

LETTERS

Tiagabine for treating painful tonic spasms in multiple sclerosis: a pilot study

Tiagabine (Gabitril, Paris, France) is a new antiepileptic drug that acts as a selective inhibitor of the γ -aminobutyric acid (GABA) transporter, GAT-1.¹ It has recently been reported to be effective in diseases other than epilepsy, such as stiff man syndrome² and neuropathic pain,³ conditions in which GABAergic mechanisms are supposedly involved. In multiple sclerosis, painful tonic spasms affect approximately 10% of patients and are usually treated with GABAergic drugs such as baclofen or gabapentin.^{4,5}

We undertook an open label pilot study of tiagabine, in a dose range of 5 to 30 mg/day, in a group of seven multiple sclerosis patients with painful tonic spasms who were non-responsive or intolerant to established drug treatment. The patients had previously been treated with gabapentin, baclofen, diazepam, or clonazepam, and were being followed in the department of neurology, PA Micone Hospital, Genoa, Italy. Four subjects were female and three were male, with a mean age of 45.1 years, mean disease duration of 7.1 years, and mean expanded disability status score (EDSS) of 4.0. Four patients had relapsing-remitting, one had secondary progressive, and two had primary progressive disease. Painful tonic spasms were defined as transient painful extensor or flexor spasms in the lower limbs, with abrupt onset and brief duration (from a few seconds to a few minutes), with repetitive and stereotypical features. The subjective level of the painful tonic spasms was scored using a three point scale previously described⁶: 0, no pain, no attack; 1, mild pain or discomfort, presents only a limited amount of time; 2, intermediate pain or discomfort: the duration moderately interferes with daily activities; 3, severe pain: intensity or frequency of symptoms seriously limiting normal daily activity. Spasticity level was scored using the Ashworth scale. Tiagabine was started at 5 mg daily and increased until spasms were relieved or to the maximum dosage of 30 mg. No other drugs with a potential influence on spasticity were allowed during the study period. The patients were clinically evaluated at baseline (T0), after pain relief was achieved (T1), and after three months from the beginning of the protocol (T2). The minimum follow up period was three

months. All specific symptomatic drug treatments used previously were discontinued one week before treatment with tiagabine was begun.

The mean dose of tiagabine was 12.8 mg daily. Relief of painful tonic spasms was successful in four of the seven patients (minimum treatment period, three months). All four patients had complete and sustained recovery within one month of initiation of treatment (a reduction of two points on the pain scale); efficacy was maintained for a period of three months in all four subjects. The Ashworth score changed by one point in one subject. The clinical characteristics of the patients and the painful tonic spasm scores before and after treatment are given in table 1.

Two patients (Nos 2 and 5) dropped out of the study because of adverse effects: one with nausea and dizziness, the other with drowsiness and weakness. These subjects had a longer disease duration and higher EDSS scores, suggesting a possible correlation between disease severity and adverse effects.

COMMENT

Typically, antiepileptic drugs are effective for treating paroxysmal symptoms in patients with multiple sclerosis at doses that are lower than those used in epilepsy. For this reason, we arbitrarily set the maximum dose of tiagabine at 30 mg/daily, while in epilepsy the maximum dose is usually 56 mg daily. Moreover, patients with multiple sclerosis treated with antiepileptic drugs more often report central nervous system side effects than patients with other diseases such as seizures or mood disorders.

The results of this study suggest a possible new treatment for painful tonic spasms in multiple sclerosis and support the postulated GABAergic mechanism of action as the key factor in the choice of drug therapy. The spasticity level, measured with the Ashworth scale, did not change during the study period, as reported in trials of other antispasticity drugs such as tizanidine. This may reflect the inability of the scale to detect mild changes, or the different pathogenesis of painful tonic spasms and spasticity. The frequency of side effects of this agent in patients with multiple sclerosis and its efficacy in the treatment of painful tonic spasms or spasticity must be confirmed in a larger study.

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Harlequin syndrome: an association with overlap parasomnia

We describe the novel association of Horner syndrome and contralateral paroxysmal facial flushing and sweating (Harlequin syndrome) with overlap parasomnia.

CASE 1

A 66 year old woman suffered right jaw and multiple limb fractures when she was 45. Since then she had recurrent sudden onset episodes of right hemifacial flushing and sweating, occurring with physical exertion and heat, rarely spontaneously, and lasting 20 to 30 minutes. Approximately one year after the trauma, her sleep became restless, being interrupted by excessive motor activity, seemingly purposeful and sometimes harmful, associated with vocalisation and a report of dreaming corresponding to the motor manifestations. Hypnagogic hallucinations and sleep paralysis could also rarely occur. Both facial flushing and sleep disturbances worsened after another accident to her face when she was 64.

Examination at age 66 showed partial ptosis of the left eyelid, myosis, and iris heterochromia with subtle enophthalmos. Anisocoria increased in dim light, and 0.01% epinephrine eye drops did not modify the size of the left pupil. Brain magnetic resonance imaging (MRI), somatosensory evoked potentials, transcranial magnetic stimulation, blink reflexes and palmar sympathetic skin responses, baseline and tilt test cardiovascular reflexes, and circadian body core temperature rhythm were all normal. Sweating—assessed by the application of alizarin powder during a heating test—was absent on the left side of the face and reduced on the right upper limb. After heating, only the right side of the face showed flushing. These changes were replicated by physical exercise. There was no lacrimal or gustatory sweating.

Twenty four hour videopolysomnographic recordings (PSG) documented five nocturnal sudden and short lasting (20 to 40 seconds) awakenings during non-rapid eye movement (NREM) sleep, during which there was mumbling vocalisation, head and trunk raising from the bed, and a subsequent change in posture. These episodes were characterised by EEG α rhythms intruding upon light or deep

Table 1 Clinical characteristics of the patients and painful tonic spasm scores before and after treatment

Case	Sex	Age (years)	EDSS	Dose	T0	T1	T2	Type	Duration (years)
1	M	34	2.5	10 mg	3	0	0	RR	5
2	M	65	7.5	5 mg	3	Se		SP	18
3	M	41	3	30 mg	3	1	1	PP	5
4	F	35	2	10 m	2	0	0	RR	6
5	F	61	6.5	5 mg	3	Se		PP	3
6	F	44	3.5	15 mg	3	0	0	RR	6
7	F	36	3	15 mg	2	0	0	RR	7

EDSS, expanded disability status scale; F, female; M, male; PP, primary progressive; RR, relapsing-remitting; Se, side effects; SP, secondary progressive; T0, study entry; T1, at pain relief; T2, after 3 months.

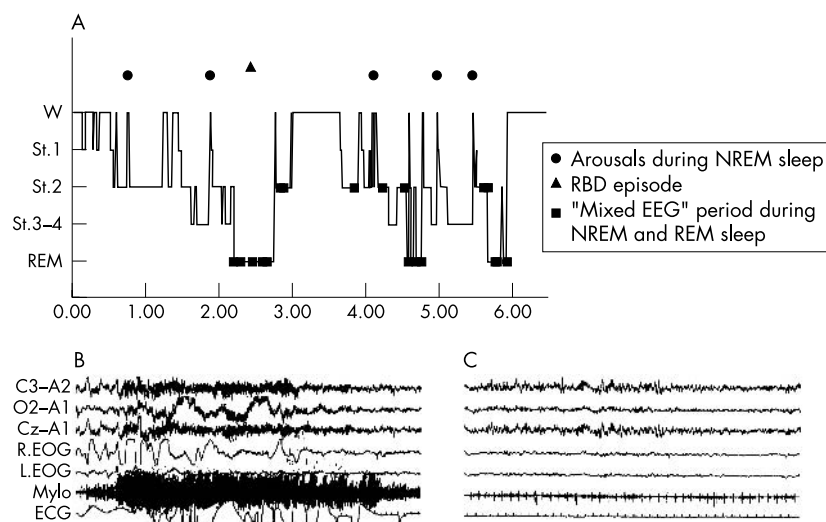


Figure 1 (A) Sleep histogram. Bullets along the top of the panel identify sudden short lasting awakenings during non-rapid eye movement (NREM) sleep, as exemplified in panel B. Black squares indicate periods with “mixed EEG” patterns, repetitively waxing and waning during NREM and REM sleep, as per panel C. The black triangle is an RBD (rapid eye movement sleep behaviour disorder) episode. (B) Videopolysomnographic (PSG) recordings (excerpts) of an arousal from NREM sleep, showing EEG α rhythms intruding suddenly upon deep NREM sleep activity. After 25 seconds the EEG again showed NREM light sleep activity. (C) PSG recordings show “mixed EEG” patterns (admixture of sawtooth waves and desynchronised high frequency/low amplitude activity with spindles and K complexes) during REM sleep. EEG (C3–A2; O2–A1; Cz–A1); L. EOG: left electro-oculogram; Mylo, mylohyoides; R. EOG, right electro-oculogram.

NREM sleep activity. During NREM sleep an EEG showed short sequences of REM-like patterns (sawtooth waves and desynchronised high frequency/low amplitude activity), sometimes with chin muscle atonia. During REM (rapid eye movement) sleep, her EEG showed typical elements but also frequent intrusions of spindles and α activities, with partial chin atonia on electromyography (EMG) and bursts of phasic EMG activity associated with vocalisation and facial movements. These transitional patterns of “mixed EEG” accounted for about 20% of total REM and S2 sleep time (fig 1). During a subsequent 48 hour Vitaport® evaluation, which confirmed the presence of “mixed EEG patterns,” the patient reported vivid dream contents related to awakenings from both REM and NREM sleep. A multiple sleep latency test showed borderline daytime somnolence (mean sleep latency, 8 minutes and 48 seconds) with frequent early microsleeps during all sessions. Chin EMG was unstable during each session, without a clear cut relation to the microsleeps.

CASE 2

A 52 year old woman presented with a two year history of sudden sweating and flushing of the left hemiface. Physical exercise and heat could cause these episodes, which also occurred spontaneously. Lacrimal and gustatory sweating were absent. At age 51, abnormal motor activities had appeared during sleep, associated with vocalisation resulting from vivid frightening dreams which the patient could report after waking. During admission, episodes characterised by sudden arousal during nocturnal sleep with screaming and fearful vocalisation were observed by room mates. From this time, nocturnal sleep became non-refreshing and

was interrupted by brief and abrupt awakenings; there was excessive daytime sleepiness.

On physical examination the right pupil was smaller than the left and did not dilate to dark. Right iris heterochromia with right ptosis and subtle enophthalmos were also present, and epinephrine 0.01% eye drops did not change the size of the right pupil. A body heating test with alizarin powder application¹ showed absent sweating in the right hemiface. Brain and spinal cord MRI and neurophysiological investigations including neurovegetative tests as in patient 1 were all normal.

Twenty four hour video PSG showed long sequences in which NREM and REM PSG features were intermingled: in particular runs of rapid eye movements and sawtooth waves intruded during stage 2 sleep associated with chin EMG fluctuations, and K complexes and sleep spindles were observed during REM sleep patterns. Chin muscle atonia was not complete during REM sleep, with brief sudden twitches and tonic EMG bursts; full blown REM sleep behaviour disorder (RBD) could not be recorded; chin muscle atonia could also appear suddenly during NREM sleep, randomly or before a leg movement. These intermingled NREM-REM sleep PSG patterns occupied 33.5% of total REM and stage 2 NREM sleep time.

COMMENT

Our patients had anhydrosis of one side of the face and long standing ipsilateral Horner's syndrome associated with both spontaneously occurring and heating/exertion induced paroxysmal hemifacial sweating, consistent with Harlequin syndrome.¹ They probably suffered a lesion of the first sympathetic neurone. While the negative dilute epinephrine eye drop test result suggested an absence of adrenergic supersensitivity

secondary to a third sympathetic neurone lesion, absent lacrimal and gustatory sweating excluding a second or third sympathetic neurone lesion.^{2,3} The exact lesion site, however, eluded us because of the negative MRI findings. In addition, our patients suffered abnormalities of nocturnal sleep, with recurrent seemingly purposeful motor activities like enacted dreams intruding into NREM and REM sleep, and PSG patterns characterised by an admixture of wake, NREM, and REM sleep EEG elements. Thus our patients had evidence for both a disorder of arousal and RBD because, from a behavioural point of view, they presented with atypical sleep with frequent muscle twitches, vocalisation, and dream-like mentation on waking. Such a mixed state of wakefulness and sleep is typical of the state dependent failure of control of the so called “parasomnia overlap” syndrome.⁴ Hypnagogic hallucinations and sleep paralysis were also reported by patient 1. Remarkably, the Harlequin syndrome was temporally linked and preceded the parasomnia overlap syndrome by one year, suggesting a possible connection between the two. Overlap parasomnia has been noted after lesions, even trauma, of the brain stem and forebrain regions,⁵ but ours is the first report of an association between Harlequin syndrome and sleep disorders in the form of overlap parasomnia syndrome. Our findings emphasise the need for an integrated approach to patients with autonomic and sleep disorders.

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An expansion in the ZNF9 gene causes PROMM in a previously described family with an incidental CLCN1 mutation

In 1997 Mastaglia *et al* described a two generation family of Macedonian origin with phenotypic features of PROMM and an incidental CLCN1 mutation.¹ Affected individuals had mild myotonia, predominantly proximal muscle weakness, and cataracts, compatible with a diagnosis of proximal myotonic myopathy (PROMM). Molecular genetic studies showed that the probanda did not have the chromosome 19 myotonic dystrophy (DM1) CTG expansion, but did have the R894X mutation in exon 23 of the muscle chloride channel gene (CLCN1). However she had only passed the R894X mutation to one of her two affected offspring. Thus the CLCN1 gene mutation did not segregate with the disease. We can now confirm that a definite genetic cause for PROMM has been identified in this family.

In 1998 a locus for a second type of myotonic dystrophy (DM2 or PROMM) was mapped to chromosome 3q21.² In 2001 it was shown that DM2/PROMM was caused by a CCTG repeat expansion located in intron 1 of the zinc finger protein 9 (ZNF9) gene.³ Inheritance of the microsatellite markers D3S1589, D3S3606, D3S1541, and D3S3684—flanking the DM2 locus—was compatible with DM2 being the disease in the family described by Mastaglia *et al*. The DM2 repeat expansion is difficult to demonstrate because of its very large size, but the presence of an expansion can be inferred by the non-inheritance of the normal sized allele from the affected parent, as in other expansions. The probanda of the family reported by Mastaglia *et al* shows only one normal sized allele for the tetranucleotide repeat region of the ZNF9 gene, and by inference she has an expanded allele. This may occur through the probanda either being homozygous for the same sized normal allele or through having one normal sized allele and one expanded allele. Her two affected offspring also only have one normal sized allele, and in both of them this is different in size from the normal sized allele in their mother. Thus they have not inherited a normal sized allele from their mother, but have inherited different normal sized paternal alleles. This family is thus suffering from DM2/PROMM.

The proband was 49 years old when initially described, and had been symptomatic for 15 years. In the six years since that description, there has been minimal worsening of symptoms, with the patient reporting a little more difficulty in climbing stairs and rising from low chairs. However, there was no deterioration in strength or increased myotonia on examination. Repeat psychometric testing has not shown further reduction in either verbal or performance IQ (74 and 75, respectively), but she had become significantly depressed, requiring treatment. A second brain magnetic resonance image (MRI), five years after the initial one, showed some increase in the extent of the periventricular white matter disease, but this was still considered mild and there was no atrophy of the parenchyma. Some subtle signal abnormality was seen for the first time in the pons.

The proband's offspring remain clinically asymptomatic with respect to cataracts, muscle problems, and cognition, at the ages of 34 and 24 years. In the initial description

both were shown to have myotonic discharges on electromyography, and this has not been repeated. However, they have now each had brain MRI, in both cases reported as being within normal limits. The younger sibling has the incidental CLCN1 mutation. The R894X mutation has been described in association with the autosomal recessive form of myotonia congenita, and so—without a mutation on the other CLCN1 allele—would not be expected to cause a disease phenotype.⁴ However, some CLCN1 mutations can cause either a recessive or a dominant mode of transmission depending on supplemental genetic factors.⁴ Thus the coexistence of the ZNF9 and the CLCN1 mutations may conceivably cause a more severe phenotype. At the present time, neither sibling has any abnormality; thus this theory cannot be proven or disproven.

As well as confirming the genetic basis of the disease in this family, this report also confirms PROMM as being a very slowly progressive and relatively benign disease. Although the MRI changes in other neurodegenerative diseases such as CADASIL can predate the clinical signs by more than 10 years (personal observation), this would not appear to be the case in PROMM. Although there has been a recent report of a patient with PROMM and schizophrenia who was intolerant of neuroleptics and susceptible to malignant hyperthermia,⁵ the proband has had several general anaesthetics without mishap. However, she had developed a psychiatric disorder in the form of depression, which is the third report of psychiatric dysfunction in PROMM patients.

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The validity of using the mini mental state examination in NICE dementia guidelines

The mini mental state examination (MMSE) is widely used as a rapid means of quantifying

cognitive function.¹ The National Institute for Clinical Excellence (NICE) guidelines concerning the use of cholinesterase inhibitors (CI) in Alzheimer's disease recommend using the MMSE as quantifiable measure to inform decisions regarding initiation and continuation of drug treatment.² Our study questions whether poor interrater reliability of the MMSE makes it an inappropriate tool for monitoring drug response.

A postal survey evaluating the MMSE section termed "attention and calculation" was conducted among all consultant neurologists in the UK. The original instructions regarding this section involve asking the patient to count backwards in sevens from 100 for five subtractions, or, if the patient "cannot or will not perform this task" to spell "WORLD" backwards, scoring the number of letters in the correct order.¹

Of the 407 questionnaires sent, there were 234 (58%) responses.

The MMSE was used in clinical practice by 91% of respondents, with 51% of respondents describing their use as "frequent". Test choice and method of scoring this section of the MMSE are shown in fig 1.

Only 10% of respondents were aware of schemes describing standardised scoring of mistakes when spelling WORLD backwards. Raters were asked to score a sample incorrect response "DRLOW". We did not allocate a "correct" score for this example since we believe the original guidance on how to score errors¹ is imprecise. Out of a maximum of five points, 51% assigned a score of three and 25% a score of one. Other scores included two respondents assigning a score of five. When scoring "93–85–78–71–64", 59% assigned a score of four points and 23% a score of one.

This survey of consultant neurologists confirmed substantial variability in the use and scoring of the serial sevens/WORLD backwards section of the MMSE. This interrater error leads to a potential score difference of up to four points for this section alone. We focused on this section of the MMSE alone to ensure brevity of the survey, as we perceived that the scoring method assigned to these questions is particularly dependant on the rater's interpretation. Rogers *et al* found the mean improvement in MMSE score after 12 weeks of treatment with CI to be 1.3 points.³ NICE guidelines for CI prescription in Alzheimer's disease give specific recommendations to stop these drugs if a patient's score deteriorates when the MMSE is repeated two to four months after commencement, or if the score falls below 12 points. Our results show that typical patterns of scoring the MMSE are too inconsistent to detect such small improvements in cognition and so may lead to inappropriate cessation of CI treatment.

The findings are in keeping with the large interrater variability previously demonstrated among a small group of psychiatrists,⁴ suggesting that the results likely to be generalisable to most doctors. Our study's incomplete response rate and finding that only half the respondents use the MMSE frequently introduces sources of selection bias, however, we believe that numbers were large enough to derive meaningful conclusions.

Should NICE use the MMSE as their recommended cognitive rating scale in Alzheimer's disease? Few of the studies showing benefit from CI use in Alzheimer's disease use the MMSE as a primary outcome

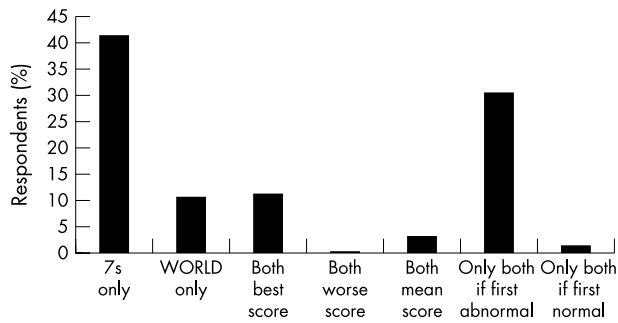


Figure 1 Use of counting backwards from 100 in sevens and spelling WORLD backwards in clinical practice.

measure. However, cognitive tests used in CI trials such as Alzheimer's disease assessment scale (ADAS-cog) are time consuming. Using a modified version of the MMSE, a standardised scheme to score errors made, or an alternative test, introduces new problems.

Although the MMSE has a number of limitations, awareness of these highlights some simple ways of improving its reliability in practice. Physicians should rigorously standardise their own testing methods. Local MMSE scoring guidelines could be instituted. It is helpful to retain completed score sheets in patient notes and to document in clinic letters whether serial sevens and/or WORLD were tested.

Because NICE estimate there to be 400 000 sufferers of Alzheimer's disease currently in England and Wales, the cost implications to the NHS regarding the appropriate use of CI's is vast. We call for inclusion of more detailed guidance on MMSE use in NICE recommendations and for further studies of new dementia treatments to use the MMSE as an outcome measure.

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"When the feeling's gone": a selective loss of musical emotion

Loss of "feeling" is a common lament in popular music:

Tragedy: when the feeling's gone
and you can't go on (Tragedy as
performed by the Bee Gees. *Spirits
have flown*, 1979.)

Here we describe loss of the feeling or emotion produced by music itself. Musical emotion can be considered at a number of levels. At the most fundamental level, dissonance produces a perception that is unpleasant to most listeners.¹ More variable is the intense pleasure that certain music may evoke in particular listeners, often described as a "shiver down the spine" or "chills",² which is likely to represent a more complex aesthetic response. We describe a patient with selective loss of this emotional response to music, due to a focal brain lesion.

A 52 year old right handed radio announcer collapsed in February 2000. He was found afterwards to have a total loss of speech comprehension and output, and a right hemiplegia. His speech recovered well, such that 12 months after the event he had only subtle output phonological problems. Motor functions recovered completely and he had no residual lateralising motor signs. However, he reported a persistent alteration in his auditory experience. He was in the habit of listening to classical music, to relax after working his night shift at the radio station, and had derived particular pleasure from listening to Rachmaninov preludes. He experienced an intense, altered emotional state or "transformation" when he did this. In common with other subjects who have this experience, the transformation was only

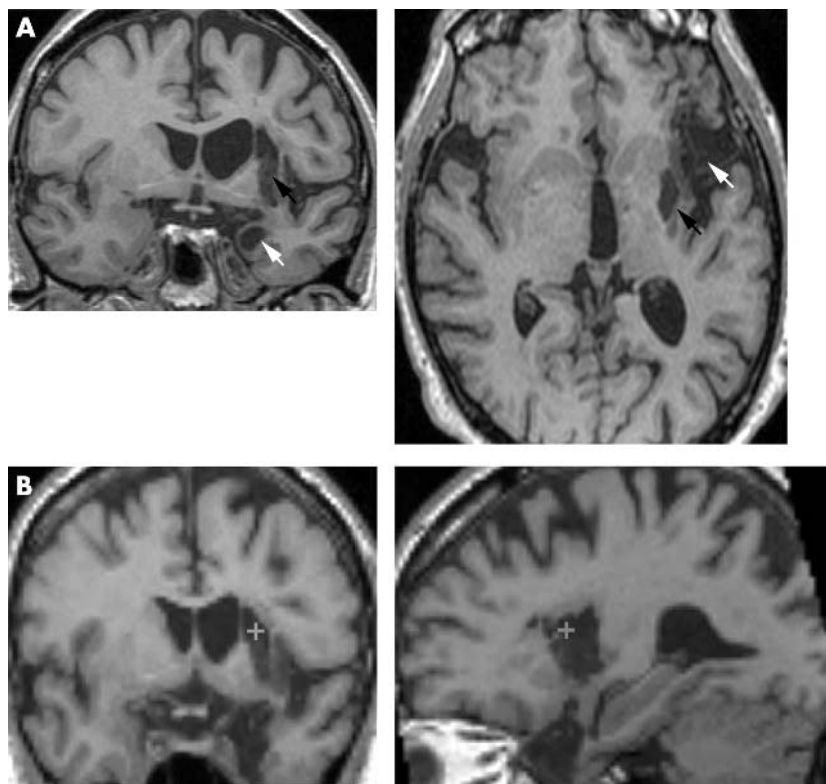


Figure 1 (A) Structural T1 weighted MRI sections of the patient's brain in the coronal (left) and axial (right) planes, showing infarction involving the left insula (black arrows) and amygdala (white arrows). (B) Coronal (left) and sagittal (right) T1 structural sections have been used to demonstrate the correspondence between the left insula lesion in our patient and the left insula activation associated with "chills" in response to music in normal subjects.² Grey crosses showing the location of peak activation in the left insula of normal subjects have been superimposed on the patient's structural brain volume. The images from the patient were normalised to the common stereotactic space of Talairach used in the previous functional imaging experiment² to allow this comparison. The correspondence indicates that the left insula is necessary for a strong emotional response to music.

produced by particular pieces, and he did not describe such an experience in response to music other than Rachmaninov's, nor to other sensory experiences. This emotional response to the music was lost following the acute event, and remained absent during the period of testing between 12 and 18 months after the stroke. During this period he was able to enjoy other aspects of life, and reported no biological features of depression. He had noticed no change in his hearing, and was still able to identify speech, music, and environmental sounds normally.

When assessed in April 2001, pure tone audiometry, auditory filter widths,³ speech audiometry, prosody perception,⁴ and music perception were all normal. Musical perception was examined using a battery of tests during which subjects are required to make same/different judgments on melody pairs that can show differences in melodic structure, rhythm, and metre.⁵ Our patient showed normal scores on tests of scale (28/30), contour (27/30), interval (28/30), rhythm (28/30), metre (29/30), and incidental memory (27/30); see <http://www.fas.umontreal.ca/psy/GRPLABS/inmcg/website/index.html> for normative data. Structural MRI revealed infarction involving the left insula and extending anteriorly into the left frontal lobe and inferiorly into the left amygdala. After normalisation to the standard stereotactic space of Talairach, the infarcted areas showed a close correspondence with left hemisphere areas activated during emotional response to music in normal subjects² (fig 1).

In a case such as this it is impossible to prove that the stroke produced a new deficit in the emotional reaction to music without direct evidence of the emotional reaction and its autonomic effect both before and after the stroke. The interest of this investigation accrues from the subjective report of the patient alone. Nevertheless, this is the first documented case of such a deficit of which we are aware, completing an important

double dissociation between musical cognition and emotional processing. Such a dissociation would require the presence of distinct substrates for musical cognition and emotion.

The cerebral basis for musical emotion has only recently been the subject of systematic study. In the clinical literature, an impaired emotional response to music is generally accompanied by disordered musical perception (amusia). However, one previously reported patient⁶ had impaired recognition of music despite a preserved affective response. In contrast, our patient strikingly illustrates the reverse dissociation, with normal recognition of music but loss of the emotional response to music. Together, these two cases complete a double dissociation between the perceptual and emotional components of music processing. This double dissociation suggests that the emotional effect of a piece of music is not predetermined by simple acoustic properties (which were processed normally in our patient).

Accumulating evidence from functional brain imaging studies in normal individuals suggests that functionally and anatomically separable neural networks mediate music perception and emotion. The perception of music involves the superior temporal lobes and inferior frontal lobes.^{7,8} In contrast, emotional processing of music engages a distributed brain network that is also recruited by other powerful emotional stimuli that produce autonomic arousal. This network includes bilateral medial limbic structures, insula, ventral striatum, thalamus, midbrain, and widespread neocortical regions.^{1,2} The present study enables us to conclude that the left insula is involved in normal musical emotional processing of music.

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