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

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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

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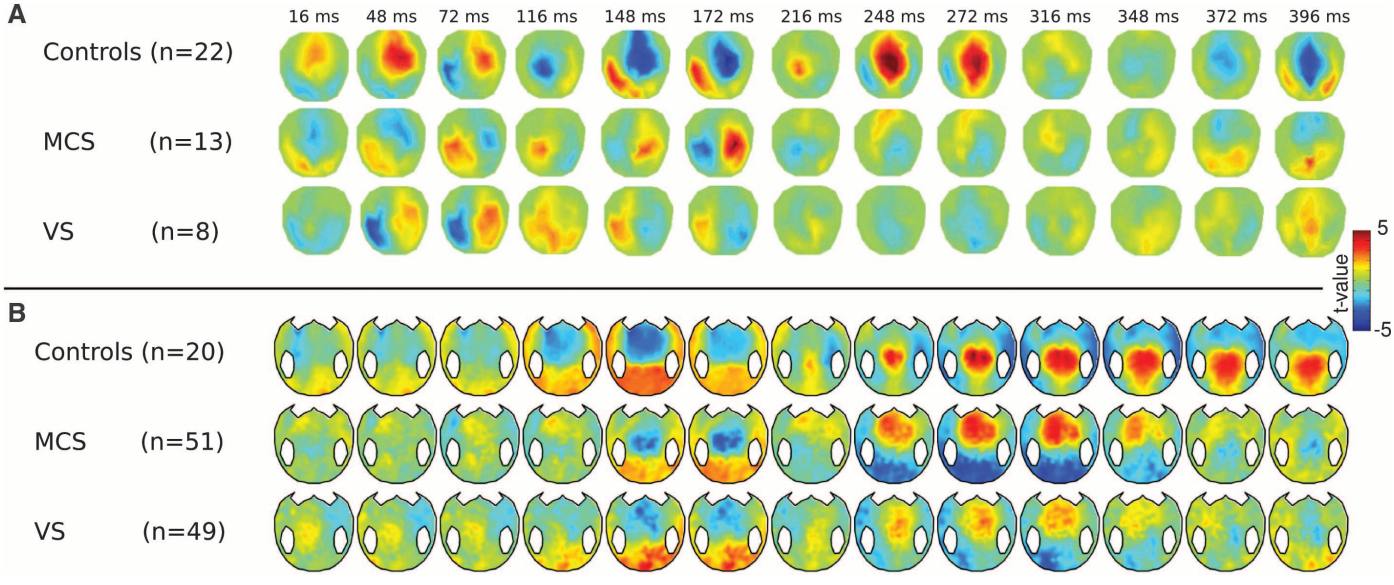

Fig. 1. MMN topography in patients with disorders of consciousness and in healthy controls. The figure shows a comparison of (**A**) *t* test maps from Boly *et al*. (*1*) for the MMN (comparison of deviant and standard trials) with (**B**) similar maps obtained from 120 recordings collected in the past 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.

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

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King *et al*. raise some technical issues about our recent study showing impaired top-down processes in the vegetative state. We welcome the opportunity to provide more details about our methods and results and to resolve their concerns. We substantiate our interpretation of the results and provide a point-by-point response to the issues raised.

We thank King *et al*. (*1*) for deconstructing our paper (*2*) showing impaired top-down processes in the vegetative state (VS). We hope our responses provide some useful clarifications.

(i) Regarding the number of patients, it would have been disappointing not to have found a common abnormality in eight well-defined VS patients. If we had needed 50 patients to obtain significant differences, we would probably end up reporting quantitatively trivial effects that had little diagnostic value [a well-known fallacy of classical inference (*3*)]. We consider the heterogeneity as a strength of our cohort selection (*2*): We discovered a common mechanism underlying impaired consciousness, irrespective of its distal causes and subsequent clinical course. The ability to generalize our finding would have been compromised had we studied a more homogenous VS group.

(ii) Previous studies have provided inconsistent results concerning the presence of mismatch negativity (MMN) in VS. Faugeras *et al*. (*4*) did not investigate the presence of a MMN (local effect) but rather show a global effect in 2 VS patients out of 27. Bekinschtein *et al*. (*5*) studied only 4 VS patients and failed to detect a MMN in some. References (*6*, *7*) report considerable variability across studies, with a MMN in about 10 to 25% of patients. In short, a significant MMN, based on some threshold criteria, is not a generic characteristic of event-related potentials

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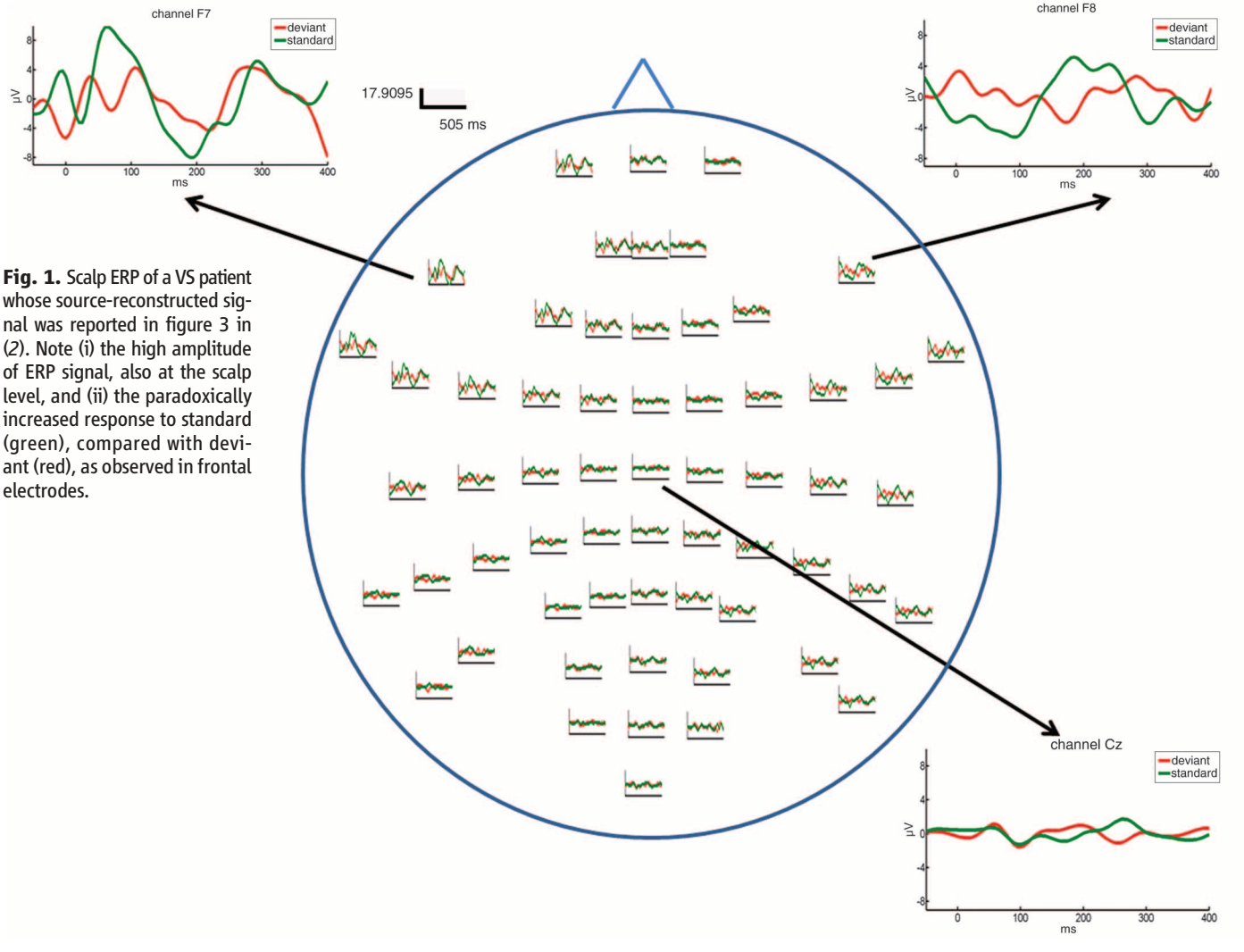

Fig. 1. Scalp ERP of a VS patient whose source-reconstructed signal was reported in figure 3 in (*2*). Note (i) the high amplitude of ERP signal, also at the scalp level, and (ii) the paradoxically increased response to standard (green), compared with deviant (red), as observed in frontal electrodes.

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(ERPs) in VS and is not a valid criterion for evaluating ERP data quality. Rather than assessing the presence of a threshold-based MMN, we examined correlations between ERP amplitude and the level of consciousness. We used a summary statistic (random effects) approach in all our analyses, ensuring that group results could not be explained by a strong effect in a minority of subjects (*8*).

(iii) With regard to ERP components and their latencies, we analyzed the whole peristimulus time window and indeed observed an ERP component corresponding to P50 in VS. We were not modeling the MMN per se (i.e., the difference waveform) but used the roving paradigm to characterize network responses to all stimuli. Waveform component latencies are defined using an ad hoc threshold on noisy time series, whereas dynamic causal modeling (DCM) looks for differences in the form of ERPs over all peristimulus time. To identify the MMN and reify it with a "latency" is not considered useful, necessary, or good practice in DCM.

(iv) It is not surprising that ERP topography is different in controls and VS patients, who are severely brain damaged. We used individual patient anatomy to account for possible differences in head conduction when performing DCM source reconstruction. Worries about signal-to-noise ratios can be discounted because differences were significant at the between-subject level using classical inference. If the data were just random fluctuations, these tests would not be significant. Differences between our data and King *et al*.'s results (*1*) might be due to differences in the stimuli [see (*9*)].

DCM source reconstruction provides a reasonable account of the scalp ERP data of the VS patient displayed in figure 3 in (*2*). In particular, the amplitudes of both scalp (Fig. 1) and source-reconstructed ERPs are bigger than typically observed in controls [figure 1 in (*2*)]. At both levels, the patient's frontal response to a "standard" is also bigger than the response to a "deviant." Merely observing ERP source reconstructions is insufficient to assert anything about backward versus forward connections; this is the role of DCM. To test models with and without laterality differences is another interesting issue, but not one that we have addressed.

(v) DCM implicit source reconstruction can efficiently reconstruct sources that are close together (*10*, *11*). Bayesian model selection (BMS) established that the use of five sources was the most appropriate for our data. ECD source reconstruction using 64 electrodes has been shown to be as accurate as an extended setup (*12*), especially when the data's signal-to-noise ratio is low (*13*). Finally, DCM uses the whole ERP time window to optimize its source reconstruction (*10*): Reconstructing only early components would not constitute a formal measure of inversion performance.

(vi) Our claim about preserved forward processes in VS was based on the involvement of frontal cortex in the generation of responses, as evidenced by BMS. At the level of quantitative parameter analyses, we can only reject the null hypothesis of no differences in the backward connections (because we used classical inference). This means that we can say nothing about the forward connections. We performed an additional analysis of variance for repeated measures, searching for an interaction between forward and backward frontotemporal connection strength in VS patients compared with controls. This interaction did not reach statistical significance ($P > 0.05$). A failure to demonstrate a significant difference can, however, not be taken as evidence for no difference (*2*). A BMS analysis on the VS subjects alone showed that model 9 (with preserved frontal forward connections but without backward connection) had more evidence than fully connected model 11 (with an 80% posterior confidence). Ideally, one would use BMS to ask about between-group differences in forward connections. However, hierarchical (between-subject) Bayesian models do not exist at present (for DCM).

Positron emission tomography measurements may fail to pick up the brief (subsecond) bottom-up afferents from auditory to frontal areas detected by ERP. Reduced frontal activation in VS could also reflect the pervasive effect of recurrent processing in the response to external stimuli (*14*). Several studies have established the importance of backward connections (*10*, *15*) and cognitive top-down processes (*16*) in long-latency component (such as P3) generation. An absence of P3 is therefore likely to reflect a disruption of backward rather than forward connections. It is probable that both forward and backward connections are important for consciousness. Our analysis suggests that backward connectivity from frontal to temporal cortex is the most consistent mechanistic abnormality underlying impaired consciousness in VS; however, this does not preclude a more widespread pathophysiology in any given patient.

We look forward to working with our peers to replicate our findings using other ERP paradigms. We would be glad to provide our help if needed.

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