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## REVIEW ARTICLE

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# Unexpected amnesia: are there lessons to be learned from cases of amnesia following unilateral temporal lobe surgery?

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### Summary

Cases of amnesia following unilateral temporal lobe surgery are rare, but they may provide important insights into human brain functioning. Such cases are reconsidered here in the light of recent developments in clinical and cognitive neuroscience. Descriptions of preoperative seizure activity in these cases indicate the potentially valuable role of ictal semiology in localizing the source of epileptiform discharges. Cases of amnesia after unilateral temporal lobectomy illustrate the complexity of intra- and inter-hemispheric propagation of epileptiform discharges and highlight possible neurophysiological mechanisms underlying false localization of abnormal EEG activity. This review points to the value of preoperative neuropsychological assessment in

providing information on the likely primary locus of pathology and in predicting outcome after surgery. The analysis of cases upholds the benefits of the Wada procedure, but it highlights the variability in Wada test procedures and the fact that Wada test scores themselves may be open to varying interpretation. These cases of postoperative amnesia are further considered in the context of the cognitive neuroscience of human memory and, in particular, mechanisms underlying the human amnesic syndrome. They confirm the critical role of bilateral medial temporal lobe structures in anterograde memory, but they also highlight the complexity in teasing apart neural mechanisms underlying remote memory loss.

**Keywords:** amnesia; temporal lobe; surgery; epilepsy; anterograde memory

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### Introduction

Temporal lobe surgery for the relief of epilepsy has been one of the major success stories in the history of both neurosurgery and the management of epilepsy (Engel, 1993). However, it is not a risk-free procedure. Since the introduction of this procedure, and especially since the 1950s, attempts have been made to minimize the risks of such surgery. In the 1950s, the occurrence of severe amnesia in several cases of temporal lobe surgery (Scoville and Milner, 1957; Walker, 1957), for either the relief of epilepsy or the treatment of psychiatric conditions, led researchers to focus on this particular cognitive side-effect of temporal lobectomy. The introduction of the sodium amytal procedure, initially intended to determine which side of the brain

specializes in language functions, was soon extended to include an assessment of memory functioning. It allowed clinicians to partly mimic the effects of temporal lobe surgery by anaesthetizing one cerebral hemisphere while the capacity of the other hemisphere to retain new information was assessed. In spite of these and other precautions, a few cases have slipped through the clinical net and have resulted in instances of amnesia following unilateral temporal lobectomy.

The purpose of this paper is to look afresh at cases of amnesia in the light of recent developments in clinical and cognitive neuroscience, to see whether we can enhance our understanding of both the epileptic and memory

manifestations of medial temporal lobe pathology. The reader is referred to a number of sources for reviews of some of the cases discussed here and for consideration of general issues relating to amnesia following temporal lobectomy (Jones-Gotman *et al.*, 1993; Rausch *et al.*, 1993; Baxendale, 1998; Simkins-Bullock, 2000).

### General clinical features of cases of amnesia after unilateral temporal lobectomy

It is difficult to obtain accurate estimates of incidence of unexpected amnesia following unilateral temporal lobectomy, and it is likely that there is an understandable under-reporting of such cases. Davies and Weeks (1993) did report one case of postoperative amnesia in a series of 58 cases of unilateral temporal lobectomy, whereas Walczak *et al.* (1990) found one case of marked deterioration in memory from a preoperative normal state in their series of 100 patients who underwent such surgery. Rausch and Langfitt (1992) estimated that, on the basis of their series, 'the prevalence of patients at risk for postoperative amnesia who otherwise met criteria for surgery fell between one and four out of 218' (p. 508), and Jones-Gotman *et al.* (1993) noted that 'the base-rate of post-resection amnesia, were all patients operated on without prior screening with the amobarbital procedure, may be less than 1%, (p. 447). In a survey reported by Rausch *et al.* (1993), six out of 72 respondents professed personal knowledge of cases of amnesia following unilateral temporal lobe surgery that followed on from test failure on the procedure.

We were able to locate nine definite cases of amnesia following unilateral temporal lobe surgery in the English-language literature. Across the cases, a variable range of investigations has been carried out, differing procedures have been employed within investigations, and varying amounts of detail have been reported. Two of the nine cases were published in Abstract form only (Rausch *et al.*, 1985; Barr *et al.*, 1992). Sufficient information for data analyses was therefore only available in seven cases.

Of the seven cases, five were male and two were female. All presented as adults, with ages ranging from 27 to 53 years. Five had an onset of epilepsy in childhood. The other two had onset ages of 25 and 38 years. Four had left temporal lobectomies, and three had right temporal lobectomies. Allowing for the relatively small number of cases, the fact that there were more males than females requires a brief comment. Although the literature on gender differences and hemispheric specificity of cerebral pathology and cognitive dysfunction is a complex one (Kimura, 2002), there is some evidence that females may fare better than males following temporal lobectomy. For example, Trenerry *et al.* (1995) reported that, in their series of cases, females improved in verbal memory functioning after left temporal lobectomy, whereas males showed a decline in memory after surgery. Davies *et al.* (1998) also found that females had a better outcome than males on verbal memory measures after left

temporal lobectomy. Berenbaum *et al.* (1997) noted that females who underwent left temporal lobectomy showed better performance than males on a word-list learning task both before and after surgery. As can be seen from Table 1, most of the patients were right-handed, although one (Loring *et al.*, 1994) was left-handed and was dysphasic following right-sided Wada injection (Table 2). As can also be seen, most patients who had left-sided surgery were right-handed. Of the three patients who had right-sided surgery, one was right-handed, one was left-handed and one was ambidextrous. Although it is not possible, therefore, to reach any specific conclusions in relation to the role of handedness in determining outcome in relation to side of surgery, handedness has been found to be a factor in some studies (Rausch *et al.*, 1991).

### Ictal semiology

Although, in the cases under review, it is easy to use the benefit of hindsight to point to ictal features that may have suggested bilateral temporal lobe involvement or involvement of the side contralateral to the operated side, it may be fruitful to consider the range of ictal manifestations of seizure activity in the more general context of recent advances in the classification and understanding of ictal semiology. We will therefore briefly review the ictal features of the patients and also offer a brief commentary on features of note in each case.

#### Case 1

This patient, reported by Penfield and Milner (1958), was a glove cutter who underwent a *left* temporal lobectomy. Automatisms comprised fumbling, humming and swallowing. Auras would include a sensation in the head and a feeling of fogginess, occasional cold feeling with goose pimples, and palpitations on a few occasions. Complex, purposeful, responsive behaviour would accompany some seizures, and examples of such behaviour included an instance of the patient cutting several gloves but having no memory for this.

#### Commentary

There were no clear lateralizing features in this case, although it is worth noting that there is a tendency for cephalic auras to be more left-lateralized in temporal lobe epilepsy (Manchanda *et al.*, 2000) and for autonomic seizures also to be more left-lateralized (Stefan *et al.*, 2002). Thus, it seems that the correct side underwent surgery, but that there may have been significant latent pathology in the other temporal lobe that contributed to the postoperative amnesia.

#### Case 2

This patient, also reported by Penfield and Milner (1958), was an engineer who underwent a *left* temporal lobectomy; the case eventually came to post-mortem (Penfield and

**Table 1** Results of EEG investigations

Case	Handedness	Side of surgery	Pre-surgical inter-ictal scalp EEG	Pre-surgical ictal/invasive EEG	Post-surgical EEG
Case 1—glove cutter (Penfield and Milner, 1958) (Penfield and Mathieson, 1974)	Ambidextrous right>left	Left	Bilateral temporal lobe abnormality, maximum on the left Occasional evidence of right temporal lobe abnormality	An ictal recording showed left temporal onset	Left frontal and right temporal abnormality Three years after surgery: Epileptic focus in right anterior temporal lobe After first operation: Left temporal lobe sharp waves and occasional bilateral temporal lobe sharp waves (on one occasion, an abnormality on the right then spread to the left) After second operation: An ictal recording showed suppression of right temporal activity, followed by right temporal sharp waves that spread to left side Large amount of fast activity, ? drug-related
Case 2—engineer (Penfield and Milner, 1958) (Penfield and Mathieson, 1974)	Right-handed	Left	Slow and sharp waves in left temporal lobe	No date reported	
Case 3 (Walker, 1957)	Right-handed	Left	On one occasion: Bilateral temporal slow activity was seen On the second occasion: Abnormal discharges were mainly from the left temporal lobe but with rare right temporal lobe spike discharge A very small number of epileptiform discharges from both temporal regions or diffuse right-sided spike/wave activity. Bilateral temporal lobe slow and sharp waves, right>left	No date reported	
Case 4 (Loring <i>et al.</i> , 1994)	Left-handed	Right		Ictal scalp EEG was non-localizing Ictal intracranial recordings showed either right temporal or bilateral onset	No data reported
Case 5 (Dimsdale <i>et al.</i> , 1964) (Warrington and Duchon, 1992) (Chan <i>et al.</i> , 2002)	Mainly left-handed, but right-handed for some activities	Right		Sphenoidal EEG pointed to a right anterior temporal lobe abnormality Penthothal injection exacerbated the right temporal lobe abnormality and caused a few spikes in left temporal lobe	Right temporal lobe abnormality that included right posterior temporal lobe sharp waves and some low-amplitude delta activity in mid-temporal regions on the right
Case 6 (Ahern <i>et al.</i> , 1994)	Right-handed	Right	Inter-ictal showed bilateral epileptiform temporal lobe abnormality, with slight right-sided predominance Left inferomedial temporal lobe epileptiform discharges Slow waves were also seen independently in both temporal lobes	Ictal scalp EEG also showed bilateral epileptiform temporal lobe abnormality, with slight right-sided predominance Ictal scalp EEG showed left temporal onset	No data reported
Case 7 (Guerreiro <i>et al.</i> , 2001)	No data reported	Left			Limited left temporal lobe abnormality Intra-operative electrocorticography showed epileptic activity in remaining anterior temporal lobe neocortex

**Table 2** Results of imaging, invasive procedures and pathology investigations

Case	Side of surgery	Brain imaging	Wada/brain stimulation findings	Neurosurgical procedure	Histopathology
1	Left	Pneumoencephalogram suggested left-hemisphere atrophy	No data reported	Left medial and anterior lateral temporal lobe removed	No histopathology reported
2	Left	Pneumoencephalogram showed moderate ventricular dilatation/cerebral atrophy	No Wada data reported During operation, stimulation of left hippocampus and parahippocampal gyrus induced attacks similar to seizures	Two-stage operation: In the first procedure, left temporal lobe neocortex removed In the second procedure, left anterior hippocampus, amygdala and uncus removed	At operation, left hippocampus, and uncus looked abnormal, 'yellow and tough' Herniations and adhesions seen, consistent with birth trauma No formal histopathology reported
3	Left	No data reported	No data reported	Anterior 6 cm of left temporal lobe removed Medial extent not indicated	Tissue reported as normal
4	Right	Left hippocampus abnormally small in volume on MRI (data obtained from postoperative scans) Preoperative scans largely normal to visual inspection)	Left-sided Wada: 8/8 objects recognized Right-sided Wada: Dysphasia, 0/8 objects recognized	4.5 cm of right anterior temporal lobe removed, including hippocampus	No histopathology reported
5	Right	Postoperative ventriculogram normal	No data reported	Right anterior temporal lobe removed, including hippocampus and amygdala	Limited samples of right hippocampus available, appeared to be normal Unresected left hippocampus later shown at post-mortem to be sclerotic, but left parahippocampal region found to be normal
6	Right	In 1987: High signal in medial temporal regions on T <sub>2</sub> MRI, more marked on the left than on the right, but with greater ventricular dilatation on the right In 1989 and 1990: MRI showed left anteromedial temporal atrophy	Wada findings not formally reported, but patient is reported to have failed Wada procedure, with poor memory performance (M. O'Connor, personal communication)	Right temporal lobectomy No further details reported	Gliosis of temporal neocortex from surgical specimen
7	Left	Bilateral arachnoid cysts in middle cranial fossa, right>left Left hippocampus smaller than right, but right hippocampus showed high signal abnormality	Left-sided Wada: Poor memory score (0/2) Right-sided Wada: Normal memory score (5/7)	Left anterior temporal neocortex, amygdala and anterior 2 cm of hippocampus removed	No histopathology reported

Mathieson, 1974). Initial seizure activity consisted of momentary lapses of conversation with evident confusion. After 3 years, attacks were accompanied by staring, followed by head-turning to the right, aimless movements of the right arm, and chewing movements. After 6 years, during seizures he would stare, become unresponsive, fumble, masticate, his head would turn to the right and he would engage in automatisms. Towards the end of the attack, the automatisms would include complex, purposeful, responsive behaviour, such as going outside and taking readings from a thermometer. The attacks would last for 5–15 min, and he would be amnesic for the whole episode. Auras would occasionally consist of illusions of absurdity and unreality.

### Commentary

Some studies of ictal semiology associated with medial temporal lobe epilepsy have noted that early head-turning is usually ipsilateral to the seizure focus (e.g. Fakhoury and Abou-Khalil, 1995; Steinhoff *et al.*, 1998; Williamson *et al.*, 1998; Dupont *et al.*, 1999). Engel *et al.* (1997) noted that there remains some debate in the literature on the value of such a sign, but they suggest that a consensus view is that 'Early, relatively casual head deviation can be ipsilateral to seizure origin, whereas forced head and eye deviation occurring later in the seizure, often as a prelude to a secondary generalized convulsive seizure, is almost always contralateral' (p. 2420). Therefore, one might have predicted a right temporal focus to the epilepsy.

### Case 3

A series of four cases of memory impairment following *left* unilateral temporal lobectomy was reported by Walker (1957), and, as also noted by Baxendale (1998), case 3 in his series is the only one that appears to be a clear example of amnesia following unilateral surgery. This patient, who underwent ablation of his *left* temporal lobe, had seizures as a child. More recently, he had for 12 years experienced attacks that were described as spells of unconsciousness, periodic confusion and no recollection for his subsequent actions. Later attacks were preceded by sensory disturbance in his left foot.

### Commentary

The left sensory disturbance might have suggested some right-hemisphere involvement, but the relatively brief description of seizure activity otherwise precludes any specific interpretation of ictal semiology.

### Case 4

This patient, reported by Loring *et al.* (1994), underwent a *right* temporal lobectomy. Three types of seizures occurred: (i) complex partial seizures that consisted of episodes of 1–3

min duration that would include impaired consciousness, picking automatisms and purposeless walking; (ii) complex partial seizures that included episodes <1 min duration that would comprise staring and lip-smacking, without prominent automatisms; and (iii) a non-specific aura evolving into tonic-clonic seizures. The first two types of seizures were much more frequent (5–20 seizures a month) than the third type (3–5 times a year).

During invasive and non-invasive EEG recordings, seizures were documented that consisted of whistling at onset, head- and body-turning to the left, and circular motions of the left arm or both hands.

### Commentary

The three types of clinical seizure activity were not helpful in localizing the epileptic focus. However, the seizures recorded during EEG investigations yielded evidence of left-sided automatisms and initial head/body-turning to the left that might perhaps lend itself to favouring a left-hemisphere focus (cf. Fakhoury and Abou-Khalil, 1995; Steinhoff *et al.*, 1998; Williamson *et al.*, 1998). Involuntary whistling has been reported in association with a right temporal lobe EEG focus (Tan *et al.*, 1990).

### Case 5

This patient, originally reported by Dimsdale *et al.* (1964), subsequently came to post-mortem and was the subject of further publications by Warrington and Duchon (1992) and by Chan *et al.* (2002). Her operation consisted of a *right* temporal lobectomy. Her epileptic attacks were usually tonic-clonic seizures, but two attacks of transient amnesia were described. In one attack, she wandered around the hospital for 45 min asking to find the bathroom, somewhere she had been very familiar with during her 1 month hospital stay. In a second episode, she appeared to have several attacks earlier in the day (one seizure was recorded on EEG), and later in the day she denied that her consultant had seen her earlier.

### Commentary

The episode of topographical disorientation may implicate right hippocampal structures (Cammalleri *et al.*, 1996; Spiers *et al.*, 2001), in accordance with the presumed site of seizure focus before surgery, but the occurrence of episodes resembling transient epileptic amnesia may suggest the possibility of bilateral medial temporal lobe involvement (Zeman *et al.*, 1998).

### Case 6

A case that was not reported as primarily dealing with temporal lobectomy for the relief of intractable epilepsy was reported by Ahern *et al.* (1994). Their patient, who had a *right*

temporal lobectomy, had temporal lobe lesions associated with paraneoplastic limbic encephalitis. He was significantly disabled by the presence of 20–30 seizures a day, and there were family pressures for surgery to relieve the seizure activity. Prolonged post-ictal confusion was common. Two types of attacks occurred: (i) the dominant type that consisted of olfactory hallucinations followed by profuse salivation, spitting, repetitive swallowing, shuddering, pilo-erection, increased heart rate and blood pressure, and a fearful expression; and (ii) episodes of confusion, non-sensical speech, together with orofacial and bilateral limb automatisms that were particularly evident on the right side of body. In addition to his seizures, he had an unusual form of memory loss that included marked memory loss for events that had occurred days or more earlier, in the context of normal performance on standard anterograde memory tests. He also displayed some degree of retrograde amnesia. After surgery, he developed a more classical amnesic syndrome (M. O'Connor, personal communication).

### Commentary

Ictal spitting has been associated with right temporal seizure origin (Kaplan *et al.*, 1999). Prolonged post-ictal confusion would tend to implicate bilateral medial temporal lobe involvement. Features of autonomic seizures (cold shivers, goose bumps) have been associated with left temporal lobe abnormalities (Stefan *et al.*, 2002). The presence of ictal dysphasia suggests a left-hemisphere focus.

### Case 7

The most recent case in this series is one reported by Guerreiro *et al.* (2001), patient 5 in their series, who underwent a *left* temporal lobectomy. He suffered two seizures a month, and these included loss of consciousness that was accompanied by manual automatisms and automatic speech, and he would occasionally walk purposelessly or just stare. Auras consisted of a non-specific pleasant feeling. Seizures would occasionally be triggered by a particular object or by a strong emotion. The attacks would normally last for 20 s, with post-ictal confusion for around 10 min.

### Commentary

The absence of post-ictal dysphasia and the presence of automatic speech may tend to point to right rather than left temporal lobe involvement in this case (Gabr *et al.*, 1989).

### Post-surgical seizure status

In two of the patients (Cases 5 and 7), seizure status after surgery was not reported. In one (Case 3), there appeared to be a complete absence of seizures after surgery, although it seems that the patient remained on anti-convulsant medication; thus, the initial pathology may have been bilaterally distributed in both temporal lobes, with memory dysfunction

and epilepsy having differing pathological foci. Another patient (Case 4) was reported as having shown no change in seizure activity after surgery, raising the possibility that the lesion had always been on the other side. In the three remaining patients (Cases 1, 2 and 6), a slight, limited improvement in seizure status was reported. Although this suggests that the major site of pathology was bilateral or on the other side, the persistence of seizures may also have been due to discharging tissue remaining beyond the site of resection in the operated hemisphere. In the case of post-surgical EEG findings (Table 1), there was little evidence that epileptiform discharges had changed to the side opposite surgery.

Since there is a wide consensus (Engel, 1993) that unilateral temporal ablation of well-localized abnormal tissue in temporal lobe epilepsy will invariably result in major improvement in seizure status, a consideration of the outcome of these cases suggests that, in six of the seven cases, the sole or major site of pathology was either bilateral or in the other hemisphere.

### Pre- and post-surgical neurophysiology

A summary of the major EEG findings in the seven cases, before and after surgery, is provided in Table 1. As can be seen, in most instances the primary pre-surgical focus of EEG abnormality was on the side that was selected for surgery. However, there was also limited evidence before surgery of occasional bilateral epileptiform discharges. After surgery, less extensive EEG data were reported, but in several cases an EEG focus remained on the side of surgery.

### Commentary

Cases of false localization arising from inter-ictal EEG recordings have been well documented. In one study, where subdural grids were implanted (Cukiert *et al.*, 2000), three out of 16 patients with temporal lobe epilepsy had inter-ictal EEG abnormalities that were contralateral to the side that eventually proved to be the lesion focus and site of subsequent surgery. In each of these cases, ictal onset was ipsilateral to the side of the lesion, and contralateral spread occurred after ipsilateral spread. A similar degree of subdural versus scalp EEG divergence was noted by Blume *et al.* (2001). Even subdural EEG may yield false localization when compared with depth electrode recordings (Alsaadi *et al.*, 2001; Eisenschenk *et al.*, 2001). Some of the EEG abnormalities found in the cases reviewed here may have represented mirror-focus discharges—in one study, such discharges occurred in ~50% of patients with temporal lobe epilepsy secondary to brain tumours (Gilmore *et al.*, 1994).

### Neuroradiology

Only three of the seven patients (Cases 4, 6 and 7) were the subject of investigations after the introduction of modern

brain imaging and after the introduction of Wada testing into routine clinical use. In the case of brain imaging, there was some degree of conflict in Case 7 between the presence of high signal in one hemisphere and the presence of atrophy or ventricular dilatation in the other (Table 2). The presence of bilateral hippocampal pathology has generally been associated with less favourable outcome after surgery (Jack *et al.*, 1992), although some cases of bilateral hippocampal sclerosis and satisfactory outcome have been reported (e.g. Jack *et al.*, 1995; Cukiert *et al.*, 2000). In the case of memory outcome measures, when bilateral hippocampal atrophy occurs in the context of left temporal lobe epilepsy, it has been associated with poorer postoperative performance on verbal memory tests (Martin *et al.*, 2001). Although hippocampal atrophy and hippocampal high signal changes often go hand in hand, there is evidence that they may contribute independently to predicting seizure outcome after surgery (Garcia *et al.*, 1994). Kim *et al.* (2001) reported that hippocampal atrophy was more common than high signal in patients with temporal lobe epilepsy and showed a higher correlation with surgical outcome in their group. However, as they pointed out, the fact that a FLAIR (fluid attenuated inversion recovery) MR sequence was not used in this study could have had a bearing on their findings, since it is likely that the use of such a sequence would have detected more cases of hippocampal high signal than standard T<sub>2</sub> imaging.

### Neuropsychology

Details of preoperative and postoperative neuropsychological testing are shown in Table 3. As can be seen, where preoperative cognitive testing was carried out, it usually provided a profile of test scores that pointed to an alternative locus of pathology to that chosen for surgery. Also, in Cases 1 and 2, both patients were able to resume occupations similar to those that they had previously carried out—the glove cutter (Case 1) continued to cut gloves and the engineer (Case 2) now worked as a draughtsman. Both were able to carry out meaningful work activity, presumably with the help of memory aids and with sympathetic employers. In terms of specific neuropsychological profiles, the patient in Case 7 had relatively spared postoperative recognition memory performance. These observations suggest that, although most of the cases in this series may, by conventional criteria, have been amnesic as a result of their surgery, it is possible that their amnesia was not as dense as might be found in some of the more severely amnesic patients reported in the literature.

### Wada testing

In all three cases with Wada testing, poor memory followed injection of sodium amytal in the hemisphere where pathology was suspected to be present and which later was the side where surgical ablation was carried out. Thus, the Wada findings correctly predicted poor outcome after surgery; but for reasons detailed below, these findings were not given due

weight before surgery. In two of the cases, details of Wada test scores were reported (Table 2). In one patient (Case 4), clear asymmetry in memory performance was present for eight items presented early in the Wada procedure, but no such asymmetry was present for five items presented at a later stage in the procedure. In another (Case 7), consideration of ‘early’ items (during which EEG was abnormal) led to a result that suggested asymmetry in performance (five items recognized out of seven versus none out of two after right- and left-sided injections, respectively). However, when only later-presented items were considered, the scores were broadly equivalent (five out of seven versus five out of five), and the test was interpreted as a ‘pass’ on both sides. The data from these two cases can therefore be seen to lend credence to the value of the Wada procedure in predicting memory outcome after temporal lobe surgery and are in accord with published findings (e.g. Sabsevitz *et al.*, 2001). It is possible that these observations may primarily hold where, as in the two cases discussed here, clear asymmetry in Wada scores was present. Nevertheless, where the Wada test is failed on both sides, suggesting the presence of bilateral pathology, satisfactory outcomes after surgery have still been reported (Kubu *et al.*, 2000).

As Acharya and Dinner (1997) have pointed out, systematic evaluation of the utility of the Wada procedure is limited by inbuilt constraints on the design of any potential trial where clinical need for, and risks of, surgery were compromised. Therefore, indirect evidence is the primary source of data relating to Wada findings and the risk of amnesia after surgery. Some authors (e.g. Loring *et al.*, 1990, 1994; Rausch *et al.*, 1993) have remarked on cases where patients have failed the Wada procedure and have gone on to conventional medial temporal lobe surgery without any ensuing amnesia. Jones-Gotman (1992) noted cases where patients have failed the Wada procedure and have shown significant (though not amnesic) postoperative memory deficits where the surgical procedure largely spared the hippocampus and parahippocampal gyrus. The presence of such cases is a reminder that surgery may be needlessly denied, or less than optimal surgical procedures used, for some patients with temporal lobe epilepsy. In addition, as Meador and Loring (1999) have pointed out, ‘the Wada test is only one of multiple tests to assess functional capacity, and poor Wada memory results must be interpreted within the context of other clinical studies’ (p. 1536).

Developments in functional brain imaging hold out the promise of providing information that will complement and perhaps eventually provide a substitute for Wada test scores in helping to predict the outcome of surgery. For example, there are now some promising findings in normal subjects that show left–right lateralization of memory, depending on the verbalizability of stimuli (e.g. Golby *et al.*, 2001). The application of such paradigms to clinical populations is the next step, and some preliminary findings have been reported. Detre *et al.* (1998) showed that presentation of a complex scene activated posterior parahippocampal cortex bilaterally

**Table 3** Results of neuropsychological investigations

Case	Side of surgery	Pre-surgical general cognitive functioning	Post-surgical general cognitive functioning	Pre-surgical memory functioning	Post-surgical memory functioning
1	Left	Deficits on tests of pictorial reasoning WAIS Verbal IQ = 102 Performance IQ = 109 Full-Scale IQ = 106	Three years after surgery: WAIS Verbal IQ = 103 Performance IQ = 115 Full-Scale IQ = 109	Normal on Benton Visual Retention Test Impaired on delayed story recall	Three years after surgery: Impaired on tests involving recall of designs, verbal paired-associates and stories, especially on delayed recall Five years after surgery: WMS Quotient = 94 Impaired delayed retention of stories and objects. Initial retrograde amnesia of several years, later reduced to several months Impaired story recall reported 38 months after surgery: WMS-R Verbal Memory Quotient = 55 Visual Memory Quotient = 93 Delayed Memory Quotient = 50 Decline on tests of verbal memory, and also on a test of delayed recall of a complex figure
2	Left	Deficits on tests of pictorial reasoning WAIS Verbal IQ = 125 Performance IQ = 110 Full-Scale IQ = 119	Five years after surgery: WAIS Verbal IQ = 133 Performance IQ = 111 Full-Scale IQ = 125	Normal on Benton Visual Retention Test Able to recall details of cognitive tests carried out 2 h earlier	
3	Left	No data reported	No data reported	No data reported	
4	Right	WAIS Verbal IQ = 79 Performance IQ = 96 Full-Scale IQ = 87 Normal on tests of language, visual spatial function and attention WMS-R Attention/Concentration Quotient = 104	38 months after surgery: WAIS Verbal IQ = 74 Performance IQ = 90 Full-Scale IQ = 81 Most other cognitive tests unchanged, except for a marked drop in visual naming score (50/60 to 28/60)	WMS-R Verbal Memory Quotient = 74 Visual Memory Quotient = 104 Delayed Memory Quotient = 83 Impaired on other tests of verbal memory, with normal performance on tests of non-verbal memory	
5	Right	WAIS IQ = 100	WAIS IQ tested on several occasions, and scores varied between 98 and 104 Performance on Picture Arrangement subtest impaired	Wechsler Memory Quotient = 80 Impaired verbal paired-associate learning and story recall	8-14 months after surgery: Impaired 30 min recall of sentences and pictures Could not repeat 'Babcock sentence' after 12 repetitions No familiarity recognition for two pictures shown 1 h earlier Marked preoperative amnesia for 10 years 8 months after surgery: Preoperative amnesia still evident No data reported, but noted to have severely impaired retention after a delay of 10 min (M. O'Connor, personal communication)
6	Right	In 1990: WAIS-R Verbal IQ = 123 Performance IQ = 122 Full-Scale IQ = 127 Normal performance on tests of language, visual spatial function, attention and executive function	No data reported	In 1989: WMS-R Verbal Memory Quotient = 117 Visual Memory Quotient = 111 Delayed Memory Quotient = 111 Normal on Rey Auditory Verbal Learning Test, and on Recognition Memory Test In 1990: Impaired on tests of longer-term anterograde memory, and on memory for public events over the previous 20 years Impairment in non-verbal memory	
7	Left	WAIS-R IQ = 88 Normal on tests of executive and language function	WAIS-R IQ = 104 Postoperative scores on executive and language function similar to preoperative levels		Impaired verbal and non-verbal recall Recognition memory appeared to be relatively spared

WAIS-R = Wechsler Adult Intelligence Scale Revised; WMS-R = Wechsler Memory Scale Revised.



in normal subjects, but asymmetric activation was found in unilateral temporal lobe epilepsy patients, and this asymmetry corresponded to the results of sodium amytal testing. Using a non-verbal memory task where subjects had to mentally navigate along personally familiar landmarks, Jokeit *et al.* (2001) also found bilateral medial temporal lobe activation in control subjects, but asymmetric activation in patients with temporal lobe epilepsy. This asymmetry was more closely related to memory test scores obtained during neuropsychological testing than to performance on visuospatial tasks. Dupont *et al.* (2000) studied the pattern of functional activations during both verbal encoding and retrieval in episodic memory tasks. In patients with left medial temporal lobe epilepsy, less marked left occipito-temporofrontal activation was seen than in control subjects, together with reduced bilateral parahippocampal activation. However, they also reported increased dorsolateral frontal activation in the epilepsy patients compared with control subjects. In a follow-up study (Dupont *et al.*, 2001), where they examined retention over longer (24 h) intervals, they found (at 24 h retrieval) reduced activation of bilateral parietal and right hippocampal areas in left temporal lobe epilepsy patients compared with control subjects.

### Implications for the cognitive neuroscience of human memory

What implications do the case studies reviewed here have for our understanding of mechanisms underlying normal and abnormal human memory? Any conclusions that are drawn must be tentative because of the relatively small number of cases that make up the corpus of studies. Those cases that came to post-mortem (Cases 2 and 5) are of particular interest, since they contribute to our understanding of the anatomical substrate of human amnesia. Although there are some cases of apparent minimal or no memory impairment following bilateral hippocampal damage, presumably because the lesions were particularly discrete (Gol and Faibish, 1967), detailed neuropsychological test results were not reported, and closer inspection of the clinical findings reported in Gol and Faibish (1967) suggests that at least some of their patients were amnesic after surgery. Nevertheless, there is some evidence that where medial temporal lesions are benign and/or long-standing (Henke and Wieser, 1996), less marked memory impairment may result.

Although there is a view that structures adjacent to the hippocampus rather than the hippocampus itself may be critical for human memory function (Gaffan, 2001), most of the evidence relating to hippocampal pathology indicates that bilateral lesions will result in significant memory loss, even where the lesions are restricted to particular CA regions (Zola-Morgan *et al.*, 1986) or occur in two stages (Oxbury *et al.*, 1997). One of the cases reviewed in the present paper (Case 5) was the subject of two further reports, and it illustrates some of the complexities involved in the parcella-

tion of factors that may contribute to human memory disorder. Evidence relating to this interesting case has been used to address the issue of the neural basis of retrograde amnesia (Chan *et al.*, 2002). The patient had a history of temporal lobe epilepsy dating from the age of 25 years. When seen in 1960, she had had an increasing number of partial seizures over a period of 28 years. Secondary generalized seizures increased to reach an occurrence of several attacks a month, and these attacks were sometimes accompanied by post-ictal confusion. There were also epigastric auras with a frequency of several episodes a day. During an in-patient stay, she was observed to have two 'confusional episodes', which were presumably ictal in origin. Over much of that period of time, she also suffered from depression and paranoia, for which she received in-patient treatment. Neuropsychological testing before surgery indicated a Wechsler Memory Quotient of 80 (20 points below her IQ score) and was characterized by poor retention of verbal material. She underwent a right temporal lobectomy in January 1961 (the site of surgery being influenced by the presence of right temporal lobe EEG abnormalities), and she was subsequently left with a dense amnesic state. Detailed histopathological findings relating to the ablated right temporal lobe tissue were not reported, but in a later post-mortem study, sections of the right neocortex and amygdala 'were examined with routine staining methods and were within normal limits' (Warrington and Duchon, 1992, p. 443). Only a limited part of the hippocampus was available for analysis; this included a short length of dentate gyrus, some end-folium (CA4) and fragments of pyramidal cell layer. The authors also noted: 'Apart from surgical artefact, the histological appearance of these regions were all within normal limits' (p. 443). Post-mortem analysis of left temporal lobe tissue showed widespread pathology within all CA regions of the hippocampus, especially regions CA2 and CA4. The granule cells of the dentate gyrus were also significantly reduced in number. A further, more recent study (Chan *et al.*, 2002) found no abnormalities in the left entorhinal and perirhinal cortices, nor in other portions of the parahippocampal gyrus. The presence of a few neurofibrillary tangles and senile plaques was considered to be age-related and not reflecting any specific pathology.

As for her postoperative neuropsychological profile, anterograde memory testing indicated a severe impairment in retaining new information, with impairments evident on recognition memory tests for faces, words and pictures. Performance on implicit memory tests was generally within normal limits. In the case of longer-term memory tests, autobiographical memory was informally assessed: '[she] was able to provide accurate basic autobiographical details going back to her school days. She had however considerable difficulty elaborating and providing details' (Warrington and Duchon, 1992, p. 438). On two tests of memory for public events and famous faces, which covered time periods going back to the 1930s and 1940s, respectively, she showed a marked, temporally ungraded impairment on recall testing.

On recognition testing, there appeared to be a temporally graded deficit for famous faces and a relatively ungraded deficit for famous news events.

There is little doubt that bilateral hippocampal pathology, both that which was long-standing and that which resulted from surgery, made a major contribution to her memory loss. It remains possible that the right temporal neocortical removal exacerbated her anterograde faces memory deficit and played a part in this deficit being more marked than that for words. Her *retrograde* amnesia is, however, more problematical. She had suffered from severe temporal lobe epilepsy from the age of 25 years. Strictly speaking, her retrograde amnesia can be considered to be 'retrograde' to her surgery or 'retrograde' to the clinical manifestation of her epileptogenic lesion in 1932. Deficits in both autobiographical memory performance (Viskontas *et al.*, 2000) and public events memory tests (Bergin *et al.*, 2000) have been associated with temporal lobe epilepsy. In addition, she suffered from a severe psychiatric condition, which probably involved her taking significant amounts of psychotropic medication. These two factors may also have contributed to impaired learning of public events information over that time period. It has been shown (Kapur *et al.*, 1999) that media exposure plays a major role in performance on public events memory tests. It is unclear how much she was interested in, and exposed to, news events over the relevant time periods of the tests in question, and this may have contributed to her very poor (at floor level) scores on sections of the public events memory tests. Finally, in the case of one of the remote memory tests, that dealing with famous faces, it has been shown that right temporal lobe neocortical lesions may impair performance (Warrington and James, 1967), and this aspect of her pathology may have contributed to her deficit on that test. Although it remains possible, therefore, that her bilateral hippocampal lesions played a role in the remote memory deficits that she displayed, some degree of uncertainty remains about the precise contribution of medial temporal lobe structures and other anatomical/clinical variables to that aspect of her memory functioning.

Although the papers relating to Case 5 make an important contribution to the debate surrounding mechanisms underlying remote memory loss, Case 2 offers only suggestive evidence on this issue, due to the absence of detailed assessment of retrograde memory functioning. This patient was reported to have had an initial retrograde amnesia stretching back 4 years, with this later reducing to a period of several months. The neuroanatomical extent of his lesion included, on the left (ablated) side, anterior hippocampus (sparing the posterior 2 cm), anterior parahippocampal gyrus including the uncus, amygdala, all three major temporal lobe gyri (superior, middle and inferior) and a portion of the occipitotemporal gyrus. The right temporal lobe pathology found at post-mortem, which was presumably long-standing and the primary cause of his epilepsy, was much more limited and included all of the hippocampus, with pyramidal cell layers and dentate gyrus involved. Although right temporal

neocortex was not found to have any pathology, there was an element of diffuse gliosis in the gyral white matter of the parahippocampal, occipitotemporal and inferior temporal gyri. Secondary changes were also seen in the fornix, more on the left than on the right, and in the anterior commissure. If one takes at face value the absence of major retrograde amnesia in this case, it would seem to contrast not only with the patient in Case 5, but also similar cases (e.g. Cipolotti *et al.*, 2001) that have been interpreted (Nadel and Moscovitch, 2001) as supporting multiple trace theory rather than the standard model of memory consolidation. A further interesting feature of Case 2, and also of Case 1, is the fact that both patients were able to take on meaningful occupational activity that was similar to that which they had previously carried out, albeit with certain restrictions, and were also able to retain some postoperative autobiographical events. Thus, the engineer was able to take up work as a draughtsman and, 4 and a half years after surgery, 'he is still able to prepare very complicated blueprints, though tending to work more slowly than before ... he is able to give some account of outstanding occasions, such as his daughter's wedding, 2 years ago. He also knows the address of the house to which he recently moved and can describe its topographical position with reasonable accuracy' (Penfield and Milner, 1958, p. 487). These observations find an echo in recent findings of spared factual learning in patients with medial temporal lobe amnesia (e.g. Vargha-Khadem *et al.*, 1997; Kitchener *et al.*, 1998; Bayley and Squire, 2002) and highlight both the selectivity and the moderate severity of the anterograde memory loss suffered by the two patients in Cases 1 and 2.

## Conclusions

Allowing for the relatively small number of patients in the series of cases with amnesia following unilateral temporal lobe surgery, there are a number of specific lessons that can be drawn from the evidence reviewed here.

1. Since false localization may arise from inter-ictal EEG and even from ictal/subdural EEG discharges, neurophysiological findings in particular need to be considered in the context of results from other investigations.

2. In a few specific instances, ictal semiology may be important in localizing the seizure source. The reports of seizure activity that are offered by patients and by carers may be subject to error. Video EEG recordings represent one of the best sources of evidence for determining the character and nature of seizure activity, but even in these settings there remains a subjective component to the interpretation of some clinical manifestations of seizure activity.

3. Preoperative neuropsychological observations, where such testing was carried out, highlighted the fact that such data may yield reliable localizing information in some instances.

4. Wada observations were made only in some of the cases, but those which were reported did indicate the utility of the

procedure in anticipating the outcome of surgery. However, Wada findings need always to be considered in the context of other clinical findings and investigations.

5. Although a variable degree of remote memory loss has been reported in association with temporal lobe surgery, the elucidation of anatomical mechanisms underlying such memory loss remains problematical, and there is no convincing evidence yet that bilateral medial temporal lobe ablation that is restricted to the hippocampus will result in major retrograde amnesia.

## Acknowledgements

We wish to thank Dr Sallie Baxendale for her comments on this paper, and Mrs Pat Abbott for her help in preparing the manuscript for publication.

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*Received December 16, 2002. Revised May 16, 2003.*

*Accepted June 26, 2003*