in astrocytes. Furthermore, KIR4.1 loss will also occur when oligodendrocytes are lost in the demyelinating process or astrocyte processes are damaged by mechanisms independent of antibody-mediated and complement-mediated immune reactions. Finally, technical issues of immunocytochemistry (eg, use of frozen vs paraffin sections) and exact staging of lesions might partly differ between the studies.

Do these findings, from independent research groups, mean that research into KIR4.1 in multiple sclerosis should end? We hope not. The reasons for the discrepancies between the investigations might be at least partly technical and call for additional work. Pathological studies using different analytical approaches are also warranted to deepen the understanding of this potentially revolutionary aspect of multiple sclerosis research. Many unanswered questions related to KIR4.1 function still remain. The coexpression of KIR4.1 and aquaporin-4 channels in endfeet of astrocytes and their synergistic effect in maintaining osmotic homeostasis is intriguing, especially when considering that most retinal pathological changes characterised by Müller cell damage are accompanied by changes of the amount or spatial distribution of both channels. Finally, the potential relation between anti-KIR4.1 antibodies and a more general dysfunction of immune-mediated mechanisms in patients with multiple sclerosis deserves further investigation.

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The Glasgow Coma Scale: time for critical reappraisal?

40 years ago, Teasdale and Jennett published their milestone Article on the Glasgow Coma Scale in The Lancet. This standardised clinical scoring system allowed clinicians to assess and communicate neurological change and quantification of consciousness; it also improved outcome prediction and guided treatment decisions. As reviewed by Teasdale and colleagues in The Lancet Neurology, the pioneering work of the Glasgow investigators revolutionised acute brain injury research and set the start of the science of coma, permitting multicentre trials and epidemiological studies that continue to develop rational algorithms for the treatment (or withdrawal thereof) of comatose patients. The role of the scale can hardly be overstated and it’s 40th anniversary should be one of celebration.

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Comment

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Since its original publication, investigators have pointed to the possible shortcomings of the Glasgow Coma Scale and have proposed alternative consciousness scales; however, none have seen the same success as the original. Will the Glasgow Coma Scale one day be dethroned and replaced, or will it remain unmovable for decades to come?

For clinical diagnosis, we note that the Glasgow Coma Scale was not designed to differentiate post-coma patients who awake (ie, open eyes to stimulation) and progressively (over days to weeks) enter a vegetative state (now also labelled unresponsive wakefulness syndrome) or a minimally conscious state. Minimally conscious state refers to those patients who show minimum (and often fluctuating) signs of consciousness but are unable to reliably communicate (table). This recently defined disorder has been further subcategorised based on the complexity of patients’ behaviours: minimally conscious state describes low-level responses (ie, visual pursuit, localisation of noxious stimulation, or contingent behaviour such as appropriate smiling or crying to emotional stimuli) and minimally conscious state MINUS who have non-verbal signs of consciousness not detected by the Glasgow Coma Scale (a diagnostic error rate we estimate at 10% in our intensive care population of patients with acute brain injury). In addition, FOUR also tests specifically for eye movements or blinking to command (requesting to open the eyes manually if closed), permitting the early detection of locked-in syndrome. This ability is much welcomed, given that clinicians might miss this infrequent diagnosis in up to half of patients.

In terms of outcome prediction, some investigators have critisised the Glasgow Coma Scale because it does not incorporate brainstem reflexes (eg, pupil and cornea) or include other clinical signs of bad prognosis such as generalised myoclonus status epilepticus. Another reservation is that the increasing use of intubation has made the scale’s verbal component impossible to measure in many coma patients. For this reason, the FOUR scale proposed a hand-position test in which the patient is asked to make a thumbs-up, fist, or victory sign. This test might be an alternative to the verbal (V) score of the Glasgow Coma Scale and remains testable in intubated patients (about three quarters of the patients with acute brain injury in our intensive care units). Thanks to its ingenious simplicity and ease of use, the Glasgow Coma Scale is, and remains, the widest used and most validated scale worldwide but, as highlighted by Teasdale and colleagues, it should evidently not be assessed or considered in isolation. As any other medical scale, it reduces the complexity of a clinical reality to a set of numbers. The past 40 years have proven that this reductionist yet standardised approach is extremely powerful. To replace or revise such a well-anchored medical standard will not happen overnight. Several other scales and adaptations of the Glasgow Coma Scale have been proposed, but so far

<table>
<thead>
<tr>
<th>Coma state</th>
<th>Vegetative state-unresponsive wakefulness</th>
<th>Minimally conscious state MINUS</th>
<th>Minimally conscious state PLUS</th>
<th>Acute confusional state</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communication</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Response to command</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Non-reflex behavior</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Eye-opening</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
</tbody>
</table>

Table: Clinical characteristics of coma and related states
none has been able to change clinical practice. In the future, multidimensional diagnostic and prognostic assessments will probably integrate information from genomics, biomarkers, electrophysiology, and neuroimaging techniques and classifiers, with knowledge from standardised behavioral scales (including user-independent automated pupil and visual pursuit assessments).

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We declare no competing interests.


Corrections

Ferrari R, Hernandez DG, Nalls MA, et al. Frontotemporal dementia and its subtypes: a genome-wide association study. Lancet Neurol 2014; 13: 686–99—The heading of panel C in figure 2 of this Article has been changed to “Frontotemporal dementia with motor neuron disease”, and some redundant information has been removed from the legend. The figure legend has also been amended to account for this change. Sub headings in tables 3 and 5 have been updated to read “behavioural variant frontotemporal dementia”. The first sentence of the second paragraph of the Discussion has been updated to read “imply complex disease mechanisms”. These corrections have been made to the online version as of June 12, 2014.

Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer’s disease: the M2G-2 criteria. Lancet Neurol 2014; 13: 614–29—In this Position Paper, INSERM U 1127 should have been added to the authors’ affiliations as follows: Centre des Maladies Cognitives et Comportementales, INSERM U 1127, Institut du Cerveau et de la Moelle épinière, Paris, France (Prof B Dubois MD, Prof H Hampel MD, S Epelbaum MD, L C de Sozzo MD). This change has been made to the online version as of July 7, 2014.