in astrocytes.[11] 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.[12] 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 homoeostasis 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.

Massimo Filippi, Maria A Rocca, Hans Lassmann
Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience (MF, MAR), and Department of Neurology (MF, MAR), Scientific Institute and University Ospedale San Raffaele, 20132 Milan, Italy; and Center for Brain Research, Medical University of Vienna, Austria (HL)
m.filippi@hsr.it

MF serves on the scientific advisory board for Teva Pharmaceutical Industries; has received compensation for consulting services or speaking activities from Bayer Schering Pharma, Biogen Idec, Merck Serono, and Teva Pharmaceutical Industries; and receives research support from Bayer Schering Pharma, Biogen Idec, Merck Serono, Teva Pharmaceutical Industries, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, Cure PSP, and the Jacques and Gloria Gossweiler Foundation (Switzerland). MAR has received speakers' honoraria from Novartis, Biogen Idec, and Serono Symposia International Foundation and receives research support from the Italian Ministry of Health and Fondazione Italiana Sclerosi Multipla. HL has received honoraria for lectures from Teva, Novartis, and Biogen and served as a consultant for Amgen and Baxter.

1 Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet* 2004; **364:** 2106–12.
2 Srivastava R, Aslam M, Kalluri SR, et al. Potassium channel KIR4.1 as an immune target in multiple sclerosis. *N Engl J Med* 2012; **367:** 115–23.
3 Bradl M, Misu T, Takahashi T, et al. Neuromyelitis optica: pathogenicity of patient immunoglobulin in vivo. *Ann Neurol* 2009; **66:** 630–43.
4 Kraus V, Srivastava R, Kalluri SR, et al. Potassium channel KIR4.1-specific antibodies in children with acquired demyelinating CNS disease. *Neurology* 2014; **82:** 470–73.
5 Lucchinetti C, Bruck W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. *Ann Neurol* 2000; **47:** 707–17.
6 Lily O, Palace J, Vincent A. Serum autoantibodies to cell surface determinants in multiple sclerosis: a flow cytometric study. *Brain* 2004; **127:** 269–79.
7 Nerrant E, Salsac C, Charif M, et al. Lack of confirmation of anti-inward rectifying potassium channel 4.1 antibodies as reliable markers of multiple sclerosis. *Mult Scler* 2014; published online April 22. DOI:10.1177/1352458514531086.
8 Brickshawana A, Hinson SR, Romero MF, et al. Investigation of the KIR4.1 potassium channel as a putative antigen in patients with multiple sclerosis: a comparative study. *Lancet Neurol* 2014; published online July 7. http://dx.doi.org/10.1016/S1474-4422(14)70141-3.
9 Jin X, Yu L, Wu Y, et al. S-Glutathionylation underscores the modulation of the heteromeric Kir4.1-Kir5.1 channel in oxidative stress. *J Physiol* 2012; **590:** 5335–48.
10 Banati M, Csecsei P, Koszegi E, et al. Antibody response against gastrointestinal antigens in demyelinating diseases of the central nervous system. *Eur J Neurol* 2013; **20:** 1492–95.
11 Schirmer L, Srivastava R, Kalluri SR, et al. Differential loss of KIR4.1 immunoreactivity in multiple sclerosis lesions. *Ann Neurol* 2014; published online April 29. DOI:10.1002/ana.24168.
12 Sharma R, Fischer MT, Bauer J, et al. Inflammation induced by innate immunity in the central nervous system leads to primary astrocyte dysfunction followed by demyelination. *Acta Neuropathol* 2010; **120:** 223–36.

The Glasgow Coma Scale: time for critical reappraisal?

See **Personal View** page 844

40 years ago, Teasdale and Jennett[1] 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[2] 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 oversetimated and it's 40th anniversary should be one of celebration.

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.[3] 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)[4] or a minimally conscious state.[5] 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 PLUS describes high-level behavioural responses (ie, command following, intelligible verbalisations, or non-functional communication).[6] It is important to identify, as early as possible, minimal signs of consciousness in non-communicative patients after brain injury. Patients in minimally conscious state have preserved emotional processing, including pain perception,[7] needing appropriate clinical and analgaesic management.

The Glasgow Coma Scale was developed before the existence of current nosological criteria and neuroanatomical understanding of disorders of consciousness. One of the most frequently observed clinical signs heralding the transition from a vegetative-unresponsive state to a minimally conscious state is the recovery of visual pursuit.[8] However, the Glasgow Coma Scale does not test for eye tracking (which has been shown to be best assessed by presentation of a moving mirror).[9] The scale Full Outline of UnResponsiveness (FOUR; an acronym for the number of components tested: eye, motor, brainstem, and respiratory function, and for the maximum score assigned to each of these components)[10] assesses visual tracking explicitly and so can identify patients in a 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).[11] 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.[12]

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.[3,10] Another reservation is that the increasing use of intubation has made the scale's verbal component impossible to measure in many coma patients.[8] For this reason, the FOUR scale[10] 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).[11]

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,[2] 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

	Coma	Vegetative state-unresponsive wakefulness	Minimally conscious state MINUS	Minimally conscious state PLUS	Acute confusional state
Communication	Absent	Absent	Absent	Absent	Present
Response to command	Absent	Absent	Absent	Present	Present
Non-reflex behavior	Absent	Absent	Present	Present	Present
Eye-opening	Absent	Present	Present	Present	Present

Table: **Clinical characteristics of coma and related states**

none has been able to change clinical practice.[3] In the future, multidimensional diagnostic and prognostic assessements will probably integrate information from genomics, biomarkers, electrophysiology, and neuroimaging techniques and classifiers,[13] with knowledge from standardised behavioral scales (including user-independent automated pupil[14] and visual pursuit assessments).

Steven Laureys, Olivier Bodart, Olivia Gosseries
Coma Science Group, Belgian National Fund for Scientific Research, Cyclotron Research Centre and Neurology Department, University and University Hospital of Liège, Liège, Belgium
coma@ulg.ac.be

We declare no competing interests.

1 Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974; **2:** 81–84.
2 Teasdale G, Maas A, Lecky F, Manley G, Stocchetti N, Murray G. The Glasgow Coma Scale at 40 years: standing the test of time. *Lancet Neurol* 2014; **13:** 844–54.
3 Laureys S, Piret S, Ledoux D. Quantifying consciousness. *Lancet Neurol* 2005; **4:** 789–90.
4 Laureys S, Celesia GG, Cohadon F, et al, European Task Force on Disorders of Consciousness. Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. *BMC Med* 2010; **1:** 68.
5 Giacino JT, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria. *Neurology* 2002; **58:** 349–53.
6 Bruno MA, Vanhaudenhuyse A, Thibaut A, Moonen G, Laureys S. From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. *J Neurol* 2011; **258:** 1373–84.
7 Boly M, Faymonville ME, Schnakers C, et al. Perception of pain in the minimally conscious state with PET activation: an observational study. *Lancet Neurol* 2008; **7:** 1013–20.
8 Majerus S, Gill-Thwaites H, Andrews K, Laureys S. Behavioral evaluation of consciousness in severe brain damage. *Prog Brain Res* 2005; **150:** 397–413.
9 Vanhaudenhuyse A, Schnakers C, Brédart S, Laureys S. Assessment of visual pursuit in post-comatose states: use a mirror. *J Neurol Neurosurg Psychiatry* 2008; **79:** 223.
10 Wijdicks EF, Bamlet WR, Maramattom BV, Manno EM, McClelland RL. Validation of a new coma scale: the FOUR score. *Ann Neurol* 2005; **58:** 585–93.
11 Bruno MA1, Ledoux D, Lambermont B, et al. Comparison of the Full Outline of UnResponsiveness and Glasgow Liege Scale/Glasgow Coma Scale in an intensive care unit population. *Neurocrit Care* 2011; **15**: 447–53.
12 Laureys S, Pellas F, Van Eeckhout P, et al. The locked-in syndrome : what is it like to be conscious but paralyzed and voiceless? *Prog Brain Res* 2005; **150:** 495–511.
13 Laureys S, Schiff ND. Coma and consciousness: paradigms (re)framed by neuroimaging. *Neuroimage* 2012; **61:** 478–91.
14 Suys T, Bouzat P, Marques-Vidal P, et al. Automated quantitative pupillometry for the prognostication of coma after cardiac arrest. *Neurocrit Care* (in press).

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 17, 2014.

Published **Online**
June 17, 2014
http://dx.doi.org/10.1016/S1474-4422(14)70077-8

Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-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 Souza MD). This change has been made to the online version as of July 7, 2014.

Published **Online**
July 7, 2014
http://dx.doi.org/10.1016/S1474-4422(14)70155-3