those of the control group, whereas the whole blood Mn concentrations were not significantly different ($p=0.086$) between the two groups.

This is the first study to evaluate the CSF Mn concentrations in patients with symmetric pallidal hyperintensities on T1 weighted MRI. Hyperintensity on T1 weighted MRI is associated with many factors, including calcification, lipid, haemorrhage, and Mn, but the pattern of MRI abnormalities in all the five patients was identical with that seen because of Mn deposition and the serum or whole blood Mn concentrations were often increased.¹⁻³ In the blood, Mn can bind to transferrin in the trivalent state and to albumin or α_2 -macroglobulin or low weight solutes in the divalent state. The blood Mn is transferred to the brain through the blood-brain barrier by several transport systems.⁴ Recently, increased Mn concentrations were recognised in postmortem tissue samples from the brains of patients with long term parenteral nutrition containing Mn, or severe cirrhosis.^{2,5} From our study, the CSF Mn concentrations were increased more than those in serum and whole blood in all patients and, in particular, patient 4, who had no parenteral nutrition or hepatic failure, showed an increase only in CSF Mn concentration. The CSF Mn concentrations are considered to reflect the accumulation of Mn in the brain tissue most directly of the three Mn concentrations. The reason why patient 4 is connected with Mn may be individual susceptibility.⁶ Moreover, Mn neurotoxicity caused neuropsychiatric symptoms including pyramidal and extrapyramidal signs.¹⁻³ The findings suggest that a high degree of correlation exists between hyperintensity and the CSF Mn concentration, and that the increase may be a most useful marker and predictor of Mn neurotoxicity in patients with symmetric pallidal hyperintensities on T1 weighted MRI. Further studies with more patients are necessary to elucidate a precise correlation between Mn neurotoxicity and the CSF Mn concentration.

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CORRESPONDENCE

The role of the nucleus intercalatus in vertical gaze holding

I was interested to read the report of Janssen *et al.*¹ of a patient with upbeat nystagmus who had had a medial medullary infarct. By contrast with our patient,² their patient had slow phases with a constant velocity, a "vestibular" type of nystagmus of central origin. As noted by Janssen *et al.*, Hirose *et al.*³ have reported on a patient with a medial medullary infarct and upbeat nystagmus; some slow phases were exponential, some of constant velocity.

In the analysis of slow phases it is useful to plot eye velocity against position rather than plot eye position against time. In this representation, the plot of a vestibular type of slow phase with constant velocity is a horizontal straight line. However, when position varies exponentially with time, velocity is a linear function of position:

$$dx/dt = -kx, x = x_0 \exp(-kt)$$

The gradient k is the decay constant. A regression line may be fitted and confidence limits for k established. A more detailed analysis⁴ of the upbeat nystagmus in our patient with a medial medullary infarct confirmed that decay constants were significantly different from zero and therefore not "vestibular". However, the decay constants for the different slow phases varied and the plot of eye velocity against position seemed to be non-linear (figure). It is not surprising slow phases attributable to "integrator failure" might not be strictly exponential. The model of the perihypoglossal nuclei as a pure integrator rests on the assumption that the statics of the eye (the oculomotor plant) can be modelled by a pure "spring and dashpot",

Position-time and velocity-position plots of the slow phase of a vertical nystagmoid jerk.

second order linear differential equation.⁵ This is an approximation for horizontal movements and a greater approximation for vertical eye movements. It also rests on the assumption that the anatomical connections are more simple than in reality. The variability of decay constants is consistent with the findings of Hirose *et al.*³ This may reflect the varying activity of other afferents to the perihypoglossal nuclei. Nevertheless, the approximate linearity of the plots suggest that part of the function of the nucleus intercalatus, the most caudal of the perihypoglossal nuclei, is integration. Perhaps the reason that such a caudal structure may be involved in vertical integration is the need to coordinate vertical head position signals from cervical afferents with integrated head velocity signals from vestibular nuclei.

It would be of interest to know whether velocity-position plots of any of the slow phases of the patient of Janssen *et al.*¹ show a non-zero gradient.

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Bronstein *et al* reply:

We thank Munro for his interest in the patient we reported in this *Journal* with a low medullary lesion and upbeat nystagmus.¹ The lesion probably involved the nucleus intercalatus, the lowermost part of the perihypoglossal nucleus, a nucleus thought to perform integration of ocular-motor signals. For the benefit of the general readership of this *Journal* we should like to clarify that the integration alluded to is mathematical integration. For instance, eye or head velocity signals arriving at such an integrator emerge as approximations of eye or head position signals. Currently accepted theories of ocular-motor function establish that a lesion to a gaze holding integrator produces nystagmus with slow phase velocity showing exponential decay. By contrast, peripheral vestibular lesions cause nystagmus with linear (constant) slow phase velocity.

The current discussion is centred on the findings in three recently reported patients with lesions probably involving the nucleus intercalatus.¹⁻³ The patients reported by Munro *et al.*¹ and Hirose *et al.*³ with large medullary lesions, had predominantly exponentially decaying slow phase velocity. Our patient, with a small paramedian lesion, had nystagmus with linearly decaying slow phase velocity.¹ Following Munro's suggestion we obtained velocity-position plots of single nystagmic beats and found most of them to be linear (horizontal line on velocity-position

Position *v* time and velocity *v* position plots of a single nystagmic beat in the patient described by Janssen *et al.*¹

plots (figure)). Only about 10%–15% of nystagmic beats showed some degree of exponential decay (velocity-position plots with a non-zero gradient). On this basis, as well as on the presence of tilt (otolith) stimulus sensitivity, we argue that a small nucleus intercalatus lesion presents clinically as a central vestibular nystagmus. Larger lesions may damage additional neuronal circuits involved in ocular-motor integration.⁴

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“Summary measure” statistic for assessing the outcome of treatment trials in relapsing-remitting multiple sclerosis

In response to the recently published paper by Liu *et al.*,¹ we wish to initiate further discussion regarding the proposed area under the curve (AUC) summary measure and comment on some inherent difficulties with this method.

In the paper, Liu *et al.* note that when constructing the summary AUC, the “essential components are the sets of serial impairment or disability data, preferably with frequent sampling points for each patient...” This is in fact a crucial point and depending on the schedule of observations, the observed plot of the expanded disability status scale (EDSS) over time can look quite different from the true curve. For example, consider figure D that has been reproduced below from the paper (figure A). This plot of EDSS over time represents a continuum, which in reality is unlikely to be fully observed as patients are not seen on a daily or weekly basis throughout a study because it is not practical to do so. Instead, patients are scheduled to return for assessment at certain times during the study.

If, hypothetically, this patient was seen every 3 months by the study investigator, the observed plot of EDSS over time would appear as figure B. However, if this patient was seen every 6 months during the study instead, the observed plot of EDSS over time would appear as figure C. These two “observed” EDSS curves look different, even though they represent the same underlying curve. It is obvious that the resulting AUC for each plot would also differ in magnitude. If patients could be measured daily to create a smooth, accurate curve, this would not be an issue. In practice, the resulting EDSS curve over time is spiky and uneven and so the AUC measurement is greatly impacted.

It is also necessary to clarify what the proposed AUC summary measure is actually measuring and how it can be interpreted. The interpretation can vary depending on such factors as how baseline values were handled in the calculation of the AUC, whether unscheduled visits were included, and which summary statistics are reported. For example, if scores are “normalised to baseline” as described in the article, patients with completely different baseline EDSS scores can have the same AUC, yet the degree of disability will be greater for the patient with the higher baseline EDSS. From a clinical perspective, the question should be raised, “Do we want to consider the disability of these patients to be the same by using the AUC summary measure?” Likewise, as the article points out, “Caution is necessary in short trials of 2 or 3 years, as fixed neurological deficits are accumulating very slowly, and an increased AUC at the end of a trial may simply represent transient disability which has either resolved or has yet to resolve.” This implies that the AUC summary measure may not be a good indication of irreversible clinical deterioration. The AUC measure may reflect exacerbations rather than sustained disability.

The concept of AUC has been used extensively in other fields with great success. Most commonly, it has been used when measuring either peaked data (outcome variable starts from a baseline, rises to a peak, and then returns to baseline) or growth data (outcome variable steadily increases or decreases with time and does not start to return to its initial value over the period of the study).² Even then, however, AUC is not used in isolation. For example, when used in pharmacokinetic modelling of blood concentration data, the maximum concentration and the time to maximum concentration are also reported. This is because the AUC alone cannot summarise the *shape* of the curve. We think that irreversible disability progression in multiple sclerosis must continue to be measured by time to event and inpatient changes in disability. Improvements in assessment of disability are more likely to come from outcome measures such as the multiple sclerosis functional composite³ that overcome issues with the EDSS such as non-linearity.

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Liu *et al* reply:

We welcome the opportunity to discuss the role of the AUC (area under the plotted curve of disability against time) as a summary measure statistic in treatment trials of multiple sclerosis, although many of the points raised by Simonian and her colleagues simply reiterate those we made in our paper.¹

The first comment considers the impact of the number of points on the shape of the disability curve. We agree that the sampling frequency will alter the shape of the curve and this is precisely why the AUC method is preferable to the conventional approach, which emphasises single or two point assessments. By taking account of data from all the assessment points, the bias highlighted in figures B and C by Simonian *et al* would have a greater chance of averaging out. Obviously, the greater the sampling frequency, the better the approximation to the disability actually experienced (figure A). For pragmatic reasons, in practice, the number of assessments are limited. Trials with a scheduled visit frequency of only 6 months^{2–3} will necessarily be less accurate in following actual in trial disability than those with higher rates of assessment^{4–6} whatever the clinical rating scale tool used. Our approach takes account of this fact.

On the important question of clinical interpretation of the AUC summary measure, we reiterate our argument that the AUC provides an index of in trial morbidity, or as we called it, “total disability experience” (summed transient and irreversible disability). This is clinically meaningful and relevant in short studies involving relapsing-remitting multiple sclerosis, in which many disability