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

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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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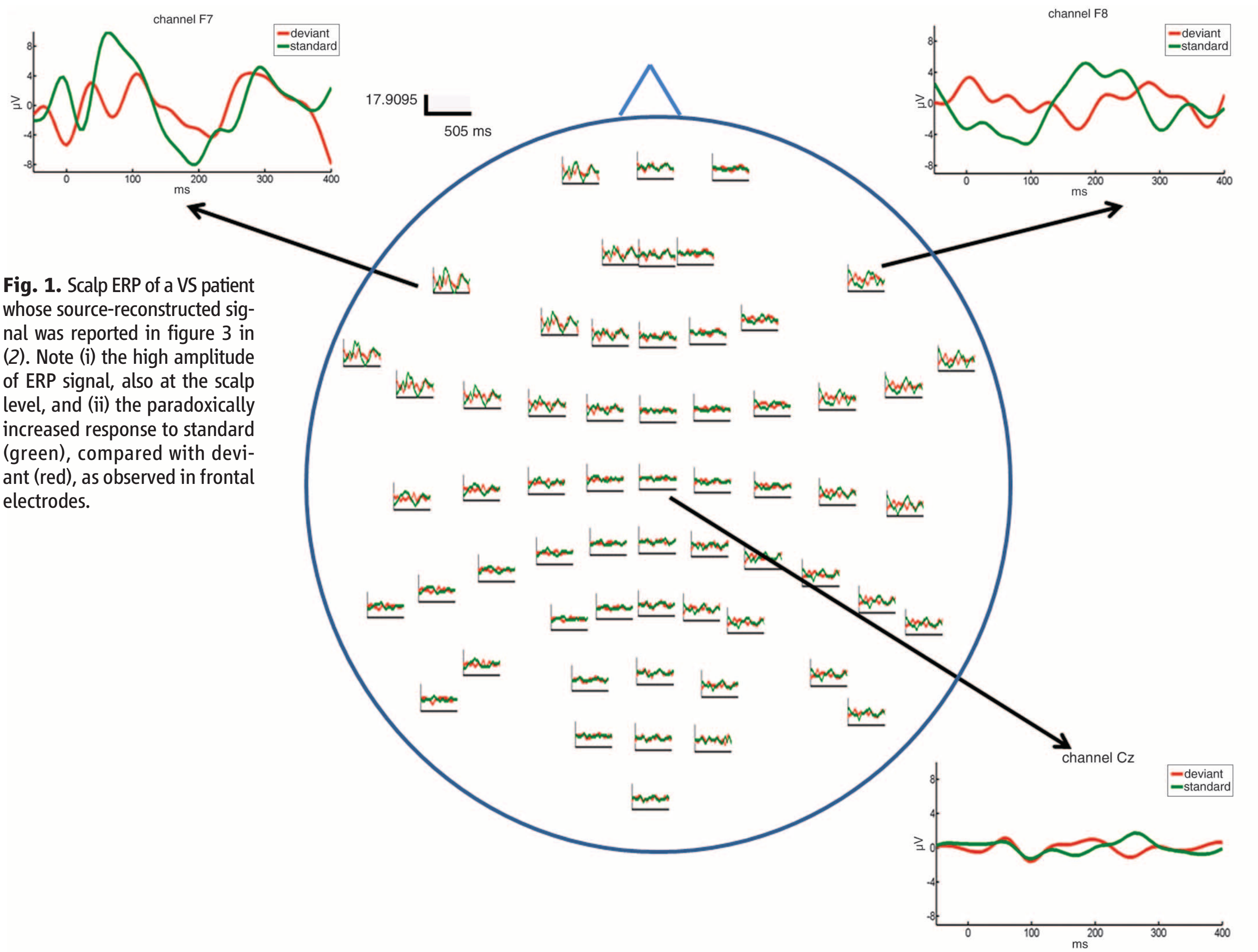

Fig. 1. Scalp ERP of a VS patient whose source-reconstructed signal was reported in figure 3 in (*2*). Note (i) the high amplitude of ERP signal, also at the scalp level, and (ii) the paradoxically increased response to standard (green), compared with deviant (red), as observed in frontal electrodes.

(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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