunction or a single cortical abnormality; rather, they may suggest a pathogenetic mechanism that can affect multiple brain regions at the same time or a similar developmental process at slightly different times depending on when a particular cortical region develops and matures in development.

One might expect then that developmental prosopagnosia would also show an elevated co-occurrence with dyslexia. Indeed, the theory that deficits in visual word processing and face processing should co-occur has been suggested (Behrmann and Plaut, 2013). However, studies examining reading ability in subjects with developmental prosopagnosia have shown very little evidence for this co-occurrence. Rubino et al. (2016) examined the reading abilities of 10 subjects with prosopagnosia and found no deficits in the word-length-effect task, a standard task for assessing reading impairment in subjects with alexia. Similarly, Starrfelt et al. (2018) found no deficits in the reading abilities of 10 subjects with prosopagnosia who each completed a series of reading tasks. Finally, Burns et al. (2017) found consistent reading deficits in one of 11 subjects with prosopagnosia, but no evidence of any word processing difficulties in the remaining 10 subjects. Together, these studies suggest that dyslexia is not present in the vast majority of cases with developmental prosopagnosia. However, this does not rule out the possibility that prosopagnosia and amusia share a common mechanism. Just as some have proposed that dyslexia and its co-occurring deficits are the result of widespread left-dominant cortical anomalies (Pernet et al., 2009; Robichon et al., 2000), it is similarly possible that the association of prosopagnosia with amusia is explained by a widespread right-hemisphere dominant dysfunction. If this were the case, we would expect to observe greater co-occurrence of developmental prosopagnosia with amusia, both right-hemisphere associated disorders, than dyslexia, a left-hemisphere associated disorder.

One reason why a mechanism can affect several processes is if they have a shared anatomic susceptibility. For example, acquired prosopagnosia is often accompanied by dyschromatopsia, because the networks for colour perception and face recognition both involve the fusiform gyri (Moroz et al., 2016). A reasonable question then is whether the networks for music and face perception overlap to indicate a potential common target. At first glance these would seem to involve quite distinct visual and auditory networks. The core face network involves occipitotemporal regions, in particular the fusiform gyrus (Kanwisher et al., 1997) and posterior superior temporal sulcus (Haxby et al., 2000), which interact with an extended network that includes the precuneus, inferior frontal gyrus, and especially the anterior inferior temporal cortex (Haxby et al., 2000). While the anatomic substrate for developmental prosopagnosia continues to be debated, recent work suggests involvement of either local abnormalities in the fusiform gyrus (Furl et al., 2011; Garrido et al., 2009; Song et al., 2015) or altered connectivity from this region to anterior temporal cortex, mediated by the inferior longitudinal fasciculus (Avidan et al., 2014; Thomas et al., 2009)(however, see (Gomez et al., 2015; Song et al., 2015)).

While the network for pitch perception also shows right hemispheric predominance (Zatorre, 2001), this is primarily a pathway from primary and secondary auditory cortices in the superior temporal gyrus to inferior frontal cortex, involving the arcuate fasciculus. Acquired defects in pitch perception are reported with lesions of the right superior temporal gyrus or frontal cortex (Ayotte et al., 2000; Hochman and Abrams, 2014; Sarkamo et al., 2009; Terao et al., 2006). These neuropsychological findings are consistent with the neuroimaging findings of congenital amusia. In congenital amusia, structural analyses find reduced white matter in the right inferior frontal gyrus (Albouy et al., 2013; Hyde et al., 2006) and thicker cortex in this region and in right auditory cortex (Albouy et al., 2013; Hyde et al., 2007). Additionally, diffusion tensor imaging shows reduced fiber connectivity in the right arcuate fasciculus (Loui et al., 2009). Functionally, fMRI studies have shown abnormal deactivation of the right inferior frontal gyrus and reduced connectivity between this structure and auditory cortex (Hyde et al., 2011).

Thus, while substantial portions of the face and pitch networks are anatomically distinct from each other, it is intriguing that there may be some convergence in the right inferior frontal gyrus or anterior temporal regions. Several studies have pointed to right inferior prefrontal areas as making a contribution to face processing (see Duchaine and Yovel, 2015 for a review of this topic). Most recently, a multivariate pattern classification study implicated a right inferior frontal face area as having a robust representation of face identity, but invariant to viewpoint, suggesting that the right inferior frontal region may be important for view-invariant face recognition in healthy subjects (Guntupalli et al., 2017). However, until recently, there has been little evidence that the inferior frontal gyrus is affected in developmental prosopagnosia. An fMRI study examining the neural anomalies observed in developmental prosopagnosia reported less face selectivity in the right inferior frontal gyrus relative to healthy control subjects (Guo et al., 2017). Another recent study with a novel fMRI inter-subject functional correlation approach reported greater face-selective functional connectivity in the right inferior frontal gyrus for control subjects than for those with developmental prosopagnosia (Rosenthal et al., 2017). However, we are unaware of any acquired cases of prosopagnosia resulting from *selective* lesions to the inferior frontal gyrus, suggesting that this region does not provide a critical contribution to successful face recognition in the same way that it does for musical processing. Lesions of the right inferior frontal gyrus are observed in some acquired prosopagnosic subjects, though – e.g. subjects 008 and 011 in (Barton, 2008) - but not as the sole lesion. Whether inferior frontal lesions produce any modulating effect on prosopagnosia is not known, but in one group study, prefrontal lesions were associated with reductions in face memory (Rapcsak et al., 2001).

Another region of potential overlap between these disorders is the right anterior temporal lobe. The posterior superior temporal sulcus is a core region of the face processing system (Haxby et al., 2000) and structural and functional anomalies in this region have been reported in developmental prosopagnosia (Garrido et al., 2009; Guo et al., 2017). However, acquired lesions of the posterior superior temporal sulcus impair perception of facial expression rather than causing prosopagnosia (Fox et al., 2011), and the reported structural changes in congenital or acquired amusia are located in more anterior regions of the right superior temporal gyrus (Albouy et al., 2013; Ayotte et al., 2000; Hochman and Abrams, 2014; Peretz et al., 1994; Stewart et al., 2006; Terao et al., 2006). This may be located more dorsal to the anterior inferior temporal region (Rajimehr et al., 2009; Yang et al., 2014), a portion of the extended face network located in the inferior aspects of the right anterior temporal lobe, and which is likely affected in patients with acquired prosopagnosia following right or bilateral anterior temporal lesions (Davies-Thompson et al., 2014).

The finding of impaired pitch perception in our subjects affects our concept of developmental prosopagnosia as a selective disorder. Much effort has been devoted to determining whether the prosopagnosic defect is specific to faces and sparing other object recognition, in the attempt to confirm or refute domain-specific accounts that postulate the existence of cortical modules dedicated to face processing (Kanwisher, 2000). However, this is predicated on an assumption that the anomaly in developmental prosopagnosia affects a single processing system, which may or may not be face-specific. Indeed, this is often touted as an advantage over studying acquired prosopagnosia, in which the large lesions are not limited to face recognition systems but often affect adjacent systems for processes such as colour perception (Moroz et al.,

2016) and topographic orientation (J.C. Corrow, et al., 2016). If developmental prosopagnosia is actually part of a syndrome with a potential for multiple sensory impairments in diverse networks, particularly those with right hemispheric dominance, then lack of selectivity may have a basis that has nothing to do with domain-specificity of the face network. That is, co-existent developmental impairments in face recognition and the recognition of other visual objects may reflect concurrent damage to multiple perceptual networks, rather than both being due to damage to a single 'domain-general' network.

The fact that we find defects in pitch perception in some but not all subjects with developmental prosopagnosia reinforces another point about this disorder, that there is substantial heterogeneity. There is evidence for heterogeneity in the mechanism of prosopagnosia, with some showing mainly deficits in face perception and others showing greater problems with face memory (Corrow and Barton, 2017; Stollhoff et al., 2011). As alluded to above, there is heterogeneity in the degree of selectivity, with some showing impairment in recognition of other objects and some not (Duchaine and Nakayama, 2005). While most subjects have intact voice recognition, another perceptual function with right hemisphere dominance (Belin and Zatorre, 2003; Belin et al., 2000), a few subjects are impaired (R.R. Liu et al., 2015; von Kriegstein et al., 2006). This again parallels the heterogeneity in developmental dyslexia, where additional sensory and motor disorders can be present in some but not all subjects (Ramus, 2004).

To our knowledge, the results of this study are the first of their kind and, therefore, it will be important to investigate whether other groups of DP also contain a disproportionate of amusics. The recruitment of large samples for in-person studies of prosopagnosia is often challenging, even in large cities, and this study is no exception. While our combined results show good evidence for a relationship between face and pitch processing, more evidence is needed to support the notion that the prevalence of amusia is higher in cases of developmental prosopagnosia than in the general population. When possible, future research could explore the utility of online methods (Germine et al., 2012) to recruit larger samples of prosopagnosic subjects. An additional challenge in conducting this research is determining the criteria by which an individual will be considered impaired in pitch perception. As pointed out by Pfeifer and Hamann (2015), the diagnostic criteria used for the classification of amusia varies across studies, making it difficult to determine a prevalence rate that is consistent across studies. Again, this is not a challenge specific to studies of amusia but common among studies investigating developmental disorders with no clear genetic or physiological marker. Standardization among researchers, at the very least, will provide the consistency needed to more easily make comparisons across studies.

In summary, our results provide initial evidence that in some, but not all, subjects with developmental prosopagnosia, the face recognition deficit is not an isolated impairment but associated with congenital amusia. Given the very different processing involved in face and pitch perception, this is almost certainly a correlative rather than a causal link. Together with prior results showing occasional subjects with voice recognition impairments, this suggests that these deficits may form part of a broader syndrome of clustering perceptual disorders, whose common theme may be a right hemispheric predominance in their processing networks. Thus they may form a counterpart to the cluster of anomalies seen in developmental dyslexia. The existence of such a syndrome indicates that the search for the pathogenesis of developmental prosopagnosia (or congenital amusia) needs to shift from a narrow focus on face processing regions to a broader view of mechanisms that can lead to distributed and variable cortical or white matter anomalies that can at times affect multiple perceptual systems.

Acknowledgements

This work was supported by Canadian Institutes of Health Research Operating Grant (MOP-102567) to JB. JB was supported by a Canada Research Chair and the Marianne Koerner Chair in Brain Diseases. BD was supported by grants from the Economic and Social Research Council (UK) (RES-062-23-2426) and the Hitchcock Foundation. G.S. acknowledges support from the National Institutes of Health (DC009823, DC008796). SB was supported by the Sidney R. Baer, Jr. Foundation and the American Academy of Neurology. S.P. is supported by a Postdoctoral Fellowship from the Canadian Institutes of Health Research. SC was supported by *National Eye Institute* of the National Institutes of Health under award no. F32 EY023479. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuropsychologia.2018.12.022.

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