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CORRESPONDENCE

Unilateral auditory hallucinations: ear or brain?

Brasić and Perry¹ convincingly describe a boy with unilateral otopathic auditory hallucinations. However, their literature review is very misleading, postulating dubious CNS causes for auditory hallucinations other than from a hyperactive ear. They also do not cite a relevant prior case.

Their paper starts: "Unilateral auditory hallucinations...are associated with contralateral CNS lesions". Their only supporting reference is Toulouse (1892), who reviewed four adults with neurological disease and unilateral auditory hallucinations, allegedly of cortical origin. These turned out to be anything but. One case (Regis, 1881) had voices in his left ear aggravated by alcohol, sounds of a bell and water in his right, impaired hearing in his left ear (thought by Toulouse to be of cortical origin!); the 1888 case had bilateral auditory hallucinations, worse on the left, abolished by blocking off the ear which was full of pus; the 1890 case, an alcoholic wine merchant, had bilateral noises (bells, whistles, rattles, etc) which alternated and changed into voices in his right ear, but there was no examination of his ears or hearing; his 1892 case, also an alcoholic wine merchant, heard voices in her left ear, and had bilateral deafness from chronic otitis media. Whatever other lesions these four patients had, there were peripheral lesions sufficient to trigger tinnitus and auditory hallucinations, although in alcoholic patients these can probably be triggered from ears with relatively normal hearing.² By contrast with these totally unconvincing cases of non-otological cortical origin, Toulouse reviewed seven cases of unilateral auditory hallucinations from homolateral ear disease, four of which were particularly convincing as the auditory hallucinations vanished (three cases) or waned (one case) with effective ear treatment. Toulouse also noted cases with quite different auditory hallucinations in opposite ears simultaneously; if of cortical origin, a quite implausible degree of functional hemispheric independence is shown.

Their next three references supposedly show that auditory hallucinations are caused by stimulatory phenomena in the CNS—namely, epilepsy (Keshavan *et al*, 1992), schizophrenia (Silbersweig *et al*, 1995), and drugs (Ketter *et al*, 1996).

Keshavan *et al* reviewed musical hallucinations. In epilepsy, they noted six cases from Hecaen and Ropert in whom music occurred as part of an epileptic aura, four of whom had concomitant ear disease; three case reports without structural brain lesions, two with pronounced deafness, the third with attacks of nausea and rotatory vertigo but no otological investigations; three of Penfield's cases with brain tumours but no ear or hearing examination. In one of these last three, seizures were of a "new and curious type", including deafness, unilateral voices, and music, starting two years after tumour removal. Far from implicating the brain, this review of musical hallucinations strongly implicates the ear. Even if epileptic patients are not known to have ear disease, this should be suspected, as Jackson and Gowers established last century that epilepsy can arise from the ear.

In their PET study on hallucinating schizophrenic patients, Silbersweig *et al* found increased blood flow in the thalamus and not the neocortex. This is not evidence that auditory hallucinations are generated in the brain; instead, it is consistent with peripheral impulses funnelling up via the thalamus.

The volunteers of Ketter *et al* "consistently (29 out of 32 subjects) reported procaine induced auditory hallucinations (unformed buzzing, ringing, or electronic sounds)". They considered procaine a selective limbic activator, even though no change in cerebral blood flow corresponded to the "auditory hallucinations". In an ear, nose, and throat clinic the above noises would definitely be labelled tinnitus, and an obvious peripheral cause usually found. In line with this, procaine causes cochlear hyperactivation (increased wave I and II amplitude in dogs)³; in view of the link between epilepsy and the ear, it is noteworthy that the EEG changed from an awake pattern to seizure activity.

The 1968 review of sensory deprivation by Petrella *et al* was cited as an example of auditory hallucinations from sensory disinhibition. I reviewed some of this literature,⁴ concluding that for musical hallucinations there is as much evidence for ear disease and labyrinthine hyperactivity as when they occur in all other conditions and diseases. Deprivation is a misnomer; in many experimental situations white noise is used to mask environmental sounds, whereas if all background noises are reduced, normal subjects will start to have tinnitus. I recently tested a 16 year old dyslexic patient who had never known silence ("silence has a permanent noise running through it"), yet had never complained of tinnitus. Sensory deprivation is more likely than deprivation, as in fact misprinted!¹

A similar case to that of Brasić and Perry¹ throws considerable light on pathophysiological processes involved. Both were tormented by voices of devils while having symptoms of unilateral ear disease; saw devils and animals interchanging; had fiery visions (fire surrounded by cockroaches, devil transforming into burning wisp of straw); possible fluid in one middle ear (blocked grommet plus air-bone gap; filthy discharge from one ear). Conspicuously omitted¹ was any mention of tinnitus, the most likely generator of the

auditory hallucinations. Fortunately, the other case was Martin Luther,⁵ who clearly described ringing in his ears, unendurable buzzing, thundering, cracks, thumps, etc. Once, he had a musical hallucination (bells of specific churches) while awake in bed because of noises in his head. Curiously, Luther did not have a simple demonic or religious explanation for his torments. Instead he blamed Satan for his Meniere's symptoms (headache, episodic vertigo, tinnitus), which in turn he recognised caused his hallucinations. In fact his symptoms were typical of otosyphilis, and there was good evidence that he had "French disease".

If Brasić and Perry still assert a CNS origin for auditory hallucinations they need an original case report, not reviews or secondary sources. Repeated appeals for non-otological neurological musical hallucinations have failed¹ (suggested cases with brainstem lesions were also deaf). I would now like to broaden the challenge to cover auditory hallucinations as well. Unless someone can come up quickly with a case of auditory hallucination due to a clear neurological lesion in someone with normal ears and hearing, the only proved cause of auditory hallucinations is otological.

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- 1 Brasić JR, Perry R. Unilateral auditory hallucinations in a boy with ipsilateral conductive hearing loss. *J Neurol Neurosurg Psychiatry* 1997;62:302.
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Brasić and Perry reply:

Gordon conjectures that otological pathology is the necessary and sufficient condition for auditory hallucinations. We disagree. We hypothesise that auditory hallucinations have many aetiologies which can be classified as otological, neurological, neuropsychiatric, and combined. Auditory hallucinations may result from the multiple effects of otopathology, such as altered signal transduction in hair cells.¹ For example, in response to minimal environmental stimuli, diseased cochlear hair cells may generate random frequencies producing white noise perceived as tinnitus in some persons. Auditory hallucinations may also result from neurological illnesses,² including after right temporal lobectomy for intracerebral hemorrhage without seizures.³ We are preparing a manuscript concerning auditory hallucinations in neurological disorders. Auditory hallucinations due to neuropsychiatric disorders are being studied, particularly in schizophrenia. On functional MRI, two patients with schizophrenia experiencing auditory hallucinations showed reduced responses of the temporal cortex to external auditory stimuli. Therefore, auditory hallucinations in some patients with schizophrenia may correspond with maximal activation of the auditory association cortex.⁴ The physiology of thinking in words was assessed utilising PET in six persons with schizophrenia who experienced auditory hallucinations, six persons with schizophrenia

who did not experience auditory hallucinations, and six normal controls. Imagining sentences spoken by another person activated the left middle temporal gyrus and rostral supplementary motor area of normal controls and schizophrenic patients without auditory hallucinations, but not schizophrenic patients with auditory hallucinations. Thus, some people with schizophrenia with auditory hallucinations seem to lack activation of portions of the brain associated with the monitoring of inner speech.³ These reports suggest that auditory hallucinations in schizophrenia are correlated with physiological abnormalities of regional cerebral blood flow in the left auditory association cortex and rostral supplementary motor area. Auditory hallucinations also are associated with combinations of otological, neurological, and neuropsychiatric disorders. For example, our patient had conductive hearing loss, bilateral tinnitus, and psychosis.³ We agree with Gordon that a thorough otological history and examination including audiology is a necessary component of the assessment of a person with auditory hallucinations.

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Cu/Zn superoxide dismutase gene mutations in amyotrophic lateral sclerosis: correlation between genotype and clinical features

We refer to the article by Radunović *et al*¹ and the kindred referred to in this article and in the article by Cleveland *et al*² as the Australian superoxide dismutase (SOD1) Gly37Arg familial amyotrophic lateral sclerosis (FALS) kindred. It did seem extraordinary that the same mutation should produce such different disease phenotypes in two separate continents. Investigations in Australia, subsequent to the publication of the paper by Cleveland *et al*,² identified the mutation in this family as His43Arg, not Gly37Arg. The mutation was identified as H43R by heterozygote sequencing and sequencing of the single strand conformation polymorphism (SSCP) seen in exon 2 from several affected family members from the kindred. The original designation of the kindred as Gly37Arg must have arisen from a sample mix up between Western Australia, North Carolina, and Chicago. It is a relief to those of us living in Australia that this

country may not after all pose an extra hazard to those carrying this SOD1 mutation. The clarification of the mutation in the family adds further weight to the data showing that different mutations may to some extent correlate with different rates of progression of FALS. The kindred has been reported correctly as His43Arg by Juneja *et al*.³ It is a particularly large kindred with over 500 known family members. There are 20 cases of FALS known to date, and 87 persons at 50% risk of having inherited the family mutation. The family is so large that on its own it represents a significant problem for genetic counselling in Western Australia. Twenty family members have received presymptomatic diagnosis in a Huntington's-like protocol based on the results of SSCP detection of the exon 2 mutation.

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Radunović and Leigh reply:

We are grateful to Drs Laing and Siddique for pointing out the error in the designation of the Australian His43Arg kindred as Gly37Arg. A Gly37Arg kindred with different phenotype to the American one,¹ however, exists in Turkey.² We are therefore still concerned that it is too early to predict particular ALS phenotypes based on the site of a CuZnSOD gene mutation. We are also worried about the lack of clinical information provided in reports on the CuZnSOD gene mutations, and a lack of evidence as to where these kindreds come from. For example, it is very likely that the Gly37Arg kindred reported by Juneja *et al*³ is the same one as reported by Cudkovic *et al*.³ All this creates confusion and we would like to see a centralised pedigree database established where detailed but anonymous phenotype and genotype data can be deposited and accessed. It is only by collating all of the available information that comments on prognosis can be made.

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- 1 Juneja T, Pericak-Vance MA, Laing NG, et al. Prognosis in familial amyotrophic lateral sclerosis: Progression and survival in patients with glu100gly and ala4val mutations in Cu,Zn superoxide dismutase. *Neurology* 1997;48:55-7.

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BOOK REVIEWS

Multiple Sclerosis. Clinical and pathogenetic basis. Edited by CEDRIC S RAINE, HENRY F MCFARLAND AND WALLACE W TOURTELLOTT. (Pp 426 £125.00). London: Chapman and Hall, 1997. ISBN: 412308908.

The modern day neurologist attempting to maintain a semblance of current knowledge on multiple sclerosis has an awesome task ahead of him. A brief perusal of Medline will give him some idea of the size of the task ahead, as one of the most written about subjects in the neurological periodicals, articles number in their thousands every year and seem to be rising at an exponential rate. I offer my respects to anyone attempting to produce a comprehensive text book to provide a synopsis of current theories on the disease particularly since they seem to become out of date with alarming alacrity, however this is certainly one of the best around. These days that is no idle statement since the number of textbooks like the number of published articles has increased substantially and the resultant competition is intense.

This book aims to provide a comprehensive text for contemporary theories on the aetiology of multiple sclerosis and current management. In a huge subject with a huge amount of raw material it has been appropriately selective with a high standard of editing and manages to deliver the essence of clinical practice in a single volume. It is divided into four parts covering clinical parameters, neuropathology and aetiology and symptomatic and disease modifying treatments. It has an international board of well respected contributors who provide a good balance of science and general practice and is well illustrated and referenced.

Affective disorders, which seem to result in one of the major sources of morbidity to patients and their families in my experience receives appropriate attention with an incisive look into neuropsychological aspects by Stephen Rao. This is characteristic of this book whose editors have clearly thought hard about every aspect of the disease, offering advice on counselling, interpreting trial data and many other subjects that are often omitted. For those who think that magnetic resonance is the only imaging medium for multiple sclerosis, David Miller explores the relevance of positron emission tomography and CT as well as exploring the relevance of imaging abnormalities in monosymptomatic disease and application as a surrogate marker of disease activity in treatment trials underlining the fact that the relationship between short term MRI activity and disability remains uncertain. I also liked Weinshenker's chapter on the natural history of multiple sclerosis. The chapter on the relevance and role of cerebrospinal fluid in the disease