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Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state

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In recent years, numerous electrophysiological signatures of consciousness have been proposed. Here, we perform a systematic analysis of these electroencephalography markers by quantifying their efficiency in differentiating patients in a vegetative state from those in a minimally conscious or conscious state. Capitalizing on a review of previous experiments and current theories, we identify a series of measures that can be organized into four dimensions: (i) event-related potentials versus ongoing electroencephalography activity; (ii) local dynamics versus inter-electrode information exchange; (iii) spectral patterns versus information complexity; and (iv) average versus fluctuations over the recording session. We analysed a large set of 181 high-density electroencephalography recordings acquired in a 30 minutes protocol. We show that low-frequency power, electroencephalography complexity, and information exchange constitute the most reliable signatures of the conscious state. When combined, these measures synergize to allow an automatic classification of patients' state of consciousness.

Keywords: consciousness; vegetative state; unresponsive wakefulness syndrome; minimally conscious state; EEG

Abbreviations: AUC = area under the curve; CRS-R = Coma Recovery Scale Revised; CS = conscious state; MCS = minimally conscious state; VS = vegetative state

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Introduction

Despite intense experimental and theoretical efforts, the neural signatures of conscious processing remain a highly debated issue: are they to be found in early (Supèr *et al.*, 2001; Pins, 2003; Koivisto *et al.*, 2006; Melloni *et al.*, 2007) or late (Sergent *et al.*, 2005; Gaillard *et al.*, 2009) responses to sensory stimulations? Is conscious processing systematically associated with re-entrant top-down processing (Lamme *et al.*, 2000; Pascual-Leone *et al.*, 2001)? Does consciousness depend on a massive exchange of information across distant cortical sites (Lumer *et al.*, 1999; Vuilleumier *et al.*, 2001; Rees *et al.*, 2002; Marois *et al.*, 2004; Gaillard *et al.*, 2009) with prefrontal cortex and cingulate cortices acting as critical communication hubs (Sahraie *et al.*, 1997; Dehaene *et al.*, 2001; Lau *et al.*, 2006)? Or, instead, can it emerge solely from localized reverberating activity (Lamme *et al.*, 2000; Pins, 2003)? Even more, can it be directly associated to the global integration of information in the brain (Tononi, 2008)? Several models share the view that global information integration and coordination of distant areas may be two specific properties of conscious processes (Lamme *et al.*, 2000; Tononi, 2008; Dehaene *et al.*, 2011).

The identification of reliable signatures of conscious processing goes beyond theoretical research, and has critical practical implications in the clinic. In particular, detecting these signatures is essential for patients with disorders of consciousness who, even during wakefulness, are seemingly unable to communicate. To better describe these disorders, a distinction has been introduced between the vegetative state (VS) and the minimally conscious state (MCS). Both exhibit similarly preserved arousal, but MCS patients show signs of intentional behaviour whereas VS patients remain largely unresponsive. Yet, even in the latter case, science and modern medicine remain hard-pressed to decide whether a patient diagnosed as VS may still be conscious but unable to communicate (Laureys, 2005; Schnakers *et al.*, 2009b; Laureys *et al.*, 2012). For instance, Owen *et al.* (2006) have shown that functional MRI could detect consciousness in some VS patients and, in a few cases, even restore communication (Monti *et al.*, 2010). Similar results may be obtained using scalp EEG, a more economical and practical technique that can be easily applied at bedside (Cruse *et al.*, 2011; Faugeras *et al.*, 2011; Goldfine *et al.*, 2011). We recently introduced a measure (weighted symbolic mutual information, wSMI) that evaluates long-distance cortical information sharing from scalp EEG and discriminates VS and MCS patients (King *et al.*, 2013b). Another recent method based on the quantification of the complexity in the EEG evoked responses to transcranial magnetic stimulation pulses has also been shown to efficiently detect consciousness in patients with disorders of consciousness (Casali *et al.*, 2013). Nevertheless, there is still no consensus amongst clinicians as to which measure may be best suited to detect residual consciousness. Part of this results from the fact that the putative signatures of consciousness have been proposed and tested in independent studies, in distinct populations and with different criteria and methodologies.

The multiplicity of theoretical proposals and the practical need to improve the diagnosis of patients with disorders of

consciousness call for a systematic assessment of the ability of each of these measures to index states of consciousness. To address this issue, we provide an extensive analysis of empirically and theoretically derived measures of conscious activity that can be extracted from a large database of EEG recordings of patients with disorders of consciousness. We show that local low-frequency power and complexity measures, together with information exchange, are markers of conscious states. These measures and their respective fluctuations can be used in synergy in an automatic classification system to improve the diagnosis of VS patients.

Materials and methods

Patients

Patients underwent EEG recording to make a clinical electrophysiological evaluation of their conscious state. During this evaluation patients were presented with the 'Local-Global' auditory protocol (Bekinschtein *et al.*, 2009), which is designed to elicit event-related potentials that help assess patients' present and future state of consciousness (Fischer *et al.*, 2004; Naccache *et al.*, 2005; Wijnen *et al.*, 2007; Bekinschtein *et al.*, 2009; Schnakers *et al.*, 2009a; Faugeras *et al.*, 2011, 2012). The Ethical Committee of the Pitié-Salpêtrière approved this research under the French label of 'Recherche en soins courants' (routine care research). Patients were recorded at least 24 h after sedation to maximize their arousal and their cognitive abilities during the auditory stimulation. Other drugs that could potentially influence EEG such as myorelaxants or anti-epileptic drugs were not controlled, but note that these drugs are not specifically related to one of the three patient groups. Recordings were performed by trained electrophysiologists (F.F., B.R. and L.N.). EEG quality and ongoing activity were verified before starting the recording. Patients that showed seizures or any clearly identifiable abnormal activity were not recorded. We performed a total of 173 patient recordings. Six recordings were discarded because they presented <200 non-artefacted trials (see below). The remaining 167 valid recordings were acquired from 113 distinct patients (79 males and 34 females, sex ratio = 2.32), aged from 16 to 83 years (mean = 48 ± 17 years). Patients were recorded one to six times. Their aetiologies matched those typically observed in disorders of consciousness: anoxia (24%), intracranial haemorrhage (35%), traumatic brain injury (24%); and other aetiologies (17%) (see Supplementary Table 4 for details). Our cohort had variable delays separating the incident and the acquisition of the EEG [mean = 178 days since onset of disorders of consciousness; median = 35 days; standard deviation (SD) = 532 days; earliest = 6 days; latest = 4383 days].

Healthy subjects

Experiments were approved by the Ethical Committee of the Pitié-Salpêtrière Hospital. All 14 healthy subjects [mean age = 21.3 ± 2.9 ; sex-ratio (male:female) = 2.5] gave written informed consent.

Behavioural assessment of consciousness

Clinical evaluation of consciousness was based on the French version of the Coma Recovery Scale Revised (CRS-R) scale (Schnakers *et al.*, 2009b), and careful neurological examination by trained neurologists

(F.F., B.R., L.N.). This scale consists of 23 items forming six subscales addressing auditory, visual, motor, oromotor, communication and arousal functions. CRS-R subscales are comprised of hierarchically arranged items. The scale enables a distinction between conscious states (CS), MCS and VS (Schnakers *et al.*, 2009b). Clinical examination and behavioural assessment were systematically performed immediately before EEG recording.

Auditory stimulation

Subjects were stimulated auditorily using the 'Local-Global' protocol (Bekinschtein *et al.*, 2009). In this protocol, patients were presented with a series of sounds that contain regularities at two different hierarchical levels. The deviations from these regularities evoke event-related potentials that are useful to evaluate the cognitive state of the patients. See Supplementary material for a complete description of the protocol.

High-density scalp electroencephalography recordings

EEG recordings were sampled at 250 Hz with a 256-electrode geodesic sensor net (EGI) referenced to the vertex. Recordings were band-pass filtered (from 0.2 to 45 Hz). Trials were then segmented from –200 ms to +1336 ms relative to the onset of the first sound. Trials with voltages exceeding $\pm 150 \mu\text{V}$, eye-movements activity exceeding $\pm 80 \mu\text{V}$ and eye-blinks exceeding $\pm 150 \mu\text{V}$ were rejected. Trials were baseline corrected over the first 200 ms window preceding the onset of the first sound. Electrodes with a rejection rate superior to 20% across trials were rejected and were interpolated. Trials with >20 corrected electrodes were rejected. The remaining trials were digitally transformed to an average reference. All these processing stages were performed using the EGI Waveform Tools Package.

Connectivity measures were based on a spatial Laplacian transformation of the EEG—a computation also known as the Current Source Density estimate (Kayser *et al.*, 2006). This transformation roughly consists, in subtracting from each electrode, the activity of its neighbouring electrodes. This has the main advantage of increasing spatial resolution and minimizing the influence of common sources on multiple distant electrodes.

Calculation of putative electroencephalography measures of consciousness

We calculated the entire set of EEG measures independently for each individual subject, trial and for every electrode ($n = 256$) or pair of electrodes ($n = 32\,640$). Connectivity measures were summarized by calculating the median value from each electrode to all of the other scalp (non-facial) electrodes. Note that, given the spatial distribution of the electrodes, this procedure enhances the weight of long-distance connections on the computed measure. As a final result, all measure distributions ended up with the same number of values per subject and trial. Finally, for each subject, these values were again collapsed to two scalars by considering the mean and the standard deviation across trials.

Except for event-related potential measures, analyses were performed on EEG data recorded during the time period when subjects were presented with undifferentiated series of tones (from 200 ms before the onset of the first tone to the onset of the fifth tone). Thus, all trials were pooled independently of the condition of auditory stimulation.

See Supplementary material for a detailed description of each measure and its computation.

Statistics

Topographical analysis

Topographical analyses were performed using a similar approach to the method above. Pair-wise comparisons across clinical states were performed with Mann-Whitney U-tests on each electrode separately. Robust regression analyses were performed across the four groups (VS, MCS, CS, and healthy controls) to test for the monotony of the changes observed across states of consciousness. Statistical significance is reported at two levels of significance ($P < 0.01$ and $P < 0.05$, uncorrected for the number of electrodes tested).

Univariate receiver operating characteristic

Pair-wise comparisons were performed across the three clinical groups (VS, MCS and CS), leading, for each measure, to three statistical comparisons (VS/MCS, MCS/CS, and VS/CS). We implemented a non-parametric statistical method (Mann-Whitney U-test) and report the effect size as the empirical area under the curve (AUC) from an empirical receiver operating curve analysis. See Supplementary methods for the computation of the AUC.

Multivariate pattern analyses

In the present case, each analysis aimed at predicting the clinically-defined state of consciousness (VS, MCS or CS) of each subject from the EEG-based measures of conscious processing. For this purpose, we used a linear Support Vector Classifier (Pedregosa *et al.*, 2011) with a probabilistic output calibration. See Supplementary material for a detailed description of the computational steps.

Results

We analysed a large set of 181 high-density 256-channel EEG recordings, corresponding to all 167 patients admitted at the Pitié-Salpêtrière Hospital and referred to us in the 2008–10 period for a clinical evaluation of their state of consciousness. In total, 75 VS recordings, 68 MCS recordings, and 24 brain-injured but conscious patients (CS) were recordings were acquired. Fourteen additional recordings were obtained from healthy control subjects. Recordings were acquired in the 'Local Global' protocol, a 30-min experimental protocol designed to probe the depth of processing of auditory regularities (Bekinschtein *et al.*, 2009) (Fig. 1). This procedure allowed us to jointly quantify the event-related potentials evoked by exogenous stimuli and the presence of endogenous fluctuations in the EEG, while maximizing and homogenizing the patients' attention and vigilance. For each recording, we systematically extracted a set of measures organized according to a theory-driven taxonomy (Table 1). Full details and motivations for each measure can be found in the Supplementary material. Here we briefly describe the most relevant aspects of each measure.

We propose to organize EEG measures according to several major dimensions (Table 1). A first distinction separates measures of the processing of external stimuli (auditory event-related potentials) from measures that are not locked to the stimuli and rather reflect ongoing brain activity. Current theories of consciousness differ in their attribution of conscious awareness of an external stimulus to early or late brain responses (Dehaene *et al.*, 2011). Therefore, we

classified event-related potentials according to their latency (early, <250 ms versus late, >300 ms). Measures of ongoing EEG activity were further classified based on: (i) dynamics of brain signals at a single electrode site versus assessment of functional connectivity between two brain sites; and (ii) whether the measure is based on spectral frequency content or on information-theoretic estimates of signal complexity, which do not presume strong specific hypotheses about the frequency content of the signal. For each measure we computed, the intertrial average, which reflects the overall mean value during the half-hour recording session, and the fluctuation of this measure (SD) during the recording period, which tests the hypothesis that stability may be a hallmark of consciousness (Schurger *et al.*, 2010).

Topographical differences across measures and groups

First we inspected whether differences in amplitude and spatial distribution of the computed measures could discriminate patients' state of consciousness. This analysis also aims at evaluating whether different measures present specific scalp topographies,

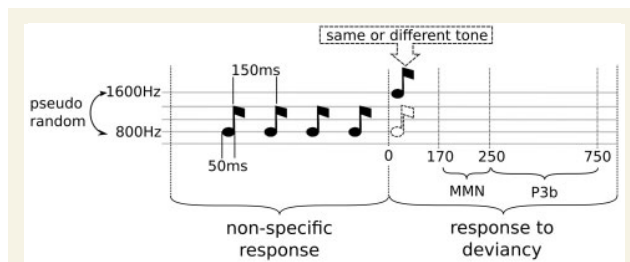


Figure 1 A multi-dimensional approach to categorize states of consciousness. Description of the experimental protocol used for patient auditory stimulation. Spectral and information-theory measures were computed in the early time window (which is identical for all trials), whereas event-related potentials were computed on the late window (response specific to the trial condition).

and thus (i) highlight optimal recording regions for clinical practice; and (ii) suggest different underlying neural systems. Figure 2 depicts a representative set of measures; the full set of topographies is presented in Supplementary Figs 1–4. The specific results obtained for each marker is discussed below.

Event-related topographies show low sensitivity to discriminate patient groups

Only two of seven sound-related potentials (Bekinschtein *et al.*, 2009) differed significantly between VS and CS patients (Supplementary Fig. 1). None of them could significantly discriminate VS and MCS patients. The MMN and the P300, two event-related potentials, which both signal the detection of violations of auditory regularities, only showed modest differences between the groups of patients. Although the MMN discriminated VS from CS and MCS from CS, confirming that it increases when consciousness recovers (Wijnen *et al.*, 2007), it did not discriminate VS from MCS. More surprisingly, univariate, electrode-by-electrode statistics of the P300 topography also failed to reveal any discrimination of VS from MCS. This finding, which partially contradicts earlier results with smaller patient samples (Bekinschtein *et al.*, 2009), may be ascribed to large interindividual variability in EEG topography (King *et al.*, 2013a), as discrimination improves when using multivariate decoding (see below).

Theta and alpha band power efficiently index the state of consciousness

Contrary to event-related potentials, most of the power spectrum measures seemed to be efficient indices of consciousness states.

These measures appeared maximally informative for electrodes over the parietal region (Supplementary Fig. 2). All spectral measures showed monotonic effects from VS to CS patients groups, and 6 of 10 succeeded in discriminating VS from MCS. Within the lower frequencies, normalized delta (1–4 Hz) showed decreasing power from VS to CS, significantly separating VS from non-VS

Table 1 Taxonomy of EEG-derived measures used to categorize states of consciousness

Event-related potentials		'Ongoing' activity			
Early components	Late components	Single electrode		Across electrodes	
		Spectrum	Information theory	Spectrum	Information theory
P1	P3a	Power in frequency bands	Permutation entropy	Phase lag index	Weighted symbolic mutual information
MMN	P3b	Spectral summaries	K complexity	Amplitude envelope correlation	
CNV		Spectral entropy		Imaginary coherence	

Measures can be conceptually organized along several dimensions: first, we distinguish measures of stimulus processing from measures computed from ongoing EEG activity. The former (event-related potentials) are further subdivided into early versus late components. The latter are classified according to the theoretical background used to derive the measure: (i) local dynamics versus connectivity: some measures are computed within each electrode, whereas others index the interactions between electrodes; and (ii) spectral (Fourier frequency analysis) versus Information Theory. Finally, for each measure, intertrial average (computed as the mean across trials) or intertrial fluctuations (computed as the standard deviation) were studied.

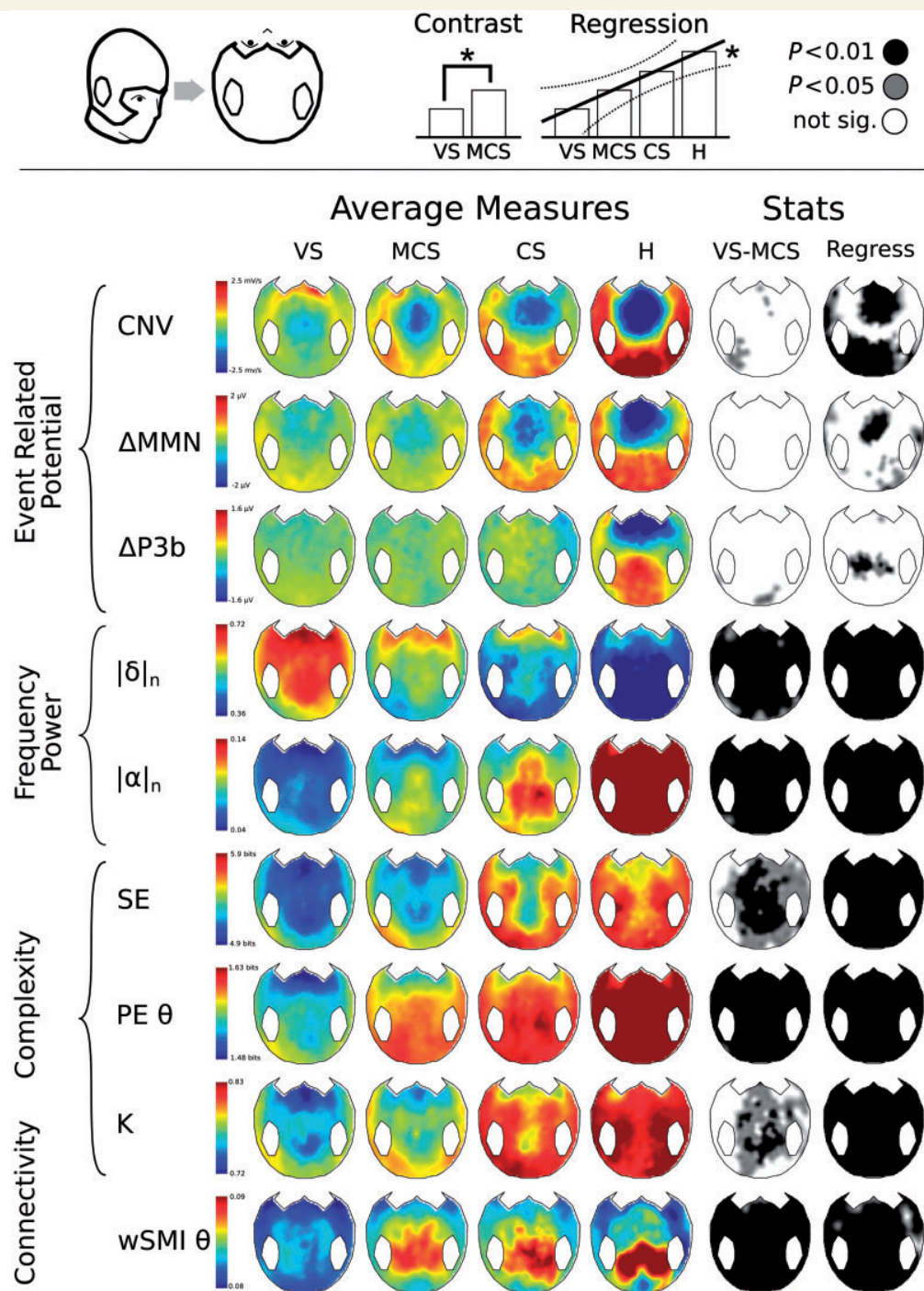


Figure 2 Scalp topography of the most discriminatory measures. The topographical 2D projection (top = front) of each measure [contingent negative variation (CNV), mismatch negativity (MMN) and P300b (Δ P3b), normalized power in delta ($|\delta|_n$) and alpha ($|\alpha|_n$) bands, spectral entropy (SE), permutation entropy in theta band (PE_θ), Komolgorov-Chaitin Complexity (K) and weighted symbolic mutual information (wSMI $_\theta$)] is plotted for each state of consciousness (columns). The fifth column indicates whether the VS and MCS patients were significantly different from one another (black = $P < 0.01$, light grey = $P < 0.05$, white = not significant, uncorrected for the number of electrodes tested). The sixth column shows the statistics of a regression analysis of the measure across the four states of consciousness (VS < MCS < CS < healthy controls (H)). Black: $P < 0.01$, light grey: $P < 0.05$, white: not significant, uncorrected for the number of electrodes tested).

patients. On the contrary, normalized theta (4–8 Hz) and normalized alpha power (8–13 Hz) increased significantly from VS to CS. Both frequency bands showed increasing power in parietal regions and significantly discriminated VS from the other groups of patients. Normalized beta power failed to discriminate between VS and MCS patients, but significantly discriminated CS from the other groups of patients.

Because of these opposing variations of low (delta) and high (alpha and above) frequencies, spectral summaries such as the median spectral frequency, which summarize the relative distribution of power in the frequency spectrum, were particularly efficient. The spectral entropy analysis showed that CS and MCS patients presented a less predictable spectral structure (higher entropy) than VS patients.

Electroencephalography complexity increases with conscious state

Algorithmic (or Kolmogorov-Chaitin) complexity (K) estimates the complexity of a sequence based on its compressibility. Several theories predict that the complexity of information integration (Tononi, 2008) or distributed processing (Dehaene *et al.*, 2011) is elevated during conscious states. In agreement with this prediction, we found that the computed measure of complexity, based on EEG compression, increased in patients with a higher clinical state of consciousness. This measure significantly discriminated VS from MCS patients, particularly for a set of electrodes over the parietal region (Supplementary Fig. 3). A complementary mathematical approach is permutation entropy, which evaluates the regularity of the probabilistic distributions of temporal patterns in the signal (Bandt and Pompe, 2002). Permutation entropy can be computed in distinct frequency bands; we found that permutation entropy-based measures were particularly efficient in the theta frequency range, discriminating VS from the other groups. Again, a greater value of permutation entropy, especially over centro-posterior regions (Fig. 2), indicating a more complex and unpredictable distribution, indexed a higher state of consciousness.

Information sharing across brain regions indexes conscious state

Similar to the spectral measures at a single recording site, measures of functional connectivity between two recording sites proved particularly efficient at lower frequencies (Supplementary Fig. 4). Amongst the spectral connectivity measures, only the phase-locking index in the delta band was significant, progressive deficits in consciousness being accompanied by greater delta synchrony. Connectivity measures based on information theory, such as weighted symbolic mutual information, demonstrated a higher sensitivity, as previously reported (King *et al.*, 2013b), inter-electrode information exchanges increased from VS to CS. VS patients presented significant lower weighted symbolic mutual information than both MCS and CS patients in the theta and alpha bands, consistent with the theoretical notion that loss of consciousness in VS reflects an impaired exchange of information across brain

areas, and particularly over medium-to-long cortico-cortical distances (King *et al.*, 2013b).

Quantifying the electroencephalography differences between groups of patients with disorders of consciousness

Although the above analysis evaluated the topographical differences across groups, judging discrimination capacity in sensor space while correcting for multiple comparisons over the large number of available electrodes poses a difficult statistical problem. To reduce dimensionality and quantify the discriminative power of each measure, we summarized spatial information by considering the average over all scalp electrodes or, in the case of event-related potentials, over predefined electrodes forming *a priori* regions of interest (see Supplementary material for details of region of interest selection). All individual trial measures were summarized in their intertrial average and in their fluctuation (SD) during the recording period. In the case of event-related measures, we also applied a systematic within-subject decoding approach for local and global responses to auditory novelty, following the procedure described in King *et al.* (2013a), which enhanced the discrimination of these conditions. This approach ultimately yielded a total of 92 measures per subject (see Supplementary Tables 1 and 2 for numerical summaries of each measure in each group).

To investigate which measures showed significant differences across groups of patients, we implemented receiver operator curves (Supplementary Fig. 5) and quantified classification performance with the AUC. A strict criterion based on false discovery rate (FDR) was applied to correct for multiple comparisons (92 values \times three tests: VS–MCS, MCS–CS and VS–CS). An AUC of 50% corresponds to chance classification. An AUC $> 50\%$ implies that the measure increases with conscious state (i.e. MCS $>$ VS), whereas AUC $< 50\%$ implies a decrease with conscious state (i.e. MCS $<$ VS).

Average spectrum, complexity, connectivity, and global responses to novelty provide efficient signatures of consciousness

Analysis of the discrimination performance of the EEG measures revealed that the most discriminative measure was weighted symbolic mutual information, which separated VS from MCS ($wSML_{\theta}$: AUC = $74 \pm 4\%$, $P_{FDR} < 0.0001$) and CS patients ($wSML_{\theta}$: AUC = $78 \pm 6\%$, $P_{FDR} < 0.001$). Power spectrum measures also performed well: increased normalized delta power separated VS from MCS (AUC = $31 \pm 4\%$, $P_{FDR} < 0.001$) and from CS patients (AUC = $19 \pm 4\%$, $P_{FDR} < 0.0002$), whereas the converse occurred in higher frequency bands, with decreased normalized alpha power segregating VS from MCS (AUC = $72 \pm 4\%$, $P_{FDR} < 0.0002$) and from CS patients (AUC = $85 \pm 5\%$, $P_{FDR} < 0.0001$). A third variable affording accurate classification

was permutation entropy in theta frequency range, discriminating VS from the other groups (permutation entropy _{θ} : MCS > VS, AUC = $72 \pm 4\%$, $P_{FDR} < 0.0002$, CS > VS, AUC = $83 \pm 5\%$, $P_{FDR} < 0.0001$). Finally, the decoding of the global effect (the event-related potential response to deviant auditory sequences; Bekinschtein *et al.*, 2009; King *et al.*, 2013a) also separated VS from MCS (AUC = $62 \pm 5\%$, $P_{FDR} < 0.05$) and CS patients (AUC = $81 \pm 6\%$, $P_{FDR} < 0.0002$).

We tested whether the discrimination performance of the EEG measures was consistent across the different aetiologies of patients. To this end, for each EEG measure, we performed an ANOVA with factors of consciousness state (three levels: VS, MCS, CS) and aetiology (four levels: traumatic brain injury, anoxia, stroke, and other). We observed main effects of state of consciousness for the same measures that showed an efficient state discrimination (Supplementary Table 5). However, no marker showed a main effect of aetiology or an interaction between state and aetiology after FDR correction for multiple comparisons (Supplementary Table 5). Similarly, we tested the effect of delay from the date of the accident. We categorized the patients according to the delay as acute (<21 days) or chronic (>21 days). Again, a main effect of state of consciousness was found for most of the successful measures but no measure showed a main effect of delay or an interaction after FDR correction for multiple comparisons (Supplementary Table 6).

One issue is that the vigilance level can be confounded with VS/MCS differences. Indeed, the clinical assessment of the CRS-R subscore corresponding to the arousal level showed a small increase in the MCS group as compared to the VS group (mean \pm SEM, MCS: 1.53 ± 0.07 , VS: 1.30 ± 0.05 , $P = 0.013$). To rule out this potential confound and isolate the variations specifically due to consciousness, we replicated the previous analysis in the subset of VS and MCS patients with CRS-R arousal subscore of 1, corresponding to patients that presented eye opening only to stimulation (VS: 52 recordings, MCS: 32 recordings). Performance of the EEG measures was essentially unchanged in this vigilance-controlled subset of patients as compared to the overall comparison (Supplementary Fig. 6 and Supplementary Table 3).

Fluctuation of measures across trials convey independent information

The stability of evoked activity has been proposed as a marker of consciousness (Schurger *et al.*, 2010). We then hypothesized that EEG variability over time, quantified as the fluctuations of a given measure across trials, might add independent information about consciousness, relative to its mere average value. The results confirmed that EEG fluctuations had important discriminative information (Fig. 3). Interestingly, we did not always observe a positive correlation between the classifying power of a given measure based on its average and on its fluctuations. Figure 4 provides a graphical comparison of discrimination power based on the mean or the fluctuation of each measure for the MCS/VS contrast. Different types of measures can be distinguished. Some simply fail to separate these two groups (e.g. low gamma power). Others show a significant increase in both the average

and the fluctuation over time for MCS compared to VS (this is the case for power in theta, alpha and beta bands, median spectral frequency and wSML _{θ}). Yet other measures exhibit dissociation between average and fluctuation. In particular, the state of consciousness is associated with a high average but a low fluctuation of algorithmic (or Kolmogorov-Chaitin) complexity (K), permutation entropy (PE) _{θ} and PE _{α} , indicating that a stable and lasting increase in complexity and entropy reflects a conscious patient. Conversely, the state of consciousness is associated with a low average and high fluctuation of power and phase-locking index in the delta band, while fluctuating slow cortical potentials, covering the delta range, are typical in the normal conscious brain (He *et al.*, 2009), stable and intense delta waves are a sign of unconsciousness in anaesthesia and deep sleep (Franks, 2008). Finally, the remaining measures were discriminative only for averages (i.e. spectral entropy) or for fluctuations across trials (i.e. phase-locking index in beta and alpha bands). The latter finding may suggest that consciousness implies a constantly fluctuating stream of transiently phase-locked brain states.

Combining measures improves discrimination

We next examined whether these EEG measures could be combined to improve discrimination of the different states of consciousness, particularly in the crucial VS/MCS comparison. One goal was to determine whether these markers act in concert, and be thus combined to improve discrimination between groups or whether these measures are redundant. In this latter case, the best measure would provide information comparable to the entire set of measures. To this aim we used a multivariate classification method based on a support vector machine (Pedregosa *et al.*, 2011). The support vector machine was applied to all VS and MCS recordings. To avoid over-fitting, the support vector machine was repeatedly fitted and evaluated on independent data sets using stratified nested cross-validation. It took as input a measure or set of measures, and output the estimated probability for a given recording to belong to the VS group. Results showed that when the classifier was set to use the best cross-validated single measure the performance reached an AUC = $71 \pm 4\%$, for the VS-MCS comparison. By contrast, when using the whole set of measures, AUC was significantly higher than when using the best single measure: VS-MCS: AUC = $78 \pm 4\%$ ($P < 0.001$). In other words, measures were not entirely redundant, and the support vector machine provided an efficient way to identify the combination of markers that leads to a better discrimination of the patients states of consciousness.

Automatic classification of patients' state of consciousness

A main clinical objective of this work was to develop an automatic system that potentially helps physicians to detect consciousness in non-communicating patients. For this, we evaluated the performance of the support vector machine classifier to differentiate VS patients from MCS patients, i.e. to reliably identify the presence of

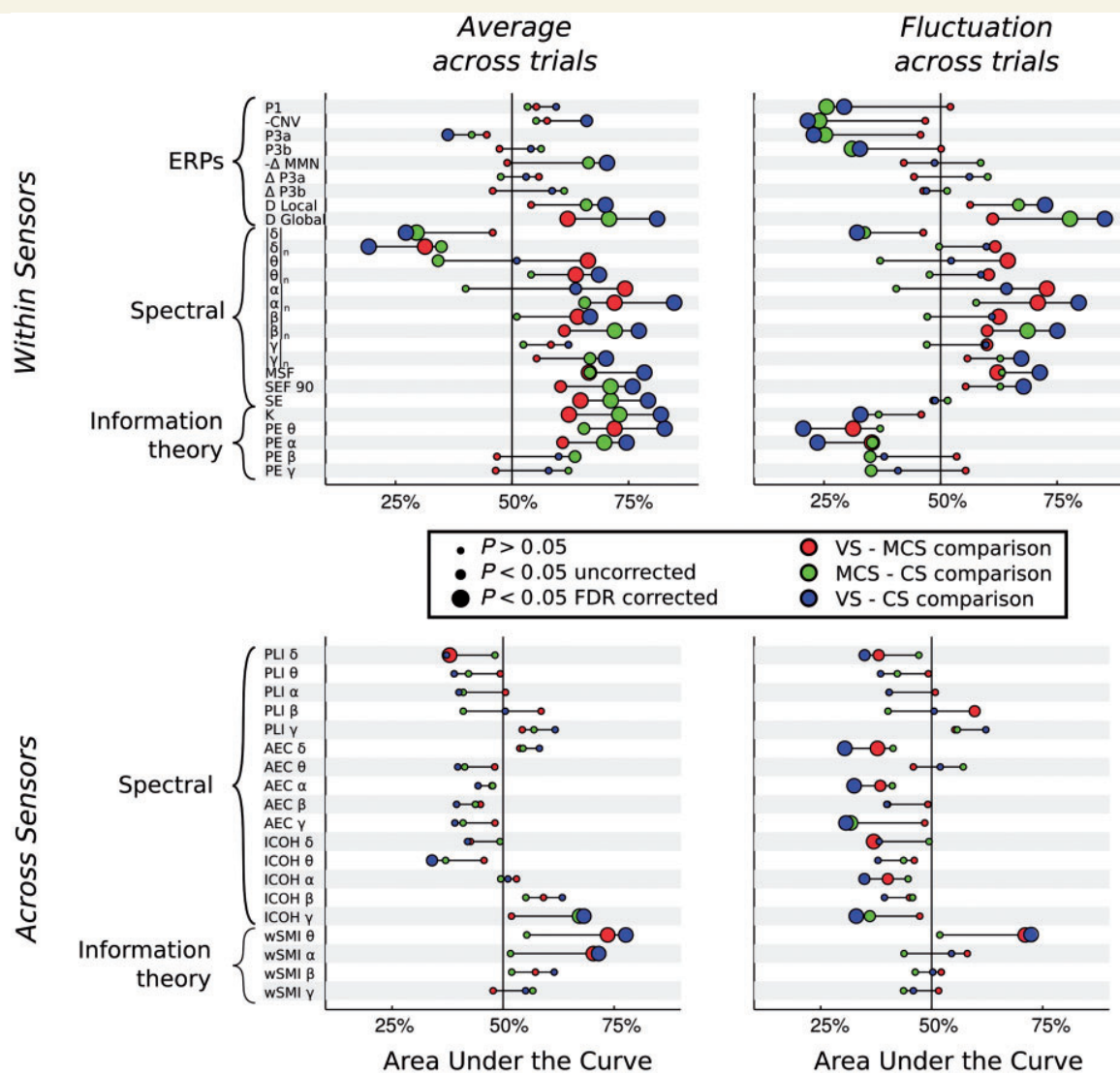


Figure 3 Discrimination power for all measures. Each line provides a summary report of its respective measure. The meaning of each acronym can be found in the Supplementary material. The measures are ordered according to the taxonomy presented in Table 1. The location of each dot corresponds to the AUC for a pair-wise comparison between two states of consciousness (see 'Materials and methods' section). Chance level corresponds to AUC = 50% (central vertical line). An AUC > 50% suggests that the corresponding measure is correlated with the state of consciousness (from VS to MCS and CS). An AUC < 50% suggests that the corresponding measure is anti-correlated with the state of consciousness. Dot colour and size indicate the type and significance of the comparison (see legend). The red colour highlights the minimal contrast between the MCS and VS states of consciousness. As the contingent negative variation and MMN are negative EEG components, their respective AUC was computed after changing the sign of their amplitudes.

a clinically detectable state of consciousness. The classifier achieved above-chance levels of accuracy [$\chi^2(2, n = 143) = 26.7, P = 10^{-7}$]: 67% (50 of 75) of VS-diagnosed patients and 76% (52 of 68) of MCS-diagnosed patients were classified in their respective clinical categories solely from their brain activity (Fig. 5). To test for robustness, we also evaluated whether the same classifier, trained to distinguish VS from MCS patients, generalized to CS patients and healthy subjects. The great majority of these recordings (89%, 34 of 38) were classified as conscious (MCS rather than VS).

To train our classifier, we relied on clinical labels (VS and MCS) that derive solely from behavioural observations and need not provide a perfect 'gold standard' (Owen *et al.*, 2006). A

disagreement between the automatic classification and the clinical label may represent an error of the classifier, but it may also indicate the presence of EEG-based information not accessible to the clinician. To investigate whether the information derived from neurophysiological activity may improve diagnosis, we tested whether VS patients classified as MCS from their EEG activity would later show signs of intentional behaviour that may have been missed at the time of the recording. Most patients classified as VS on both clinical and EEG-based criteria showed no signs of regaining consciousness in the six weeks following EEG recording [recovery < 21 days: 10 (20%); recovery within 21–42 days: 1 (2%); no recovery: 39 (78%)]. By contrast, among the clinically

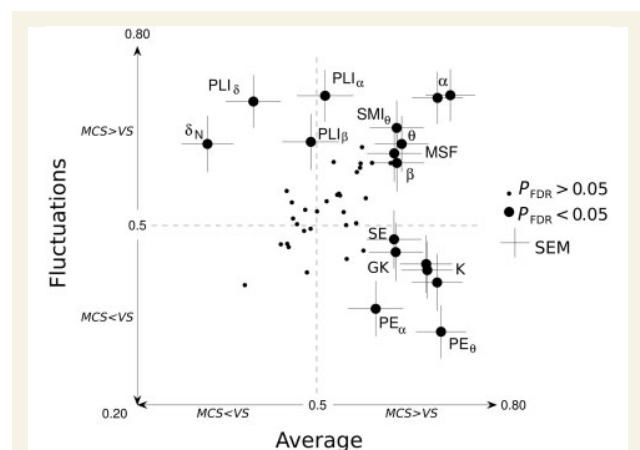


Figure 4 Summary of the measures discriminating VS and MCS patients. Each measure is plotted in a 2D graph. Acronyms meanings can be found in the Supplementary material. The x-axis indicates discriminatory power for each measure's average across trials, whereas the y-axis indicates discriminatory power for their respective fluctuations across trials. For instance, the Kolmogorov-Chaitin complexity (K) measure appears in the bottom right quadrant, suggesting that its average value is significantly higher in MCS than in VS, whereas its standard deviation, conversely, is higher in VS than in MCS. Large circles indicate significant measures ($P_{FDR} < 0.05$). Non-significant measures are indicated with small dots.

VS patients classified as MCS based on their EEG activity, the proportion of those who later showed signs of consciousness significantly increased [recovery < 21 days: 8 (32%); recovery within 21–42 days: 3 (12%); no recovery: 12 (48%); unknown: 2 (8%)]. The number of subjects who recovered consciousness was significantly higher for VS patients classified as MCS than for those classified as VS [$\chi^2(2, n = 73) = 4.99, P = 0.025$]. It should be emphasized that clinical assessment at the time of the recording, based on the full CRS-R or its subscores, neither predicted the VS patients' recovery nor the automatic classification category (Supplementary material). We then investigated which of the EEG measures that successfully identified the state of consciousness were also efficient in predicting the recovery of VS patients. Results show that the patients recovering from VS (recovery < 42 days), relative to non-recovering ones, tended to exhibit a higher contingent negative variation, higher normalized power in the theta frequency band, and smaller phase-locking index in the delta frequency band. These results should be considered exploratory, however, given that these results achieved significance only at an uncorrected $P < 0.05$ level (Supplementary Table 7).

In summary, within a behaviourally indistinguishable group of clinical VS patients, neurophysiological measures provided information about the future improvement of consciousness, suggesting a better functional status at the time of recording than the one indicated by the clinical diagnosis.

Discussion

We systematically evaluated putative signatures of consciousness in a large data set of high-density bedside EEG recordings of

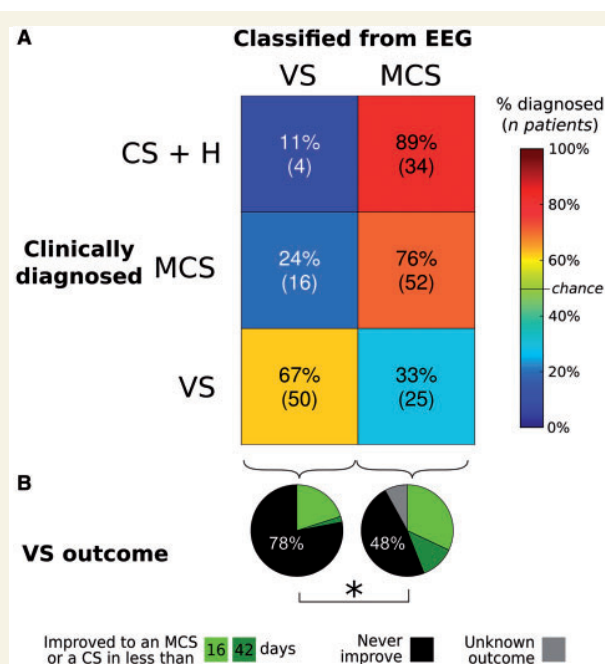


Figure 5 Comparison of EEG-based classification with clinical diagnosis and patients' outcome. (A) Confusion matrix showing, on the y-axis, the clinical diagnosis (VS, MCS or CS/Healthy), and on the x-axis, the prediction using the automatic classifier based on EEG measures (VS or MCS). The number of recordings and their respective percentages within each clinical state category are reported in each cell. For VS and MCS patients EEG-based classification matches the clinical diagnosis in a majority of cases. Using the same classifier (trained to predict VS or MCS state) the top cells show the predicted condition for CS and healthy subjects. The majority of these recordings were classified as MCS. Non-matching cells can suggest inappropriate classifications, but may also indicate that EEG measures are detecting information unseen by clinicians. (B) The pie charts show the clinical outcome of the VS patients, as a function of whether EEG measures classified them as VS or in a higher state of consciousness (MCS or CS). The probability of recovery was significantly higher ($P = 0.02$) for patients classified into a higher state of consciousness than for patients predicted to be truly VS.

patients suffering or recovering from disorders of consciousness. An important feature of our study is that we included all patients with disorders of consciousness within a ~2-year period, thus ensuring an unbiased sampling and maximizing clinical relevance. By testing 92 candidate measures arising from previous empirical and theoretical research, we showed that patients' EEG contains many useful features that discriminate between VS and CS. Each of these measures can thus index consciousness, either directly, or indirectly through its consequences on arousal, instruction understanding, active maintenance of stimuli and instructions in working memory, and task monitoring, etc. Crucially, only a few of these measures were effective in discriminating the minimal contrast between VS and MCS patients. We focus the discussion on this subset of measures, which seem most relevant to the objective identification of conscious processing from the patterns of EEG activity.

Spectral power analysis revealed that alpha and theta power was significantly lower in VS than in MCS patients, whereas delta power showed the opposite pattern. Similar increases in low-frequency oscillations are a classical observation in coma and deep sleep (Posner *et al.*, 2007). Here we demonstrate their relevance to distinguish VS from MCS patients, as recently reported in smaller groups of patients (Fellinger *et al.*, 2011; Lehenbre *et al.*, 2012; Lechinger *et al.*, 2013). The fronto-parietal topography of these spectral effects is consistent with a crucial role of fronto-parietal networks in a 'global workspace' mediating a serial stream of conscious states at theta-like frequencies (100–300 ms per state) (Alkire *et al.*, 2008; Vanhaudenhuyse *et al.*, 2010; Dehaene *et al.*, 2011; Laureys *et al.*, 2012). This regional hypothesis should be confirmed with cortical source analysis, which was not attempted here given the difficulty of obtaining an accurate source model in patients with massive brain and skull damage (King *et al.*, 2011).

Spectral measures also exhibited greater fluctuations in MCS than in VS patients. This finding agrees with the definition of MCS as a fluctuating state (Giacino *et al.*, 2005) and shows that, contrariwise, a stable state of increased delta and reduced alpha-theta power is a solid sign of unconsciousness. Finally, the structure of the EEG spectrum, as measured by spectral entropy, was increased in MCS and CS as opposed to VS patients. This finding was previously reported to be relevant only in the acute stage and in a much smaller subset of patients (14 VS versus 9 MCS) (Gosseries *et al.*, 2011).

Multiple EEG measures of signal complexity (spectral entropy, permutation entropy, algorithmic complexity) discriminated VS from MCS patients. Indeed, both the average and the intertrial stability of EEG complexity increased monotonically with the patients' state of consciousness. This result confirms that the complexity of cortical activity indexes consciousness, as explicitly formulated for instance by the dynamic core model of Tononi (2008). According to this model and related ones (Seth *et al.*, 2011), a minimal level of complexity in neuronal signals is required to encode a rich and differentiated representation, thus singling it out from the vast repertoire of potential contents of consciousness. Regions specifically implicated in the coding of conscious representations would thus show higher complexity during conscious than during unconscious states, as observed here.

We found that consciousness was indexed not only by a high information complexity, but also by a stability of this complexity, with reduced fluctuations during the 30-min recording. This result extends to spontaneous EEG the findings of a recent functional MRI study showing that neural activation patterns are more reproducible when evoked by a visible than by an invisible stimulus (Schurger *et al.*, 2010). We hypothesize that this phenomenon reflects one property of the conscious brain, which is to achieve both a reproducible perception of identical sensory stimuli while keeping an internal stream of computations of roughly constant complexity even in the absence of sensory stimulation.

One of the most striking differences between patients was an increase in functional connectivity measures around the theta (4–8 Hz) frequency band ($wSMI_{\theta}$) in MCS as compared to VS patients (also see King *et al.*, 2013b). This result strengthens previous findings relating long-distance synchronization with conscious

states in patients with disorders of consciousness in similar frequency bands (Schiff *et al.*, 2005; Lehenbre *et al.*, 2012; Leon-Carrion *et al.*, 2012). In addition to generalizing this finding to a large data set, our results clarify the topography of this large-scale increase in communication. We observed a maximal effect over mesio-parietal areas, in close agreement with recent work showing the crucial role of precuneus and posterior cingulate as 'hubs' in a long-distance cortical network that may underlie conscious integration (Schiff *et al.*, 2005; Vogt and Laureys, 2005). Future research should investigate whether a more detailed description of this functional connectivity network, possibly aided by directional connectivity analyses such as Granger causality (Gaillard *et al.*, 2009; Barrett *et al.*, 2012; Lee *et al.*, 2013), may also help to distinguish these clinical groups.

The importance of long-distance cortical communication and signal complexity in consciousness fits with a set of perturbational transcranial magnetic stimulation-EEG studies conducted in patients with disorders of consciousness (Rosanova *et al.*, 2012), sleep (Massimini *et al.*, 2005) and anaesthesia (Ferrarelli *et al.*, 2010), which revealed that the prolonged propagation of transcranial magnetic stimulation-induced activation to distant sites systematically correlates with consciousness. More recently a quantification of the structure of EEG-evoked responses to the transcranial magnetic stimulation pulse has been presented (Casali *et al.*, 2013). In a small cohort of normal subjects and patients, this measure, coined perturbational complexity index, was found to discriminate conscious state across a broad range of physiological, pharmacological and pathological conditions. Further research should test whether a similar measure can be obtained without the transcranial magnetic stimulation excitation (Sitt *et al.*, 2013). It may not be irrelevant that, in the present study, long-distance communication and complexity were measured while patients were stimulated with a series of auditory tones. Our results may partially reflect the brain state evoked by these stimuli, thus paralleling those triggered by a transcranial magnetic stimulation pulse. Recording EEG while patients are stimulated with a challenging set of auditory stimuli, as we did here, presents several advantages, including increased vigilance and the capacity to simultaneously evaluate evoked and spontaneous brain activity patterns. Nevertheless, future research will be needed to disentangle which of our measures would continue to be discriminative when applied to resting-state EEG.

We also found larger fluctuations of functional connectivity in MCS than in VS patients, in particular in phase-locking index (from delta to beta) and in weighted symbolic mutual information ($wSMI_{\theta}$). Recent studies conducted with epileptic patients with implanted electrodes (SEEG) for presurgical mapping reported that loss of consciousness during the transition from partial simple to partial complex seizures was marked by a sudden excessive increase in cortico-cortical and thalamo-cortical synchrony (Lambert *et al.*, 2012; Arthuis *et al.*, 2009). Our results lead to the testable prediction that this excessive synchrony, also observed in propofol anaesthesia (Supp *et al.*, 2011), would cause a marked decrease of information complexity, which would in turn mark the loss of consciousness.

EEG studies using active cognitive tasks to probe conscious states often use event-related potentials as their main outcome

measure (Bekinschtein *et al.*, 2009; Schnakers *et al.*, 2009a). Indeed, the auditory regularities violation task used here was designed to dissociate the automatic and supposedly unconscious MMN from the P3b complex associated with conscious access. We previously demonstrated that this P3b component, which indexes the detection of the violation of a global regularity, can be useful as a specific marker of consciousness in individual patients, sometimes in advance of a clinical diagnosis (Faugeras *et al.*, 2011, 2012). The present results, however, indicate that this traditional event-related potential averaging approach lacks sensitivity in comparison with other EEG-based measures. Event-related potential components may still contribute importantly to diagnosis, but mostly when analysed with a multivariate pattern analysis procedure that deals with interindividual differences (King *et al.*, 2013a), particularly in patients whose event-related potential topography may be significantly distorted relative to the normal population.

The present results also show that event-related potential fluctuations across trials provide a sensitive measure of conscious state. Consistent with a previous functional MRI study (Schurger *et al.*, 2010), consciousness was characterized by more stereotyped responses to external stimuli. This result could also reflect the fact that VS patients presented a greater power of spontaneous low-frequency EEG signals, non-phase-locked with incoming stimuli and thus interfering with the reproducibility of evoked signals.

Our conclusions are supported by a large sample of patients with various aetiologies, robust methods controlling for multiple comparisons, and a focus on the minimal contrast between VS and MCS patients. It could be argued that differences in vigilance, rather than consciousness, also distinguish MCS and VS patients. Indeed, the CRS-R subscore of vigilance, measured just before the recording session, was slightly larger in MCS than in VS patients. However, most of the identified measures that distinguished VS from MCS patients remained significant when contrasting individuals with matched levels of vigilance. Thus, vigilance *per se* is unlikely to contribute to the identification of the relevant measures.

A significant gain in discrimination was obtained by combining several EEG measures. This is an important result for both theoretical and clinical reasons. Theoretically, this gain of information suggests that our markers tap onto distinct and dissociable features of conscious states. From the medical perspective, our results stress the usefulness of combining a subset of EEG measures (spectral, informational and connectivity-based).

Although most patients were correctly decoded on the basis of their EEG measures, the number of disagreements between the automated and clinical diagnoses remained too high for individual diagnosis. In particular, 24% of MCS patients, who manifested clear-cut behavioural signs of consciousness on some occasions, were classified as VS. We note, however, that the present study was based on a single half-hour EEG recording. As the minimal conscious state is defined by the presence of fluctuating signs, assessed by repeated clinical evaluation, it seems entirely possible that our examination was performed at a moment when these patients' consciousness lapsed. In the future, multiple sessions or even with EEG recordings might yield an improved clinical

discrimination. Although our accuracy in discriminating patients is roughly comparable to that reported by other groups (Schnakers *et al.*, 2008; Fellinger *et al.*, 2011; Gosseries *et al.*, 2011; Fingelkurts *et al.*, 2012; Lehembre *et al.*, 2012), these previous studies used smaller sample sets and were focused on quantifying the power of a single EEG measure in discriminating pre-selected groups of well-differentiated patients (e.g. non-overlapping CRS-R scores for MCS and VS groups). The present study, by contrast, tackles the more difficult problem of identifying residual consciousness in a serial cohort of all patients admitted to our clinic. Structural MRI was also reported to be efficient in discriminating patients (Fernández-Espejo *et al.*, 2011). Further work will explore if the combination of multimodal (MRI + EEG) information can achieve a better performance.

Conversely, 33% of clinically VS patients were classified as MCS by their EEG patterns. Not all of these misclassifications may be errors, however. Rather, in a subset of clinically defined VS patients, our decoder demonstrably discovered information indicating a better functional status, as indicated by a higher rate of clinically detectable recovery in the months after EEG recording. This result fits with previous functional MRI findings indicating that the vegetative state is not a homogeneous category, and that some VS patients may actually be minimally or even fully conscious (Owen *et al.*, 2006).

In conclusion, because EEG is a time-resolved, low-cost, widespread, and easily repeatable method, it may supplement MRI or functional MRI to identify VS patients with residual consciousness or with a potential for future recovery. Our results point to the possibility that a reduced set of EEG measures, selected for example on the basis of their individual discrimination power, and potentially computed from a few scalp electrodes, could ultimately serve as a reliable bedside tool to probe consciousness in patients with disorders of consciousness.

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Supplementary material

Supplementary material is available at *Brain* online.

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