Comment on "Preserved Feedforward But Impaired Top-Down Processes in the Vegetative State"

Jean-Rémi King,[1,2,3,4]* Tristan Bekinschtein,[5] Stanislas Dehaene[7,1,3,6]

Boly *et al*. (Reports, 13 May 2011, p. 858) investigated cortical connectivity patterns in patients suffering from a disorder of consciousness, using electroencephalography in an auditory oddball paradigm. We point to several inconsistencies in their data, including a failure to replicate the classical mismatch negativity. Data quality, source reconstruction, and statistics would need to be improved to support their conclusions.

Using electroencephalography (EEG) combined with an auditory oddball paradigm, Boly and collaborators (*1*) investigated the cortical connectivity pattern among 21 patients suffering from disorders of consciousness. Activities from the bilateral primary auditory cortices (A1), the bilateral superior temporal gyri (STG), and the right inferior frontal gyrus (IFG) were estimated, and connection strengths were inferred with dynamic causal modeling (DCM). It was concluded that patients in a vegetative state (VS) differ from normal subjects and patients in a minimally conscious state (MCS) in a single aspect: reduced top-down feedback from IFG to STG.

Although such a top-down anomaly would be compatible with several converging theories of conscious processing (*2*–*4*), the data presented so far do not provide unambiguous support for the conclusions.

First, only a small and heterogeneous sample of patients is studied (13 MCS patients and only 8 VS patients, with different etiologies and recorded from 12 days to 27 years after onset). Their EEG recordings seem noisy, judging from the fact that the classical mismatch negativity (MMN), which is frequently detectable in individual subjects with MCS, VS, and even coma (*5*–*8*), does not appear to be present [see figure 2 and figure S1 in (*1*)]. Instead, their event-related potentials (ERPs) are abnormal both in terms of topography and time course, with significant effects appearing too early for the MMN. For instance, across their 8 VS patients, an effect of sound deviancy is reported as shortly as 48 ms after the tone change [figure 2 in (*1*)], with a surprisingly high significance level of $p < 10^{-3}$ given that, at this time, their figure S1 does not even indicate consistent signs for all patients (in fact, the group statistics appear dominated by a single individual, patient VS1). The small ERP component found around 50 ms has been previously observed in healthy subjects performing identical paradigms [e.g., (*9*)] but is believed to reflect stimulus-specific adaptation rather than genuine mismatch detection. Individually, the vast majority of their patients failed to present a significant MMN at any latency [(figure S1 in (*1*)]. Although bedside recordings may be noisy and lesions may distort the ERPs, we and our colleagues routinely record the MMN with satisfactory latencies and standard topographies in similar patients (Fig. 1). Detection of this ERP component should be an indispensable quality check prior to source reconstruction and a fortiori to DCM.

Second, from these scalp data, the authors attempted to reconstruct the activation of five distinct but close cortical regions, using MMN source

[1]Commissariat à l'Energie Atomique et aux Energies Alternatives, Division of Life Sciences, Institute of Bioimaging, Neurospin, Gif sur Yvette, 91191 France. [2]Ecole Doctorale Cerveau Cognition Comportement, Université Pierre et Marie Curie-Paris 6, Paris, 75005 France. [3]Institut National de la Santé et de la Recherche Médicale, Cognitive Neuroimaging Unit, Gif sur Yvette, 91191 France. [4]Institut National de la Santé et de la Recherche Médicale, Institut du Cerveau et de la Moelle Épinière, UMRS 975, Paris, 75013 France. [5]Medical Research Council, Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge CB2 7EF, UK. [6]Université Paris 11, Orsay, 91400 France. [7]Collège de France, 11 Place Marcelin Berthelot, Paris, 75005 France.

*To whom correspondence should be addressed. E-mail: jeanremi.king@gmail.com

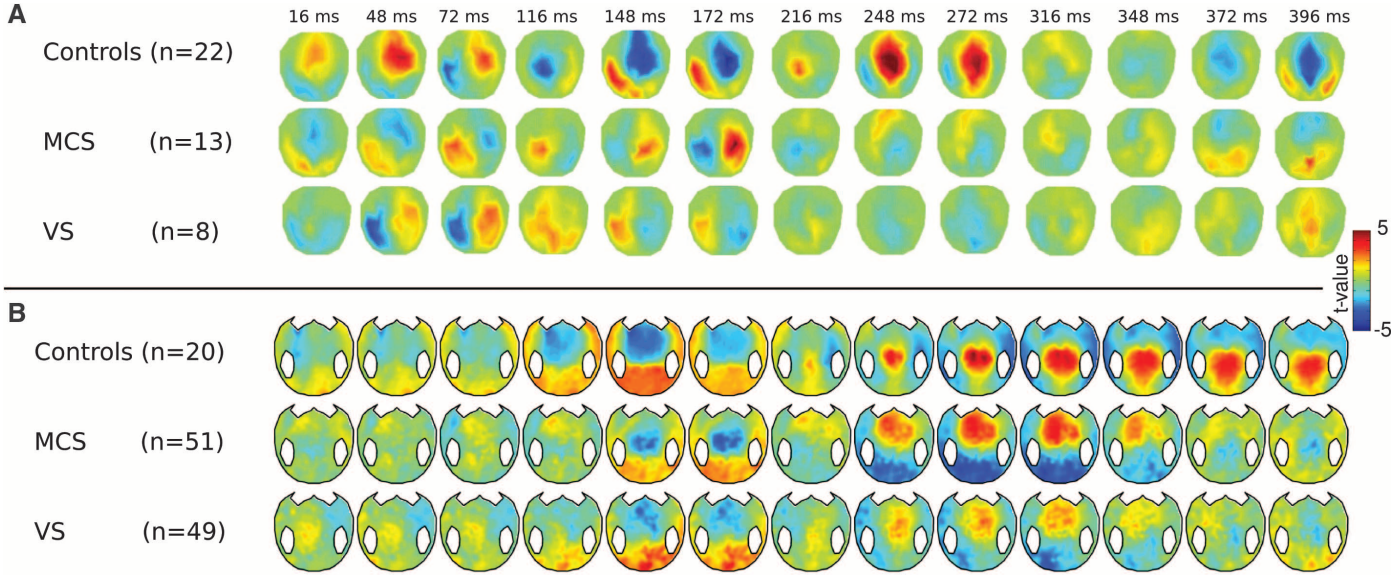

Fig. 1. MMN topography in patients with disorders of consciousness and in healthy controls. The figure shows a comparison of (**A**) *t* test maps from Boly *et al*. (*1*) for the MMN (comparison of deviant and standard trials) with (**B**) similar maps obtained from 120 recordings collected in the past three years in Lionel Naccache's laboratory, Hôpital de la Salpêtrière, Paris [intermediate results published in (*5*, *7*)]. Note that we kept the uneven temporal spaces from figure 2 in Boly *et al*. (*1*). The higher-resolution data and larger numbers of patients lead to a quiescent period (up to ~100 ms) followed by a classical frontocentral MMN (~100 to 200 ms) and P3a (~200 to 300 ms), with similar topography in all groups.

localizations previously reported in healthy subjects. Yet accurate resolution of forward and inverse problems, even with the help of the strong priors imposed by the DCM method, should be particularly difficult with noisy bedside EEG recordings and variably damaged skulls and brains. In fact, the source reconstructions presented in figure 3 in (*1*) for a single VS patient show several implausible features: (i) activity two to five times greater than in the control subject in most regions (note the different scales); (ii) an almost entirely left-lateralized A1 response, which is unexplained and inconsistent with the claim of preserved feedforward activity; and (iii) greater frontal activity for the standard tones than for the deviant tones, which is inconsistent with all previous functional magnetic resonance imaging and ERP results on the MMN (*6*, *10*). It would be reassuring if the accuracy of DCM source reconstruction were first validated in every individual—for instance, by demonstrating a consistent localization of early auditory ERPs to bilateral superior temporal regions.

Finally, the statistical tests that are reported do not exclude an additional impairment of feedforward processes in VS patients. The conclusions are based solely on the nonsignificance of a corrected-level two-sample *t* test on individual feedforward connections. Yet such an insensitive test does not prove an absence of impairment. The authors should report the critical interaction needed to test whether the feedback connection from IFG is significantly more impaired than other feedforward connections.

Prima facie, the massive lesions typical of VS patients, which frequently involve distributed white matter anomalies (*11*), are likely to affect both feedforward and feedback connections from PFC. The existence of a feedforward impairment in bringing auditory information to associative and prefrontal cortices is strengthened by the frequent absence of P3a and especially P3b ERP components in VS patients (*5*–*8*). Indeed, previous work by the same team demonstrated that auditory stimuli failed to evoke activation beyond auditory cortices in VS patients, suggesting either a feedforward disconnection or direct lesions of higher cortices (*12*, *13*). In normal subjects, intracranial recordings suggest that both feedforward and feedback causal relations of posterior regions to prefrontal cortex are involved in conscious access (*14*). We believe that bidirectional disconnections and, in many cases, direct PFC, thalamic, and brain stem lesions are likely to provide a more complex but more realistic picture of the vegetative state (*11*, *15*).

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Acknowledgments: We are grateful to L. Naccache and F. Faugeras for letting us reanalyze the data they collected. This work was supported by DGA (Direction Générale de l'Armement), INSERM, CEA, and a senior grant from the European Research Council to S.D. (NeuroConsc program).

20 June 2011; accepted 7 October 2011
10.1126/science.1210012

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Science **334** (6060), 1203.
DOI: 10.1126/science.1210012