Auditory temporal processing deficits in patients with insular stroke

D.-E. Bamiou, MD, MSc, MPhil; F.E. Musiek, PhD; I. Stow, BA (Hons), Dclin Psy; J. Stevens, MBBS, DRACR, FRCR; L. Cipolotti, PhD; M.M. Brown, MD, FRCP; and L.M. Luxon, BSc (Hons), MB, BS, FRCP

Abstract—*Objective:* To assess central auditory function in a series of patients with stroke of the insula and adjacent areas. *Methods:* The authors recruited eight patients with stroke affecting the insula and adjacent areas and eight neurologically normal controls (matched to the patients for age, sex, handedness, and hearing thresholds). The lesion spared the adjacent auditory areas in three patients and included other auditory structures in five cases. The authors conducted pure-tone audiometry and tympanometry and a central auditory test battery, which included the dichotic digits, and three temporal tests, the duration pattern, frequency pattern, and gaps in noise tests. They collected information from the hospital notes on symptoms at presentation and neuropsychological assessment data during the acute phase. *Results:* The central auditory tests gave normal results in all controls. The temporal tests gave abnormal results in all three cases in which other auditory areas were spared, as well as in the other five cases. Results of the gaps in noise test were abnormal contralaterally to the lesion in three and bilaterally in five cases. The central auditory deficits did not cosegregate with the presence of cognitive impairment during the acute stage. *Conclusion:* Insular lesions may affect central auditory function and, in particular, temporal resolution and sequencing, consistent with neuroimaging studies.

NEUROLOGY 2006;67:614–619

The human insula (Brodmann areas 13 to 16) subserves visceral sensory and motor, motor association, vestibular, and somatosensory functions.[1,2] Physiologic experiments have identified the presence of auditory responsive units in the insular cortex,[3] whereas labeling studies have found connections of the insula with the medial geniculate nucleus, the primary and association auditory area, and the temporal pole and superior temporal sulcus.[1,4] However, the function of the insula as a component of the central auditory nervous system remained, until recently, unexplored.

Single case studies report impaired central auditory function in the presence of lesions of the insular cortex.[5-7] Sophisticated neuroimaging studies also indicate that the insulae participate in networks that may subserve different auditory processes.[8-10] However, both approaches have their limitations. Case studies have so far reported on lesions that affected the insula as well as other auditory structures, because vascular lesions restricted to the insular cortex are rare,[11] whereas in neuroimaging studies, the insula forms part of a network responsible for auditory processing. It is therefore difficult to establish the specific auditory functions of the insula. This study aimed to assess central auditory function in a series of patients with ischemic lesions of the insula and of adjacent cortical and subcortical areas, with and without involvement of other auditory structures, by means of a validated central auditory test battery to enhance our understanding of the role of the insula in audition.

Methods. *Subjects.* Patients with stroke that affected the insula and adjacent auditory cortex/subcortex, who were admitted to Acute Brain Injury Unit or seen in the One Stop Stroke Clinic at the National Hospital for Neurology and Neurosurgery, were identified by their brain MRIs and invited to participate in the study. Inclusion criteria were the presence of a unilateral lesion of the insula with or without involvement of the adjacent areas of the auditory cortex, and symmetric audiometric thresholds with average audiometric thresholds at 0.5, 1, 2, and 4 kHz better than 30 dB HL. Exclusion criteria were the presence of aphasia or psychiatric disorders. We also recruited an equal number of healthy controls from the hospital staff and from spouses/partners of patients. The controls were matched to the subjects for age, sex, handedness, audiometric thresholds (±5 dB), and audiometric configuration.

Each patient and control underwent standard baseline audiometric tests and central auditory tests for the purposes of the study. Assessment of the subjects took place at least 4 weeks after the acute onset of the stroke. All patients had a brain MRI, which was conducted 1 to 2 weeks after the onset of the vascular event. The majority of the patients had neuropsychological assessment conducted 3 to 8 days after stroke. The study was approved by the Ethics Committee of the National Hospital for Neurology and

From the Neuro-otology Department (D-.E.B., L.M.L.), Neuropsychology Department (I.S., L.C.), and Radiology Department (J.S.), National Hospital for Neurology and Neurosurgery, Queen Square, London; Academic Unit of Audiological Medicine, Institute of Child Health, London (D-.E.B.); The Stroke Research Group, Institute of Neurology, University College London (M.M.B.); Audiological Medicine, University College London (Institute of Child Health), University of London, UK (L.M.L.); and Auditory Research, Communication Sciences, DCP Comm Center, Unit 1085, University of Connecticut, Storrs, CT (F.E.M.).

Disclosure: The authors report no conflicts of interest.

Received September 10, 2004. Accepted in final form April 11, 2006.

Address correspondence and reprint requests to Dr. Doris-Eva Bamiou, Neuro-otology Department, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK; e-mail: dbamiou@ion.ucl.ac.uk

Table 1 *Summary of lesion details and central auditory test results*

	Side	Insula	Other	DDT scores		FPT scores		DPT scores		GiN thresh	
				R%	L%	R%	L%	R%	L%	Rms	Lms
1	L	Total	Corona radiata	57	75	44	67	36	26	8	6
2	R	Anterior (limen)	putamen	92	90	10	30	37	37	8	10
3	R	Middle short gyri		95	50	6	6	43	46	12	12
4	R	Posterior	STG, TrG, temporal parietal	100	97	82	82	52	52	8	8
5	L	Posterior	STG, TrG	57	90	70	72	36	30	10	8
6	L	Total	Frontal temporal	100	90	6	6	28	44	15	4
7	R	Total	Frontal temporal	100	85	56	52	48	51	6	8
8	R	Total	IFG	90	20	60	72	68	48	10	8

DDT = Dichotic Digits Test; FPT = Frequency Pattern Test; DPT = Duration Pattern Test; GiN = Gaps in Noise Test; thresh = threshold; R% = right ear percentage score; L% = left ear percentage score; Rms = right ear milliseconds threshold; Lms = left ear milliseconds threshold; STG = superior temporal gyrus; TrG = transverse temporal gyrus; IFG = inferior frontal gyrus.

Neurosurgery. Written informed consent was obtained from both subjects and controls.

We recruited eight right-handed patients (five men, three women; age range = 36 to 79 years; mean age = 63 years) and an equal number of age- and sex-matched controls. The lesion characteristics are shown in table 1, and the brain MRIs are shown in figure 1.

Patients with stroke of the insula and adjacent areas without involvement of auditory cortical/subcortical areas. Case 1 is a 79-year-old man who presented with mild right-sided weakness and dysphasia. Brain MRI showed an infarct on the left side, involving the entire insula and the corona radiata. Case 2 is a 74-year-old woman who presented with left-sided weakness, slurred speech, and episodic vertigo, nausea, and unsteadiness that resolved within 1 hour. Brain MRI showed an infarct on the right side, involving the putamen and the insula limen. Case 3 is a 78-year-old woman who presented with mild speech difficulty. Brain MRI showed an infarct on the right side, involving the short gyri of the insula and encroaching the long gyri.

Patients with stroke of the insula and adjacent areas with involvement of auditory cortical/subcortical areas. Case 4 is a 39-year-old man who presented with left facial and upper and lower limb weakness. Brain MRI showed an infarct on the right side, involving the transverse and superior temporal gyrus, the posterior superior temporal lobule, the inferior parietal lobule, and the posterior insula. Case 5 is a 65-year-old man who presented with headache, seizures, and subsequent right limb weakness. Brain MRI showed an arteriovenous malformation on the left side, involving the transverse and superior temporal gyrus and the posterior insula. Case 6 is a 43-year-old man who presented with right facial weakness, upper and lower limb weakness, and expressive and receptive dysphasia. Brain MRI showed an infarct on the left side, involving the entire insula, the striatum, and the adjacent frontal and temporal gyri. Case 7 is a 51-year-old man who pre-

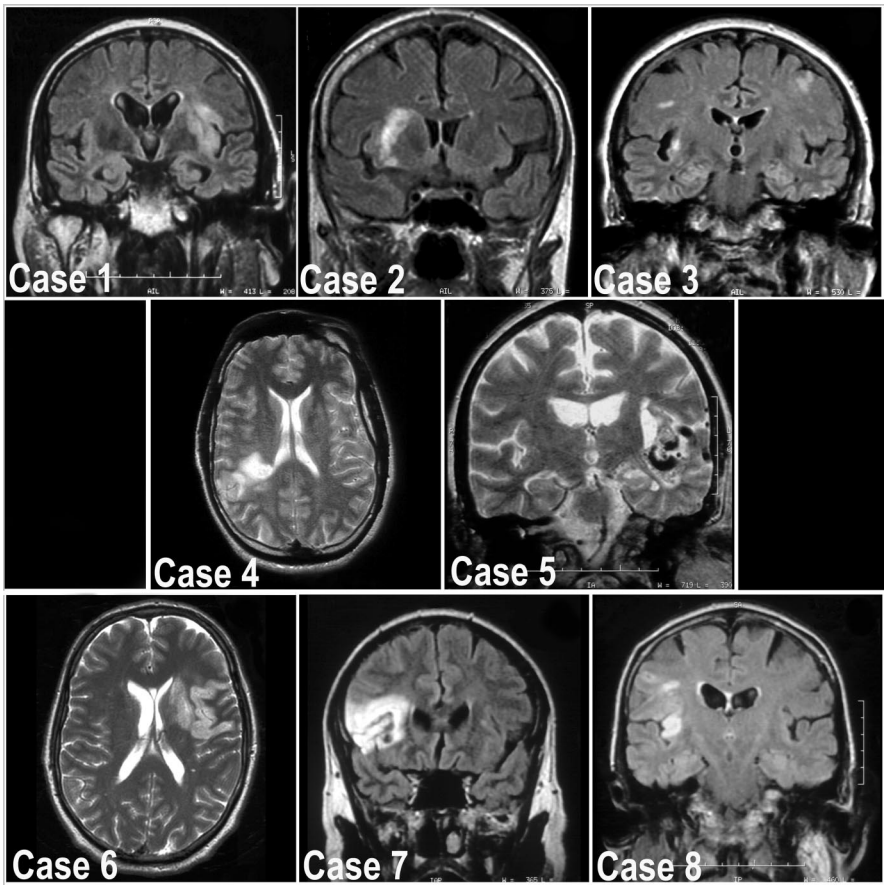

Figure 1. Fast spin echo (T2-weighted) TR 6,000 milliseconds, TE/EF 106, axial (Cases 1 and 5) and coronal acquisition (Case 2) images. Fluid-attenuated inversion recovery, TR 10,000 milliseconds, TI 2,500, coronal acquisition images (Cases 3, 4, 6, 7, and 8).

sented with headache, unsteadiness, and left arm and leg weakness. Brain MRI showed an infarct on the right side, involving the entire insula and the adjacent frontal and parietal operculi. Case 8 is a 78-year-old woman who presented with slurring dysarthria and left-sided hemiparesis. The brain MRI showed an infarct on the right side, involving the entire insula and the inferior frontal gyrus.

Test procedures. All test procedures were conducted in a sound-treated room. We conducted pure-tone audiometry and tympanometry. Pure-tone audiometry was carried out in both ears using a GSI 61 audiometer with TDH-49 earphones in a sound-treated room following the procedure recommended by the British Society of Audiology.[12] Tympanometry was obtained in both ears with a continuous probe signal tone of 226 Hz at 85 dB SPL using a GSI-33 Middle Ear Analyser. Tympanograms were considered normal if middle ear pressure was greater than −150 daPa and compliance was greater than 0.3 mL.

We used a central auditory test battery that consisted of a dichotic speech test (digits), two pattern tests (frequency and duration), and a temporal resolution test (Gaps in Noise [GiN]). Normative values were available for all tests, which were available on compact disc (CD). The CD was played with a Sony CD player and routed through the speech circuitry of the GSI 61 audiometer. The test stimuli were administered to the patient via the audiometer with TDH-49 earphones in a sound-treated room. All central test material was presented at a 50-dB sensation level, with sensation level referenced to the pure-tone audiogram average (at 0.5, 1, 2, and 4 kHz).

Dichotic Digits Test. The Dichotic Digits Test (DDT)[13] is composed of naturally spoken digits from 1 to 9, excluding 7. A different pair of digits is given simultaneously to each ear, and the listener has to repeat all four digits. The outcome measure is the percentage of correct responses for each ear. Normal scores are 90% or better for each ear, or 80% in the presence of a high-frequency loss.[14] After a brief practice session, a list of 40 paired digits was administered to the listeners in each ear.

Frequency Pattern Test. The Frequency Pattern Test (FPT)[15] stimuli consist of three tone burst sequences, which are a combination of low- (880 Hz) and high-frequency (1,122 Hz) tones. Each sequence is composed of two bursts of the same and one burst of a different frequency. The listener is required to name the sequence (e.g., high-high-low). The outcome measure is the percentage of correct responses. Normal scores are 75% or better, and the specificity of the test in separating cochlear vs central auditory lesions is 88%.[15] A total of 30 patterns were presented monaurally to each ear after a brief practice session.

Duration Pattern Test. The Duration Pattern Test (DPT)[16] stimuli consist of three tone burst sequences, which are a combination of long (500 milliseconds) and brief (250 milliseconds) tones of 1,000 Hz. Each sequence is composed of two bursts of the same and one burst of a different duration at 300-millisecond interstimulus intervals. The listener is required to name the sequence (e.g., short-long-short). The outcome measure is the percentage of correct responses. Normal scores are 70% correct or better, and the specificity of the test in separating cochlear vs central auditory lesions is 92%.[16] A total of 30 patterns were presented monaurally to each ear after a brief practice session.

Gaps in Noise Test. In the GiN test,[17] the patient is monaurally presented with a 6-second burst of white noise in which zero to three gaps of varying duration (2 to 20 milliseconds) are embedded. The patient has to identify the number of gaps in each noise burst. This test provides two scores, the correct detection score (percent of correct answers) and the gap detection threshold, which is defined as the shortest gap duration that the patient can correctly identify in 50% of the trials (i.e., in three out of six trials for each gap duration). Normal results are a threshold of 6 milliseconds or better and a correct score of 50% or better (from our own normative data collected from 40 healthy adults aged 20 to 55 years). Stimuli were presented monaurally after a brief practice session.

Brain MRIs were all performed on a Sigma 1.5-T system (General Electric, Milwaukee, WI, Echo Speed+). Axial and coronal fast spin-echo fluid-attenuated inversion recovery images were routinely obtained on all cases. These images were used to evaluate the distribution of each lesion.

Neuropsychological assessment. All of the assessments were performed in the acute phase (3 to 8 days after stroke). The standardized tests used varied according to the patients' overall level of cognitive ability. However, they assessed the same range of cognitive functions, including premorbid intelligence (National Adult Reading Test [NART]),[18] current intelligence (Wechsler Adult Intelligence Scale–Revised short version [WAIS-R]),[19] memory (standard or short version Recognition Memory Test),[20,21] confrontation naming (Graded Naming Test),[22] visuoperception (subtests from the Visual Object and Space Perception Battery [VOSP]),[23] executive function (Stroop Test[24], Weigl Sorting Task[25]), semantic and phonemic verbal fluency[26,27] and Proverb Interpretations,[28] and speed of information processing (Cancellation tasks, Digit Copying).[29,30] In all three patients for whom language difficulties were evident, further tests of language comprehension (Test for the Reception of Grammar)[31] and spelling and calculation tasks were administered (oral graded difficulty spelling[32] and calculation tests[33]).

Intellectual impairment was judged to be a difference of 15 points or more between NART and WAIS-R IQ scores or a defective score on the WAIS-R if the NART was not administered. Five patients were assessed on both the WAIS-R and NART. One patient was only assessed on the WAIS-R (Case 6), because of an acquired dyslexia. Impairment on memory, naming, spelling, and calculation tasks was a score below the fifth percentile for age-adjusted norms. Visual perceptual functions were impaired if performance on selected VOSP subtests was below the 5% cutoff. Impairment on at least two tests sensitive to executive dysfunction constituted "executive" impairment. Time scores 2 SDs or more above the normal range on speed of information processing tests were considered impaired.[29]

Table 2 *Frequency Pattern and Duration Pattern Tests: Summary percent score results in subjects and controls*

	Subjects	Controls
FPT right ear	41 (30)	97 (6)
FPT left ear	48 (30)	96 (6)
DPT right ear	43 (12)	89 (11)
DPT left ear	41 (9)	94 (9)

Data are presented as mean (SD).

FPT = Frequency Pattern Test; DPT = Duration Pattern Test.

Results. *Standard baseline audiometric test results.* Patients 2 and 8 had a symmetric mild to moderate high-frequency hearing loss, whereas the other subjects had normal hearing. Two of the age-matched controls had a mild to moderate high-frequency hearing loss, whereas the other controls had normal hearing. Tympanograms were normal in all patients and controls.

Central auditory tests. All of the controls had normal results on the DDT, FPT, DPT, and GiN in both ears. Summary results for the controls are shown in tables 2 and 3.

Patients with stroke of the insula and adjacent areas without involvement of auditory cortical/subcortical areas. Case 1 had normal average hearing thresholds, with ab-

Table 3 *Gaps in Noise Test: Summary of threshold results in subjects with left- and right-sided lesions and in controls*

	Subjects left lesion	Subjects right lesion	Controls
GiN threshold right ear	11 (3)	8 (2)	4 (1)
GiN threshold left ear	6 (2)	9 (1)	5 (1)
GiN score right ear	29 (18)	46 (6)	71 (7)
GiN score left ear	51 (18)	46 (9)	63 (8)

Data are presented as mean (SD).

GiN = Gaps in Noise Test.

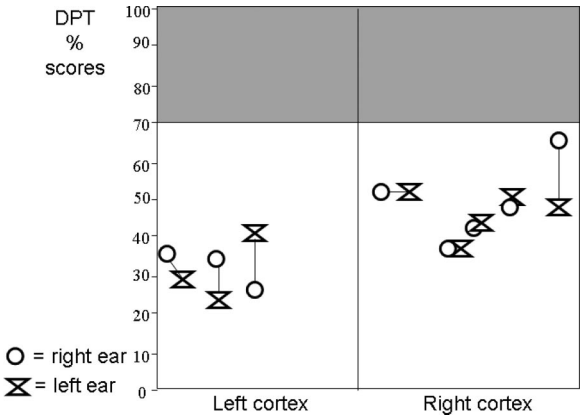

Figure 2. Scatter plot of duration pattern test (DPT) results in left vs right cortex lesions (gray shaded area represents normal range).

normal right and left DDT scores (right < left). FPT and DPT scores were abnormal in both ears, and the GiN was abnormal on the right. He had difficulties understanding text that was being sung. This was probably the most informative case, because other auditory areas were spared.

Case 2 had symmetric mild to moderate high-frequency hearing loss in both ears, with bilaterally normal DDT scores. DPT, FPT, and GiN were abnormal in both ears. She reported problems understanding speech in background noise and problems localizing sounds, as well as some problems recognizing melodies, understanding text that was sung, and understanding intonation/inflections in people's voices.

Case 3 had normal average hearing thresholds and a normal DDT score on the right, but an abnormal DDT score on the left. FPT, DPT, and GiN were bilaterally abnormal. She reported problems with understanding speech in background noise, localizing sounds, sound discrimination, understanding intonation and inflections in a voice, and understanding text that was being sung.

Patients with insular stroke with involvement of auditory cortical areas. Case 4 had normal average hearing thresholds and normal DDT and FPT scores in both ears. DPT and GiN were abnormal in both ears. He had difficulties recognizing people from their voices.

Case 5 had normal average hearing thresholds, with a normal DDT in the left and abnormal DDT in the right ear. FPT, DPT, and GiN were bilaterally abnormal. He had difficulties conducting a conversation in a crowded meeting, localizing sounds, discriminating some sounds, and distinguishing intonation and voice inflections.

Case 6 had normal average hearing thresholds and normal DDT scores in both ears. FPT and DPT scores were abnormal in both ears. GiN was abnormal in the right and normal in the left ear. He had severe difficulties with understanding speech in noise, recognizing people from their voices, recognizing melodies, discriminating sounds, distinguishing male from female voices, hearing rhythm in songs, and distinguishing intonation and voice inflections, as well as localizing the source of sounds.

Case 7 had normal average hearing thresholds, with a normal right DDT score, an abnormal left DDT score, and abnormal FPT, DPT, and GiN in both ears. He reported problems understanding speech in crowded places and understanding text that was being sung.

Case 8 had a symmetric mild to moderate high-frequency hearing loss in both ears, with an abnormal left DDT score. FPT, DPT, and GiN were abnormal in both ears. She reported problems understanding speech in background noise, distinguishing intonation and voice inflections, and understanding text that was being sung.

Group results. Side and site of lesions. The DDT was abnormal in five cases. Four of these five cases had abnormal scores in the ear contralateral to the lesion, whereas one case with a left total insular and corona radiata lesion had abnormal scores in both ears, but the scores were more reduced in the ear contralateral to the lesion.

Patients with left-sided lesions had lower DPT scores than patients with right-sided lesions for both the right ear ($p = 0.035$, CI of the difference = −30.9 to −1.6) and the left ear ($p = 0.045$, CI of the difference = −26.5 to −0.38) (figure 2).

The GiN test was abnormal in all eight cases. Thresholds were bilaterally abnormal in five cases (four with a right and one with a left lesion) and abnormal only in the ear contralateral to the lesion in three cases (two with a left and one with a right lesion).

Neuropsychological assessment results. Table 4 summarizes the neuropsychological test results, which were available in six patients. Only two patients (Cases 3 and 8) did not show any cognitive impairment. The remaining

Table 4 *Summary of neuropsychological test scores*

Case	NART FIQ	WAIS-R FIQ	WAIS-R VIQ	WAIS-R PIQ	RMF	RMW	GNT	OD or IL*	Executive function	Speed of information processing
1	127	124	129	108*	35/50* (<5%ile)	43/50 (50–75%ile)	24/30 (75–90%ile)	18/20	Failed*	>2SD*
2	100	87	93	81*	22/25 (10–25%ile)	24/25 (50%ile)	14/30 (5–10%ile)	19/20*	Failed*	NT
3	107	110	104	121	24/25 (50%ile)	21/25 (10–25%ile)	23/30 (75%ile)	18/20	Passed	<2SD
6	NT	68*	65*	75*	27/50* (<5%ile)	NT	2/30* (<1%ile)	20/20*	Passed	NT
7	100	90	104	77*	48/50 (>75%ile)	37/50 (50%ile)	23/30 (75%ile)	18/20	Failed*	NT
8	122	112	111	110	25/25 (>75%ile)	25/25 (>75%ile)	22/30 (50–75%ile)	19/20	Passed	<2SD

* Impaired scores.

NART = National Adult Reading Test; FIQ = Full Scale IQ; WAIS-R = Wechsler Adult Intelligence Scale–Revised; VIQ = Verbal IQ; PIQ = Performance IQ; RMF = Recognition Memory Test for Faces; RMW = Recognition Memory Test for Words; GNT = Graded Naming Test; OD = Object Decision; IL = Incomplete Letters; Executive function = Stroop Test, Weigl Sorting Task, semantic and phonemic verbal fluency; Speed of information processing = Cancellation tasks or Digit Copying; NT = not tested; %ile = percentile.

four patients showed a variety of cognitive deficits at the acute stage. One patient (Case 6) had a global Full Scale IQ impairment, whereas three others (Cases 1, 2, and 7) had a selective Performance IQ impairment. No patients showed verbal memory deficits or visuoperceptual impairments. The patient with naming deficits (Case 6) had prominent language problems. His spontaneous speech was hesitant, with anomic pauses, and he was impaired on a test of sentence comprehension (Test for Reception of Grammar), as well as a test of spelling and calculation.

Discussion. We assessed central auditory function in eight patients with strokes of the insula and adjacent areas by means of a central auditory test battery that incorporates three temporal processing tests (FPT, DPT, and GiN). Three of our cases without lesions of the primary and association auditory cortex (Cases 1, 2, and 3) and with relatively preserved cognitive functioning even during the acute phase had abnormal results for all three temporal tests and reported some difficulties with hearing. This finding is striking because these tests have a low false-positive rate, with specificity that ranges from 88% for the FPT,[15] to 92% for the DPT,[16] to 94% for the GiN.[17] In the presence of normal or near normal audiograms, their perceived hearing difficulties should be attributed to the presence of impaired temporal processing. Results of the three temporal tests were similarly abnormal in 5:5 of the remaining cases, in which the lesions involved additional auditory responsive areas. This finding is again interesting because the sensitivity of the tests in identifying cortical lesions of the auditory system is around 85% for the FPT and DPT[15,16] and 67% for the GiN.[17] Overall, these findings are in keeping with the hypothesis that the insula is an integral component of the central auditory pathway, consistent with the well-developed connections between the insula and auditory cortex and subcortex.[1,4]

The GiN threshold was increased contralateral to the lesion in three cases and bilaterally in five cases. Previous studies report increases in gap detection thresholds in the ear contralateral to the site of the brain lesion for gaps in narrow-band noise.[34] The GiN findings may indicate that the insula is important for temporal resolution, although the bilaterality of the GiN findings may also reflect different acoustic properties of the noise used in the test, i.e., white in our study vs narrow-band in other studies.[34,35]

The FPT and DPT deficits may be reflected in the patient-reported difficulty with understanding text that is sung, which was present in all three cases without involvement of auditory cortical areas. A recent single-unit recording study in squirrel monkeys showed that neurons from the granular field of the posterior insula contribute to the encoding of complex frequency modulated signals, and that syllable-like elements of the natural monkey call are better encoded than synthesized signals.[36] Ablation experiments in cats have shown that the insular-temporal region of the cat brain is vital for the animal's ability to discriminate temporal auditory patterns (e.g., A-B-A vs B-A-B).[37] Other authors[9] have similarly found a deficit in discrimination of fast but not slow auditory sequences in a patient with a right insular lesion and suggested that this reflected a deficit in tone sequencing. Our findings may thus be interpreted as indicating that the human insula participates in the encoding of complex sound modulation, consistent with the previous studies in both animals and humans.

The DDT was abnormal in two of three cases with the more circumscribed lesions. Case 1, who had a left-sided stroke affecting the entire insula and corona radiata, but sparing the primary auditory cortex, had deficits in both ears, but more pronounced in the ear opposite the side of the lesion. The same laterality effect has been noted in a single case study with an insular lesion.[6] The DDT was normal in another patient who had a lesion limited to the insula limen and putamen, in which case the extent of the lesion may not have been sufficient to produce a deficit in the test. The DDT results are broadly consistent with the sensitivity of this test in demonstrating lesions of cortical auditory areas, which is reported to be 75%.[14]

In our study, all patients had unilateral insular lesions, with some extending to a variety of cortical and subcortical areas. We are aware that this is a major limitation, and caution must be exerted when interpreting our findings. However, we deemed of importance to contrast performance for left vs right lesions. Looking at the group results, the DPT scores were worse in cases with left-sided lesions, consistent with the theory that proposes a left-auditory cortex specialization for temporal processing.[38] These findings may also be consistent with the PET findings[10] in six young, healthy subjects that showed that musical rhythm judgment, as assessed by a task of identifying whether the lengths of the intervals and notes in the given music sequence were regular or irregular, mapped to the left insula.

It is difficult to establish to what extent cognitive or language factors may have affected our findings, because the only information available came from psychometric assessment during the acute stage of the stroke. However, the central auditory deficits did not cosegregate with the presence of cognitive impairment during the acute stage; e.g., both Cases 3 and 8, who had entirely normal cognitive function during the acute stage, had abnormal results for all of the central auditory tests, and conversely, the only patient with a full IQ impairment during the acute stage (Case 6) had entirely normal results in one of the central auditory tests. In addition, none of the patients demonstrated verbal memory deficits. Overall, our findings may thus provide further evidence that insular lesions affect central auditory function and temporal resolution and sequencing in particular; however, further studies are needed to replicate

and extend the current findings and to establish specific functions of the different parts of the insula.

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