in individuals who have emerged from minimally conscious state, thereby representing an electrophysiological correlate of the between-network anticorrelations. Moreover, the similarity we noted within the brain network connectivity in individuals who have emerged from minimally conscious state and some with clinically defined unresponsive wakefulness syndrome suggests that these patients should not be labelled as having unresponsive wakefulness syndrome with preserved islands of consciousness, but rather as having functional locked-in syndrome. Indeed, in our opinion, a pattern of spared between-network anticorrelations is inconsistent with the diagnosis of unresponsive wakefulness syndrome.

Finally, we advise on the potential usefulness of combining functional neuroimaging and electrophysiological methods for investigation of chronic disorders of consciousness in patients to overcome the high misdiagnosis rate and help the clinician in differentiating the effect of under arousal, sensory impairment, motor dysfunction, and cognitive disturbance as potential causes of behavioural unresponsiveness. Indeed, paired approaches could improve understanding of the neural correlates of consciousness, enable precise diagnosis and prognosis of disorders of consciousness, and furnish a valid support to design individually adapted clinical and neurorehabilitative management.

We declare no competing interests.

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Authors’ reply

We thank Rocco Salvatore Calabrò and colleagues for their comments about our cross-sectional study of the neural correlates of consciousness in patients who have emerged from a minimally conscious state. Our results showed that between-network anticorrelations were present in patients who had emerged from a minimally conscious state and healthy controls, whereas they were not present in patients with disorders of consciousness—ie, unresponsive wakefulness syndrome and minimally conscious state. This difference suggests that network interactions play a crucial part in sustaining cognitive functions that are necessary to recover from disorders of consciousness. Thus, Calabrò and colleagues inferred that a pattern of spared between-network anticorrelations was inconsistent with a diagnosis of unresponsive wakefulness syndrome, suggesting the potential role of this connectivity pattern in the detection of patients with functional locked-in syndrome.

We agree with Calabrò and colleagues that some patients labelled as having unresponsive wakefulness syndrome or minimally conscious state in the behavioural assessment might show a greater degree of brain connectivity than that expected from their clinical status; however, a few points need to be considered. First, in our study, we investigated the connectivity and metabolism patterns in patients and controls to improve understanding of the neural mechanism underlying sufficient consciousness for functional communication or object use, without inferring any diagnostic classification or predictive model. Such findings, therefore, need further investigation for possible diagnostic or predictive clinical applications.

Functional locked-in syndrome refers to the dissociation between impaired motor responsiveness and preserved functional communication that can only be measured with complementary non-clinical testing. As such, this clinical state can be identified solely through tests showing motor independent evidence of communication—eg, active mental imagery functional MRI paradigms such as playing tennis and brain computer interfaces based on electroencephalography or event-related potentials, or other measures such as pupil dilation. Neither resting-state functional MRI nor fluorodeoxyglucose (FDG)-PET enable the establishment of functional communication and thus cannot identify a patient in functional locked-in syndrome. Hence, a multimodal approach is needed for the clinical assessment of patients who have disorders of consciousness.

In our opinion, the differentiation between functional locked-in syndrome and non-behavioural minimally conscious state is important. Non-behavioural minimally conscious state defines a dissociation between behavioural motor dysfunction and the identified preserved higher cognitive functions only measurable with complementary non-clinical testing. In these patients, no evidence of communication is needed and preserved covert cognitive functions might be detected with tests such as resting-state functional MRI, FDG-PET, resting-state electroencephalography (EEG), active functional MRI showing command following but no functional communication, and EEG combined with transcranial magnetic stimulation.
Correspondence

Furthermore, we agree that the reduction of misdiagnosis is imperative and has been a major challenge for research on disorders of consciousness in the past few decades. However, we would like to emphasise the importance of increasing the accuracy of long-term outcome prediction, which could potentially guide clinicians in decisions about therapeutic intensity and goals of care, and guarantee an improved quality of life for patients and their carers.

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Haematoma expansion and vitamin K antagonist reversal

We read with interest the results of the international normalised ratio (INR) normalisation in patients with coumarin-related intracranial haemorrhages (INCH) trial reported by Thorsten Steiner and colleagues. Their trial was the first multicentre, randomised controlled comparison of fresh frozen plasma (FFP) and four-factor prothrombin complex concentrate (PCC) in patients with intracranial haemorrhage related to vitamin K antagonists (VKA-ICH). In the INCH trial, PCC resulted in more effective INR normalisation (goal INR ≤1·2) within 3 h of initiation and less haematoma expansion at 3 h and 24 h.

We recognise the importance of these findings, although several limitations must be taken into consideration when interpreting the results of the INCH trial. Although an INR goal of 1·2 or less might be a clinically significant endpoint, FFP is unlikely to produce this degree of INR reversal. Use of this INR goal as the primary measure of efficacy might have been inherently biased and favoured PCC administration.

The representation of data for the outcome of haematoma volume reported by Steiner and colleagues must be called into question. The mean absolute change in haematoma volume in the FFP-treated group was 23·7 ml (SD 28·4) and in the PCC group was 9·7 ml (20·9; p=0·023). Although we agree that there seems to be a smaller haematoma volume at 3 h in the PCC group than in the FFP group, the presentation of data when the standard deviation is higher than the mean suggests that these data are not normally distributed. A more appropriate way to present these data would be as median (IQR) with the appropriate statistical test.

Furthermore, a systolic blood pressure goal of less than 160 mm Hg might be reasonable in patients with VKA-ICH. Even though this was accomplished in both groups by the end of intervention, the systolic blood pressure was about 13 mm Hg and 10 mm Hg higher in patients who received FFP at baseline and 3 h after the intervention, respectively. Although blood pressure control was not a prespecified outcome in the INCH trial, this has been associated with haematoma expansion and must be taken into consideration when examining this outcome. Previous findings have shown that with each 10 mm Hg increase in systolic blood pressure, the odds for neurological deterioration (odds ratio 4·45, 95% CI 2·03–9·74), haematoma expansion (1·86, 1·09–3·16), and unfavourable outcome (2·03, 1·24–3·33) are all significantly increased.

Also, Steiner and colleagues suggest that because of the large number of patients needing rescue PCC administration in the FFP group, early reversal with high concentrations of clotting factor replacement is crucial. We agree that early administration of PCC for reversal of INR to a goal of 1·2 or less is important in prevention of haematoma expansion. However, the cause of expansion is multifactorial. This is evident from Steiner and colleagues’ findings of 44% of patients with haematoma expansion at 3 h despite 67% achieving the INR goal in the PCC group. Additionally, a dose-dependent association with thromboembolism has not been fully assessed.

The INCH trial provides the first prospective data showing a benefit of PCC in patients with VKA-ICH. Larger randomised trials of alternative dosing of PCC and assessment of clinical outcomes are needed to find the best balance between anticoagulation reversal and adverse outcomes.

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