Neutralising antibodies to interferon beta during the treatment of multiple sclerosis

G Giovannoni, F E Munschauer 3rd, F Deisenhammer

The significance of the generation of antibodies in response to interferon beta administration is discussed

Patients with multiple sclerosis (MS) receiving interferon beta may develop neutralising anti-interferon beta antibodies (NABs) during treatment. These NABs are clinically relevant and reduce the clinical efficacy of interferon beta. Although there is lack of consensus on how these antibodies should be measured, the relative prevalence of NABs induced by different interferon beta products seems to be consistent between studies. Subcutaneous interferon beta-1b (Betaferon) is the most immunogenic, followed by subcutaneous interferon beta-1a (Rebif), with intramuscular interferon beta-1a (Avonex) being the least immunogenic. Differences between the interferon beta products with regard to their structure/biochemistry, formulation, dose, route of administration, and dose frequency are likely to contribute to these observed differences in immunogenicity. This editorial highlights the consequences of NAB formation on the biological and clinical activity of interferon beta and the implications NABs have for the practising neurologist and patient with MS.

BACKGROUND
Interferon beta is an established first line treatment in relapsing remitting MS. As has been observed with other biological agents, antibodies are sometimes generated in response to interferon beta administration. A subset of these antibodies inhibit or neutralise the clinical activity of interferon beta. This editorial will attempt to clarify technical issues of NABs measurement, the clinical significance of NABs, differences between the currently available interferon beta products, and the clinical implications of NAB development.

ANTIBODIES ELICITED BY INTERFERON BETA
An immune response against protein based drugs is not unusual. For example, neutralising antibodies have been reported during treatment with interferon alfa for viral hepatitis B and C, hairy cell leukaemia, and other types of cancer, during treatment with bovine or porcine insulin for diabetes mellitus, with human growth hormone and factor VIII and IX therapy in haemophilia.

Antibodies can be measured using a "binding assay", such as an ELISA. Only a subset of binding antibodies is neutralising. An in vitro or bioassay is required to identify NABs. A binding assay is usually preferred. The presence of antibodies, before specifically screening for neutralising activity—that is, if the patient is negative for binding antibodies, there is no need to test for NABs. NAB positivity is defined by the ability of a serum sample to neutralise an in vitro biological activity of interferon beta. Although there are many biological activities of type I interferon, the most common assays utilise its antiviral effects or its ability to induce the MxA protein (myxovirus-resistance protein). The antiviral assay is currently the standard method recommended by the World Health Organisation to measure interferon activity and is based on the measurement of the virus induced cytopathic effect. Unfortunately, different laboratories often use different cell lines and viruses and hence these assays are not standardised. The MxA induction assay is becoming increasingly popular. Of the usual biological markers of interferon beta activity in peripheral blood (neopterin, β-2-microglobulin, 25' oligoadenylate synthetase, and Mx proteins (A and B)), Mx proteins have a relatively high dose dependent specificity for type I interferons.

PROBLEMS ASSOCIATED WITH NABS ASSAYS
(1) NABs assays are not necessarily a measure of antibodies that bind interferon beta. This can lead to false positive readings because of non-antibody factors that inhibit the antiviral activity of the interferon. To avoid this NAB quantisation should include serial sample dilutions along with controls for toxicity and endogenous interferon activity for each serum sample.

(2) The NAB positivity rate varies depending on the selected sensitivity of the assay. This depends on the type of cells, the virus used, the amount of virus added, the initial dilution of the test serum, and the amount of interferon added to the assay that the antibodies must neutralise. In the case of the MxA assay, the method and reagents used to quantify Mx production are critical. The amount of interferon added to the bioassays is one of the more controversial aspects; adding too much interferon can result in identifying patients as positive when they have levels of NABs that are probably clinically irrelevant.

(3) The interpretation of when a patient is NABs positive varies from study to study. Some regard positivity as being two consecutive positive results (Berlex/Scherering) whereas others base positivity on a single positive result (Serono/Biogen). Furthermore, there is no consensus among the pharmaceutical industry with regard to the level of titre at which NABs become biologically relevant, and therefore the proportion of patients developing NABs is reported using different titre cut off levels.

CURRENTLY LICENSED INTERFERON BETA PRODUCTS USED IN THE TREATMENT OF MS
Three interferon products have been marketed for the treatment of MS: Betaferon (Schering AG), which is marketed as Betaseron (Berlex Laboratory) in the United States, Avonex (Biogen), and Rebif (Ares-Serono). Product characteristics are compared in table 1. The immunogenicity of these three products has been examined in all of the phase 3 and phase 4 clinical trials. The lack of standardisation of assay techniques and definitions of seropositivity make it very difficult to compare the reported immunogenicity of the different products between clinical studies. However, a sufficient number of studies have now been performed to draw some conclusions. Among the licensed products, interferon beta-1b is more immunogenic than the interferon beta-1a products. The difference in immunogenicity between interferon beta-1b and interferon beta-1a is not surprising given that interferon beta-1b has a cysteine to serine substitution at position 17, a deletion of the N-terminal methionine residue, and, unlike the natural protein is produced in E coli bacteria and is therefore non-glycosylated. Interferon beta-1a on the other hand is produced in mammalian cells, from the natural human gene sequence and is glycosylated.

Abbreviations: MS, multiple sclerosis; NAB, neutralising anti-interferon beta antibody.
Somewhat surprising is the reported differences in immunogenicity between the two interferon beta-1a preparations, Avonex and Rebif. This may be attributable to differences in the manufacturing, storage, and formulation of these products. For example, the difference in the immunogenicity between the closely related interferon alfa-2a and interferon alfa-2b (interferon alfa-2a was approximately 10 times more immunogenic than interferon alfa-2b) was attributed to a difference in the manufacturing, storage, and formulation of these products. Differences in the immunogenicity of interferon beta-1b have been observed for Avonex. The interferon beta-1a Avonex preparation used in the pivotal phase 3 trial resulted in 24% of the treated patients developing NABs. However, the immunogenicity has subsequently decreased fivefold to between 2% and 5%, presumably as a result of the introduction of a new manufacturing process for the commercial product. In comparison, 12.5–24% of patients treated with a different interferon beta-1a formulation (Rebif) develop NABs. This difference may be explained by the route, dose, and frequency of protein administration.

In the OWIMS study 5.3% of patients receiving interferon beta-1a (Rebif) 22 µg subcutaneously weekly developed NABs compared with 16.3% receiving 44 µg subcutaneously weekly. Similarly, in a dose comparison study of interferon beta-1a patients receiving 30 µg by intramuscular injection weekly had a lower rate of NABs formation than the group receiving 60 µg by intramuscular injection weekly. 2.2% compared with 5.8% (Professor M Clanet, platform presentation ENS 2001). In comparison in the PRISMS study of interferon beta-1a (Rebif) and its extension phase, about 14% of patients receiving 44 µg three times a week developed NABs compared with 24% receiving 22 µg three times a week. The lower incidence of NABs in the high dose Rebif group may be a spurious finding as a result of persistent circulating interferon beta-1a quenching or artificially lowering NAB titres. At least 10% of serum samples from patients receiving Rebif 22 µg thrice weekly have detectable levels of interferon beta-1a up to 48 hours after a subcutaneous injection. You would expect this figure to be higher with Rebif 44 µg thrice weekly. Another comparison of the immunogenicity of the interferon beta-1a products comes from the recently completed 12 month head to head EVIDENCE study, 25% of patients receiving Rebif 44 µg thrice weekly developed NABs compared with 2% of Avonex treated patients (http://www.fda.gov/ohab/review/finsber03072021.pdf). Although these results are preliminary and incomplete they are not consistent with the PRISMS study and need clarification. However, they do provide further evidence that there are differences between the two interferon beta-1a products with regard to their ability to induce NABs.

### Table 1: Currently licenced interferon beta products used to treat RRMS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Betaferon/ Betaseron interferon-1b</th>
<th>Avonex interferon-1a</th>
<th>Rebif interferon beta-1a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Schering AG, Germany / Berlex, CA, USA</td>
<td>Biogen, France</td>
<td>Ares-Serono, UK</td>
</tr>
<tr>
<td>Approved</td>
<td>1995 in Europe</td>
<td>1997 in Europe</td>
<td>1998 in Europe</td>
</tr>
<tr>
<td>Site of production</td>
<td>E coli bacteria cells</td>
<td>Chinese hamster ovary cells</td>
<td>Chinese hamster ovary cells</td>
</tr>
<tr>
<td>Amino acid sequence</td>
<td>Cysteine mutation at position 17</td>
<td>Identical to human interferon beta</td>
<td>Identical to human IFNβ</td>
</tr>
<tr>
<td>Glycosylated</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>18.5 KDa</td>
<td>22–24 KDa</td>
<td>22–24 KDa</td>
</tr>
<tr>
<td>Excipients</td>
<td>Human serum albumin, di and monosodium phosphate, sodium chloride final pH 7.2</td>
<td>Human serum albumin, di and monosodium phosphate, sodium chloride final pH 7.2</td>
<td>Mannitol, human serum albumin, sodium acetate, acetic acid, sodium chloride, final pH 3.8</td>
</tr>
<tr>
<td>Therapeutic use</td>
<td>RRMS, secondary progressive MS</td>
<td>RRMS</td>
<td>RRMS</td>
</tr>
<tr>
<td>Therapeutic effect</td>
<td>Decreases frequency and severity of relapses</td>
<td>Decreases frequency of relapses</td>
<td>Decreases frequency and severity of relapses</td>
</tr>
<tr>
<td>Average weekly dose</td>
<td>875 µg</td>
<td>30 µg</td>
<td>22 µg and 44 µg</td>
</tr>
<tr>
<td>Specific activity</td>
<td>32 MIU/mg</td>
<td>&gt;300 MIU/mg</td>
<td>&gt;300 MIU/mg</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Subcutaneous (SC) only</td>
<td>Intramuscular (IM) only</td>
<td>Subcutaneous (SC) only</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>but different in effect</td>
<td>IM availability is threefold higher than SC</td>
<td>SC and IM produced equivalent exposure to IFNβ</td>
</tr>
<tr>
<td>Assay used for NABs analysis</td>
<td>CPE</td>
<td>CPE</td>
<td>CPE</td>
</tr>
</tbody>
</table>
The effect of interferon beta initially seemed to have little clinical and MRI efficacy in the presence of NABs. However, the impact of NABs on the clinical benefit of interferon-beta treatment is now more clear than that for interferon alfa, and the development of NABs to interferon beta has been shown to be inhibited by NABs. Studies have shown a consistent correlation between the presence of NABs and decreased efficacy (table 2). The beneficial shift in immune cell populations has been shown to be produced by NABs. The development of NABs to interferon beta is probably not an all or nothing phenomenon with the avidity, a measure of both titre and antibody affinity, as well as the dose of interferon playing a part. Rudick et al showed that the development of NABs to interferon beta-1a (Avonex) resulted in a titre dependent reduction in Mx protein and loss of therapeutic benefit. With interferon beta-1b (Betaseron), where

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Duration of follow up</th>
<th>Assay</th>
<th>Betaferon (Betaseron)</th>
<th>Avonex</th>
<th>Rebif</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fernandez et al.</td>
<td>12 months</td>
<td>CPE</td>
<td>31 24</td>
<td>No 22 14</td>
<td>No</td>
</tr>
<tr>
<td>Ross et al.</td>
<td>24 months</td>
<td>ANB</td>
<td>311 60</td>
<td>NR 140 NR</td>
<td>NR 143 about 50 NR</td>
</tr>
<tr>
<td>Jacobs et al.</td>
<td>Up to 30 months</td>
<td>CPE</td>
<td>— —</td>
<td>— 141 1 (18 m) 24 (24–30 m)</td>
<td>—</td>
</tr>
<tr>
<td>Myhr et al.</td>
<td>Mean = 11 months</td>
<td>ANB</td>
<td>10 80</td>
<td>NR 9 22</td>
<td>NR</td>
</tr>
<tr>
<td>Rudick et al.</td>
<td>24 months</td>
<td>CPE</td>
<td>43 7 (12–18 m)</td>
<td>Yes 70 6 (18 m)</td>
<td>Yes</td>
</tr>
<tr>
<td>Jacobs et al.</td>
<td>24 months</td>
<td>NR — —</td>
<td>158 14 (1 y)</td>
<td>NR — —</td>
<td></td>
</tr>
<tr>
<td>Giovannoni et al.</td>
<td>Mean = 31 months (range = 12–48 m)</td>
<td>CPE</td>
<td>32 38</td>
<td>No 18 6</td>
<td>No</td>
</tr>
<tr>
<td>Kiviolek et al.</td>
<td>Mean = 8–11 m (range 1–46 m)</td>
<td>CPE</td>
<td>48 44</td>
<td>No 20 5</td>
<td>No</td>
</tr>
<tr>
<td>Deisenhammer et al.</td>
<td>17 months</td>
<td>MxA</td>
<td>28 50 (1 y)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Rice et al.</td>
<td>8 years</td>
<td>MxA</td>
<td>0 50 (1 y)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cook et al.</td>
<td>16 months</td>
<td>MxA</td>
<td>64 39 (&gt;1:20)</td>
<td>Yes 98 9 (&gt;1:20)</td>
<td>Yes</td>
</tr>
<tr>
<td>European Study Group</td>
<td>36 months</td>
<td>MxA</td>
<td>360 27 3</td>
<td>Yes —</td>
<td>—</td>
</tr>
<tr>
<td>IFNβ MS Study Group</td>
<td>36 months</td>
<td>MxA</td>
<td>91 38 (3 y)</td>
<td>Yes —</td>
<td>—</td>
</tr>
<tr>
<td>Antonelli et al.</td>
<td>24 months</td>
<td>CPE</td>
<td>— —</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>OWIMS</td>
<td>48 weeks</td>
<td>CPE</td>
<td>— —</td>
<td>—</td>
<td>—</td>
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<tr>
<td>PRISMS-2</td>
<td>24 months</td>
<td>CPE</td>
<td>— —</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PRISMS-4</td>
<td>48 months</td>
<td>CPE</td>
<td>— —</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>INCOMIN</td>
<td>24 months</td>
<td>CPE</td>
<td>96 30 (1 y)</td>
<td>No 88 7 (1 y)</td>
<td>No</td>
</tr>
<tr>
<td>SPECTRIMS</td>
<td>36 months</td>
<td>CPE</td>
<td>31 31</td>
<td>— 44 2</td>
<td>52 15</td>
</tr>
<tr>
<td>Bertolotto</td>
<td>6–18 months</td>
<td>CPE</td>
<td>29 31</td>
<td>294 5 (&gt;1:5) 2 (&gt;1:20)</td>
<td>298 33 (&gt;1:5) 25 (&gt;1:20)</td>
</tr>
<tr>
<td>EVIDENCE</td>
<td>12 months</td>
<td>CPE</td>
<td>31 31</td>
<td>— 44 2</td>
<td>—</td>
</tr>
</tbody>
</table>

Elisa = enzyme linked immunosorbent assay. ANB = antiviral neutralisation bioassay. CPE = cytopathic effect. AVA = anti-viral activity. *EVIDENCE Study, 2002, preliminary data, http://www.fda.gov/cber/review/finbser030702r1.pdf. **In the EVIDENCE study p values were not presented, but the memorandum mentions that there were differences between NAB+ve and NAB-ve patients receiving Rebif 44 µg sc thrice weekly. The beneficial shift in immune cell populations has been shown to be produced by NABs. The development of NABs to interferon beta-1a (Avonex) resulted in a titre dependent reduction in Mx protein and loss of therapeutic benefit. With interferon beta-1b (Betaseron), where

For interferon beta treatment normally induces.

Perini showed that interferon beta treatment of MS patients results in a decrease in the CD16+, CD14+ cell population. Patients that become NAB+ revert to pretreatment levels of these cells. All these studies indicate that the biological effects of interferon beta are inhibited in patients with NABs.

In the pivotal interferon beta-1a (Avonex) trial, a strong trend towards reduced treatment benefit on MRI disease activity in NABs positive patients was seen. The PRISMS four year, but no two year, data provide the clearest correlation between positive NAB status and loss of therapeutic benefit. With interferon beta-1b (Betaseron), where
the incidence of NABs is sufficiently high and develops earlier, clinical effects have been seen in two year studies (see table 3). As expected NAB positive patients have less systemic side effects or flu-like symptoms compared with NAB negative patients. No differences with regard to local or cutaneous reactions between the NABs positive and negative patients were noted.

**Strategies to reduce or reverse the development of NABs**

Patients with low titres of NABs tend to become NAB negative and occasionally titres oscillate between low positive and negative over time. Whether these conversions or oscillations are attributable to technical aspects related for example to the timing of the sample collection in relation to treatment or represent “B cell tolerance” needs further clarification. In the case of interferon beta-1b some NAB positive patients revert to NAB negative status over two to five years of follow up. Similarly, it has been reported that NAB positive interferon beta-1a (Rebif) treated patients can also revert to negative status. In the PRISMS four year study the proportion of patients who were NAB positive at least once but not at the last visit was 0% with 22 µg thrice weekly and 13% with 44 µg thrice weekly. This second observation suggests a dose effect and may explain why the reversion from NAB positive to negative may be more commonly observed with interferon beta-1b (Betaferon) in which the actual quantity of interferon beta protein administered is greater—that is, 875 µg/week for Betaferon compared with 30 µg/week for Avonex and 66 or 132 µg/week for Rebif. In our experience patients with high titres of NABs seldom revert to being negative.

Reducing or reversing the development of NABs to recombinant therapeutic proteins in potentially life threatening conditions is a high priority, for example, in haemophilic patients intensive immunosuppression is used to reverse NABs formation to factor VIII. In an open labelled study of 161 MS patients, receiving interferon beta-1b (Betaferon, 8 MIU subcutaneously on alternate days), randomised to receive either intravenous methyl-prednisolone 1 g monthly for 12 months compared with no corticosteroids the prevalence of NABs at 15 months in the prednisone treated group was 12.1% compared with 26.8% in untreated group, a relative reduction of 54.9%. Interestingly, in one study in which NAB positive Betaferon patients were directly switched to Avonex, 53% and 75% reverted to NAB negative after one and two years, respectively. Combining other immunosuppressive therapies with interferon beta, for example, azathioprine or mitoxantrone, to reduce the incidence of NABs is another strategy worthy of investigation. The induction of tolerance is the proposed mechanism that underlies the observed reduction in NABs to recombinant factor VIII when haemophilic patients are transferred from intermittent to continuous replacement therapy and may also explain the disappearance of NABs in some patients treated with higher doses of interferon beta administered more frequently.

**IMPLICATIONS FOR THE PRACTICING NEUROLOGIST**

The following conclusions and/or recommendations can be made:

1. The evidence that NABs abrogate the biological and clinical effects of interferon beta is beyond reasonable doubt.
2. NABs are cross reactive between different interferon beta products and interferon beta-1b is more immunogenic than interferon beta-1a.
3. The immunogenicity of the different interferon beta preparations should be one of the factors that need to considered when starting treatment.
4. Ideally patients taking interferon beta who have ongoing disease activity—that is, frequent disabling relapses—should be screened for NABs, particularly if the clinician is considering switching preparations and/or increasing the dose of interferon beta. If positive another treatment such as glatiramer acetate or mitoxantrone hydrochloride should be considered. Interferon therapy can only be reconsidered if the patient becomes NAB negative.
5. Once high titre NABs have developed they tend to persist. If reversal of NABs positivity does occur it tends to be in patients with low titres.
6. In the UK routine screening for NABs cannot be performed at present in view of the poor availability of validated assays, the lack of assay standardisation, and the lack of clinical data regarding the significance of low titre NABs.
7. If routine screening becomes available the optimal time to test for NABs is between 6–12 months for interferon beta-1b and 12–24 months for interferon beta-1a.
8. Whether interferon beta therapy should be stopped in all patients who are NAB positive, irrespective of their disease activity, requires further study. This question can only be answered using standardised clinical protocols and well validated assays.

**CONCLUSION**

There are accumulating data that indicate that NABs are clinically relevant in MS patients receiving interferon beta therapy. Neurologists need to consider this when starting treatment and assessing treatment failures. At the same time neurologists need to keep the issue of NABs in perspective. NABs are clearly not the only reason for treatment failures. Not all patients respond to interferon beta treatment and the reasons for this are still unknown. Unfortunately, no factor has yet been identified that reliably predict responsiveness. The issue of NABs has particular relevance in the UK in which interferon beta therapy has been deemed by the National Institute of Clinical Excellence (NICE) not to be cost effective. If interferon beta treatment were to be stopped in all patients who became NAB positive this would clearly have a positive impact on the long term cost effectiveness of interferon beta treatment.

**Conflicts of interests**

All authors have participated in meetings sponsored by, and received travel grants and honorariums from, pharmaceutical companies marketing treatments for multiple sclerosis; our departments have received financial support for participation in randomised controlled trials of interferon beta-1b (Betaferon, Schering), interferon beta-1a (Avonex, Biogen; Rebif, Serono), glatiramer acetate (Copaxone, Teva), and mitoxantrone (Novatrone, Immunex) in multiple sclerosis. All authors have received honorariums for acting in an ad hoc capacity as advisors to various pharmaceutical companies who have drug development programmes for multiple sclerosis. GG is the principal investigator at the National Hospital for Neurology and Neurosurgery in a trial of Natalizumab (Anemegen) sponsored by Biogen Inc; GG is also a member of the editorial board of a MS related publication sponsored by Serono. FD is currently a...
treating physician in the Antegren trial, sponsored by Biogen, the BENEFIT trial, sponsored by Serono, and the BEAN trial, sponsored by Schering. FEM serves as an ad hoc consultant to Biogen.

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Authors’ affiliations
G Giovannoni, Department of Neuroinflammation, Institute of Neurology, London, UK
F Deisenhammer, Department of Neurology, University of Innsbruck, Innsbruck, Austria

Correspondence to: Dr G Giovannoni, Department of Neuroinflammation, Institute of Neurology, Queen Square, London WC1N 3BG, UK. G.Giovannoni@ion.ucl.ac.uk

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Temporal lobe epilepsy

Surgical treatment of temporal lobe epilepsy
S F Berkovic

It is important that presurgical evaluation of patients with temporal lobe epilepsy is carried out by multidisciplinary teams

The paper published in this issue by Jutila et al (this issue, pp 486–94) adds to the literature regarding surgical treatment of temporal lobe epilepsy.1 This paper presents results from a national centre for adults in Finland. The strength of this report is that it has long term follow up from a relatively defined population. The benefit of temporal lobectomy in treatment of refractory temporal lobe epilepsy has been accepted for many years and a recent creative controlled trial from a Canadian group clearly established its efficacy over medical therapy.2 The efficacy of treatment appears to be maintained over the long term, although there is a significant attrition of cases who are initially seizure free for the first 12 months. However, according to the Finnish experience reported here, such late relapses generally do not represent a return to severe intractable temporal lobe epilepsy. Can selection of cases be improved and why do not all patients respond?3 These issues have been central to over 100 studies of temporal lobectomy in the last decade (for review see Hennessy et al). Relatively few markers have emerged as definitively helping in choice of patients. The finding of a localised lesion on magnetic resonance imaging and a predominance of focal seizures were positively associated with good outcome by Jutila et al, findings that are supported by earlier reports.4 The current study also found earlier age of onset as predictive of good outcome, but this has not emerged as a robust factor in previous studies.5 Methodological problems in such post hoc analyses can be critical.6 Improvement in our ability to select cases for operation, and perhaps more importantly reject inappropriate cases, will await more detailed studies. However, Jutila et al found that some of their “palliative” cases, by which they meant patients in whom there were less convincing evidence for a unilateral confined epileptogenic zone, did have a significant seizure free rate. The study emphasises the importance of a multidisciplinary team in the complex presurgical evaluation of candidates. Seizure surgery should be performed in centres with multidisciplinary expertise and experience to maximise outcomes.

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Author’s affiliation
S F Berkovic, Director, Epilepsy Research Institute, Level 1, Neurosciences Building, Austin & Repatriation Medical Centre, Banksia Street, West Heidelberg, Victoria 3081, Australia
Correspondence to: Professor S F Berkovic; s.berkovic@unimelb.edu.au

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Alzheimer’s disease

Hippocampal atrophy and neocortical dysfunction in early Alzheimer’s disease
J-C Baron

Is there a relationship between medial temporal lobe atrophy and brain dysfunction in Alzheimer’s disease?

Although it would appear straightforward that neuronal loss in and by itself explains the cognitive deficits in Alzheimer’s disease (AD), things are considerably more complicated as shown by Garrido et al (this issue pp 508–16). In this elegant study of nine patients with very mild AD, the authors assessed the relationships between hippocampal volume (assessed with structural magnetic resonance imaging (MRI) and voxel based morphometry), and the changes in cerebral perfusion (mapped with single photon emission computed tomography (SPECT)) during a verbal recognition memory task. Increasing hippocampal atrophy was associated with reduced activation of the extensive left sided network normally engaged by this episodic task, but also with increased activation in several frontal regions. They interpret these findings as suggesting that medial temporal lobe (MTL) pathology negatively modulates structures belonging to this network and reciprocally connected with the hippocampus, while also positively modulating activity in non-specific executive control centres—also indirectly connected to the hippocampal complex—probably reflecting an attempt by the AD brain to maintain performance by increased attentional/strategic load.

Although this study has some acknowledged limitations, the results are convincingly robust. Furthermore, they are entirely consistent with other work. Using positron emission tomography, Meguro et al reported a significant correlation between the degree of hippocampal atrophy and the severity of resting state glucose hypometabolism in the ipsilateral parietotemporal association cortex (PACx).7 This correlation remained significant even after controlling for degree of dementia, thus ruling out a simple effect of disease severity. This suggested that the striking PACx hypometabolism present from the very early stages of AD may not simply reflect the degree of local pathology but also in part a remote effect...
Alzheimer’s disease

Meaningful treatment outcomes in Alzheimer’s disease

A Burns

Goal Attainment Scaling allows for problems identified by patients and carers to be the focus of treatment

The explosion of interest in clinical trials for the treatment of the symptoms of Alzheimer’s disease has resulted in an industry developing instruments, which assess the disorder and the changes that can occur as a result of interventions. The ability to quantify phenomena is an essential prerequisite to measure the effects of any treatments. The question of the relevance of a purely cognitive approach to monitoring change in Alzheimer’s disease—that is, the understandable doubt as to the clinical relevance of, say, remembering eight as opposed to four of a list of 12 words—led to the development of global assessment scales, which reflect the myriad expressions of the disease. Originally they were uncomplicated, their comparative simplicity was their strength, rating patients as improved, the same, or worse, on a seven point scale. The rationale was that if a clinician noticed an improvement, then that in itself was significant. Their ability to capture changes in cognitive function, improvements in behavioural and psychological symptoms, and maintenance of daily functioning in conjunction with caregiver reports, attest to their strength.

In the paper by Rockwood et al (this issue, pp 500–7), the beneficial effects of treatment are further explored using a technique called Goal Attainment Scaling (GAS). GAS is similar to global assessments, but measures individual problems identified by patients and carers, elicited by an open ended introductory question. Zero is taken as the baseline on a five point scale and follow up captures symptoms which are a lot better (+2), a little better (+1), no change (0), a little worse (−1), and a lot worse (−2). Thus, attention is concentrated on specific problems identified by patients and their carers which become the goals of treatment. In a study of 108 patients with mild to moderate Alzheimer’s disease, patients and carers identified a mean of nine goals per subject compared to three identified by their doctors. Patients and carers were particularly likely to value leisure activities and social interaction and they also show a consistent improvement across all goals. For physician ratings, some goals improved and others deteriorated. There was a modest, correlation between GAS scores, a global assessment, and cognitive function.

GAS represents a novel way of measuring meaningful outcomes for patients and carers in Alzheimer’s disease, but there is no reason to think it would be any different for other types of dementia. Patients’ expectations of treatment and their aspirations for improvement can now be documented. The technique helps us to challenge how we should measure the effects of interventions in dementia, puts the patient and their carer at the forefront of determining benefits, and also helps to challenge our assumption that every aspect of a patient’s illness needs to improve for that treatment to be regarded as successful.

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Charles Bonnet hallucinations

Cortical bricks and mortar

D H ffytche

The cortical microanatomy of cells in retinotopic regions may determine the geometry of hallucinations

... il voit les Bâtiments s'élèver sous ses yeux et lui offrir toutes les Parties qui entrent dans leur Construction extérieure.

Charles Bonnet's visually impaired grandfather, although remembered (through the eponymous syndrome) for his hallucinations of figures, animals, and objects, also saw brickwork and scaffolding patterns. Largely ignored in the literature, these grid-like phenomena are experienced by more than 70% of patients with visual hallucinations secondary to eye disease. They are also reported by patients with visual pathway infarcts and by normal sighted subjects during visual sensory deprivation, stroboscopic stimulation, the hypnotagogic state, and under the influence of psychedelic drugs. Their ubiquitous and stereotyped nature led Heinrich Klüver to propose that the pattern geometry reflected a fundamental visual mechanism, although he realised that its identification would await future developments in visual neuroscience. In this issue, Burke provides new neurophysical observations of his own hallucinated brickwork and dot patterns which bring us a step closer to understanding their underlying neurobiology (this issue, pp 535–41). 3

Burke's hallucinations followed the development of bilateral macular holes and were seen in sufficient detail to estimate the visual angle subtended by repeating pattern elements. When transformed into cortical distance, Burke found a striking similarity between the separation of brickwork courses in his hallucinations and the separation of cytochrome oxidase stripes in the extrastriate visual cortical area, V2. Similarly, he found the separation of hallucinated dots matched the separation of cytochrome oxidase blobs in the primary visual cortex, V1. Cytochrome oxidase staining identifies cortical subcompartments which, Burke argues, are particularly susceptible to deafferentation due to their high metabolic demands. In macaque visual cortex, V1 blobs have a higher concentration of cells specialised for colour than the surrounding interblob regions. Similarly, V2 stripes, depending on their thickness, have a higher concentration of cells specialised for orientation/direction or colour. The retinotopic organisation of V1 and V2 is such that neighbouring cells along the axis of a V2 stripe or along a row of V1 blobs code a specific trajectory within the visual field. Burke proposes that, following deafferentation of macular visual cortex, increased spontaneous activity in V2 stripes results in stereotyped brickwork hallucinations and, in V1 blobs, dot pattern hallucinations.

A link between cortical architecture and the geometry of pathological visual percepts was suggested as early as 1941 by Karl Lashley, with respect to his own migraine aura, and several anatomical explanations have been offered. 4 Burke's hypothesis moves the field forward in that his is the first to account for different types of pattern hallucination and, in particular, to provide a plausible explanation for brickwork. Our current understanding of visual hallucinations is that they result from activity within populations of cells which correlate with percepts of specific visual attributes. If Burke's proposal is correct, it suggests that, in retinotopic regions at least, the cortical microanatomy of such cells defines the geometry of their associated hallucinations—in a sense, “seeing” the brain from the inside.

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Author's affiliation
D H ffytche, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK
Correspondence to: Dr D H ffytche; d.ffytche@iop.kcl.ac.uk

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