Probing consciousness with event-related potentials in the vegetative state

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ABSTRACT

Objective: Probing consciousness in noncommunicating patients is a major medical and neuroscientific challenge. While standardized and expert behavioral assessment of patients constitutes a mandatory step, this clinical evaluation stage is often difficult and doubtful, and calls for complementary measures which may overcome its inherent limitations. Several functional brain imaging methods are currently being developed within this perspective, including fMRI and cognitive event-related potentials (ERPs). We recently designed an original rule extraction ERP test that is positive only in subjects who are conscious of the long-term regularity of auditory stimuli.

Methods: In the present work, we report the results of this test in a population of 22 patients who met clinical criteria for vegetative state.

Results: We identified 2 patients showing this neural signature of consciousness. Interestingly, these 2 patients showed unequivocal clinical signs of consciousness within the 3 to 4 days following ERP recording.

Conclusions: Taken together, these results strengthen the relevance of bedside neurophysiological tools to improve diagnosis of consciousness in noncommunicating patients. *Neurology*® **2011; 77:264–268**

GLOSSARY

CRS-R = Coma Recovery Scale–Revised; **ERP** = event-related potential; **MCS** = minimally conscious state; **VS** = vegetative state.

Evaluating abnormal states of consciousness may be extremely challenging when relying only on the clinical examination alone. EEG-based paradigms have many advantages over fMRI for monitoring patients with altered consciousness because of 1) the millisecond-range resolution, 2) the low cost and noninvasiveness, 3) the ability to monitor at the bedside, and 4) the possibility of designing dedicated systems for clinical use.

We recently designed a new test of consciousness using high-density scalp EEG in an auditory odd-ball paradigm.[1] This test capitalizes on 2 properties which are specific to conscious processing[2–4]: one has to be conscious of a mental representation to actively maintain it in working memory, and to use it strategically. Our test evaluates cerebral responses to violations of temporal regularities. Short-interval violations due to the unexpected occurrence of a single deviant sound among a repeated train of standard sounds led to an early and automatic response in auditory cortex, the mismatch negativity ERP component. Moreover, long-term violations, defined as the presentation of a rare and unexpected series of 5 sounds, led to a late and spatially distributed response that was present only when subjects were attentive and aware of the auditory rule and of its violations (P3b component). Our observations showed that this

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rule violation effect is a specific signature of conscious processing, although it can be absent in conscious subjects unaware of long-term auditory regularities.

In this work, we explored the relevance of this rule violation effect test in 31 patients who were in vegetative states of various chronicity. Our main objective was to assess the added value of our test in patients in whom detailed clinical examination and Coma Recovery Scale–Revised (CRS-R) scoring failed to detect any reliable evidence of consciousness. The second objective of this study was to explore the prognostic value of the test by following each of these patients, and to correlate the ERP test with early and late outcomes.

METHODS

Standard protocol approvals, registrations, and patient consents. This study has been approved by the ethical committee of the Salpêtrière Hospital (Paris, France).

Controls. Ten controls were recorded (age 20.3 ± 0.7 years; sex ratio [M/F] 2.3). Data from 2 subjects were discarded due to excessive movement artifacts.

Patients. We report here all recordings of patients in vegetative state (VS) from November 2008 to February 2010. Patients with clinical criteria of VS, irrespective of delay from

Table Patients' characteristics and outcomes

Patient no.	Age, y	Sex	Etiology	Lesion site	Delay, days	CRS-R Total	CRS-R Subscores	ERP	Outcome <7 d	Outcome >6 mo
1	62	F	ADEM	Diffuse white matter hyperintensities	25	1	0/0/0/0/0/1	+	MCS	MCS
2	47	F	Anoxia	—	54	3	1/0/1/0/0/1	–	Dead	Dead
3	48	F	Anoxia	Diffuse gray and white matter hyperintensities	14	3	0/0/1/1/0/1	–	VS	Dead
4	61	M	ICH	IVH + diffuse white matter hyperintensities	25	3	0/0/0/1/0/2	–	Dead	Dead
5	29	F	Anoxia	Diffuse brain atrophy	85	4	1/0/1/1/0/1	–	VS	Dead
6	65	F	Anoxia	Diffuse cortical and basal ganglia hyperintensities	20	4	1/0/1/1/0/1	–	VS	VS
7	74	F	Anoxia	Diffuse brain atrophy	610	5	1/1/1/1/0/1	–	VS	Dead
8	44	M	ICH	Left cerebellar hematoma + IVH	42	5	1/0/1/1/0/2	–	VS	MCS
9	67	M	ICH	Right frontal hematoma + IVH	25	5	1/1/1/1/0/1	–	VS	Dead
10	41	M	ICH	Left frontoparietal hematoma + ICA aneurysm + left MCA and ACA vasospasm	350	5	1/0/1/2/0/1	–	VS	VS
11	46	M	Stroke	Bilateral mesencephalic + cerebellum + thalamic + occipital stroke	89	5	1/0/1/1/0/2	–	VS	Dead
12	51	M	TBI	Right convexity SDH + bilateral hemorrhagic cortical contusions	15	5	1/1/1/1/0/1	+	MCS	Dead[a]
13	43	F	TBI	Severe brain atrophy (cortical cavitations)	2,555	5	1/0/1/1/0/2	–	VS	VS
14	22	M	Anoxia	Diffuse cortical and basal ganglia hyperintensities	16	5	1/0/1/1/0/2	–	VS	CS
15	40	M	TBI	Right temporofrontal EH + left hemispheric SDH	62	6	1/1/2/1/0/1	–	VS	Dead
16	76	M	Anoxia	Diffuse leukoencephalopathy	25	6	1/1/2/1/0/1	–	MCS	Dead
17	70	F	ICH	Left frontal hematoma + ACoA aneurysm + left MCA and ACA vasospasm	17	6	1/1/2/1/0/1	–	Dead	Dead
18	39	M	ICH	ICA aneurysm + left caudate hematoma	37	6	1/1/1/1/0/2	–	VS	CS
19	62	M	ICH	ACoA aneurysm + interhemispheric hematoma + IVH	19	7	1/1/2/1/0/2	–	VS	CS
20	29	M	TBI	Right frontoparietal SDH + IVH	33	7	2/1/2/1/0/1	–	VS	CS
21	45	M	Anoxia	Mesencephalic + right hemispheric cerebellar hyperintensities	19	7	2/1/1/1/0/2	–	VS	Dead
22	76	F	Anoxia	Diffuse brain atrophy	46	8	2/1/2/2/0/1	–	MCS	CS

Abbreviations: ACoA = anterior communicating artery; CRS-R = Coma Recovery Scale–Revised; CS = conscious state; EH = extradural hematoma; ERP = event-related potential; ICA = internal carotid artery; IVH = intraventricular hemorrhage; MCA = middle cerebral artery; MCS = minimally conscious state; SAH = subarachnoid hemorrhage; SDH = subdural hematoma; UA = unresponsive awake state (criteria of vegetative state irrespectively of delay); VS = vegetative state.

[a] The patient died from a fatal hemorrhage recurrence on day 34.

disease onset (both early and longstanding states), were included. Patients were recorded without sedation since at least 24 hours. Among the 31 recordings 9 were discarded after evaluation of EEG quality (appendix e-1 on the *Neurology*® Web site at www.neurology.org). This high rate of rejection (29%) reveals one of the limits of this technique. The 22 valid datasets included 13 men and 9 women, aged from 22 to 76 years (mean 51.7 years), with both early and late recordings (mean 190 days; median 29 days; SD 546 days; earliest 14 days; latest 2,555 days; table).

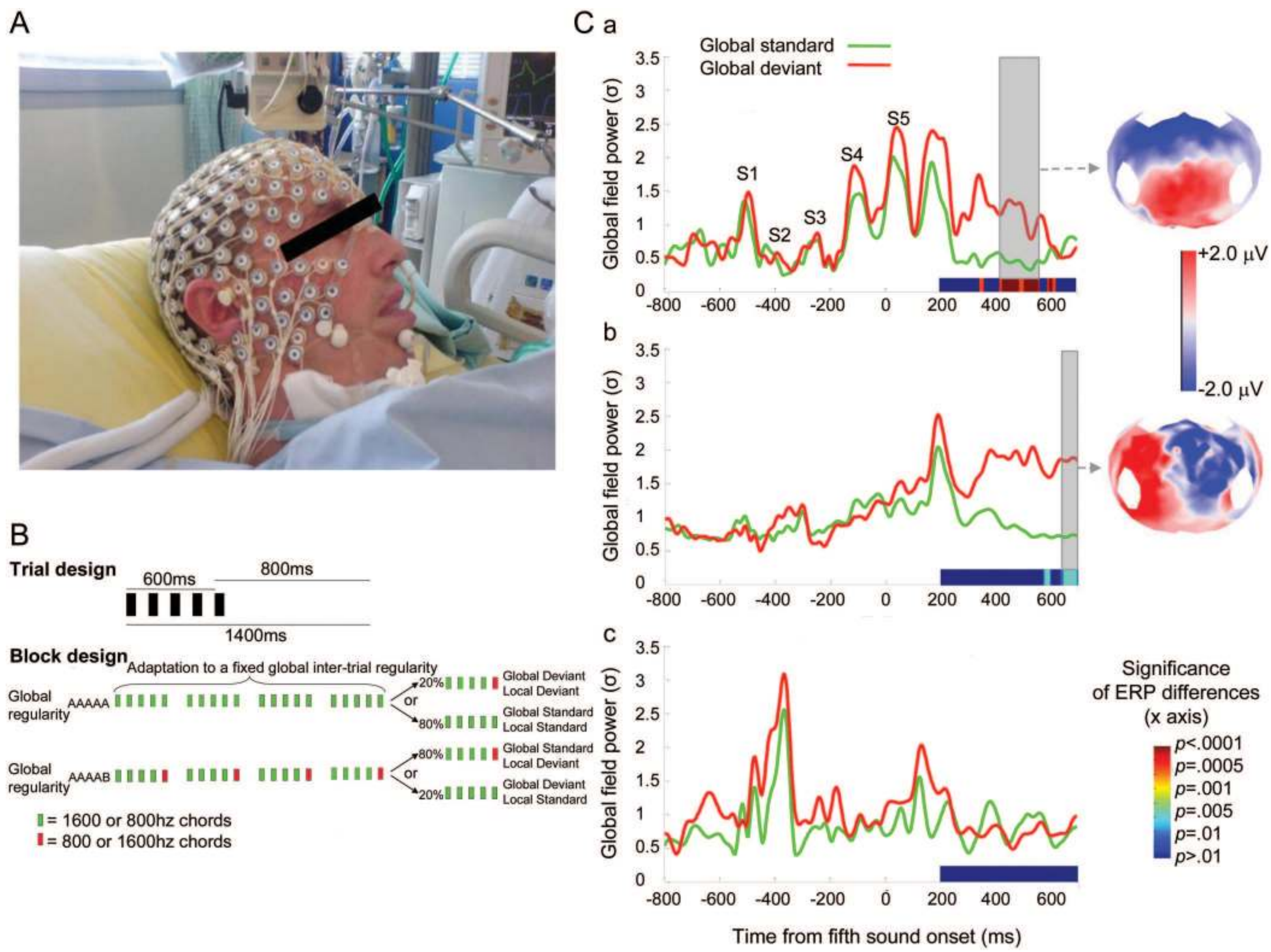
Behavior. The clinical definition of VS was based on the French version of the CRS-R scale.[5] It was carried out after careful neurologic examination by trained neurologists (F.F., L.N.), immediately before ERP recording.

Stimulation and ERPs. We used our previously published auditory protocol while recording high-density scalp EEG (EGI, Eugene, OR). See reference[1] and appendix e-1 for details.

RESULTS A rule violation ERP effect was present in each of the 8 controls (100%) within the 300–700 msec temporal window after the onset of the fifth sound, replicating our previous findings (see control group 1 in reference[1]). Among the 22 patients, 2 (9%) showed a significant effect (figure). None of the remaining 20 patients was deaf, and early cortical responses to the tones could be identified on all ERP recordings, thus discarding a trivial interpretation of the absence of rule violation effect.

One of the 2 patients was a 62-year-old woman with a severe form of acute disseminated encephalomyelitis following a spontaneously resolving flu-like episode. MRI showed extensive bilateral hemispheric hyperintensities on fluid-attenuated inversion recovery images, with gadolinium enhancement on T1-

Figure Test design and illustration of bedside recording in intensive care unit (ICU)



(A) Bedside recording in ICU. Photography of the recording setting in a patient in the ICU (with the patient's permission). Installation of the net and EEG calibration requires about 15 minutes. Earphones are then applied, task instruction delivered, and EEG recording starts. (B) Auditory paradigm. On each trial 5 sounds were presented. Each block started with 20–30 frequent series of sounds to establish the long-term regularity before delivering the first infrequent rule deviant stimulus. (C) Three representative results. Global field power of rule standard (green) and rule deviant (red) trials are plotted for one conscious control subject (C.a), for a patient with a rule violation effect (C.b), and for a patient without rule violation effect (C.c). Early peaks to each of the 5 sounds (S1 to S5) are indicated for the control subject. Statistical significance of event-related potential (ERP) differences within the time window of the rule violation effect is indicated by a color code on the X axis. Voltage topography maps averaged across time windows of significant ERP effects are displayed on the right. Panel C is reprinted from Bekinschtein et al.[1]

weighted sequence. She was recorded 25 days after disease onset. Neurologic examination immediately before ERP recording showed preserved brainstem reflexes, with slight anisocoria (right < left). Babinski and Hoffmann signs were observed on the left side. All tendon reflexes were present. Eye-opening was systematically obtained under auditory or nociceptive stimulation. However, even when arousal was stimulated, no behavioral sign of consciousness could be obtained (CRS-R = 1/23).

The second patient with a positive ERP test was a 51-year-old man who had a severe traumatic brain injury with a massive acute right-hemispheric subdural hematoma which required surgical treatment. MRI then revealed additional hemorrhagic cortical contusions located in both occipital and frontal areas, and in the left mesial temporal lobe. He was recorded 15 days after trauma. Neurologic examination immediately before ERP recording showed preserved brainstem reflexes, with a slow stereotyped flexion response to nociceptive stimulation. A left Babinski sign was present, and all tendon reflexes were present. Eye-opening was systematically obtained under auditory or nociceptive stimulation, and CRS-R reached 5/23.

Both patients reached criteria of minimally conscious state (MCS) 3 and 4 days after ERP recording, respectively. By contrast, in the 20 remaining patients with a negative result, early recovery of consciousness was observed in only 2 cases within the first week ($\chi 2 = 9.90$, $p = 0.002$; Fisher exact test: $p = 0.026$), indicating that the global effect was significantly predictive of overt consciousness recovery. When studying outcome within a longer time frame (>6 months), 7/20 initially VS patients without ERP effect reached either an MCS or conscious state ($\chi 2$ test = 3.18, unilateral $p = 0.037$).

DISCUSSION A rule violation effect was observed in 2 patients who met clinical criteria of VS, suggesting that they consciously identified rule deviants. The relative weakness of their effect may correspond to fluctuations of consciousness or to partial execution of the task (e.g., conscious identification of targets without counting). In any case, as shown previously,[1] the mere identification of rule deviant trials requires conscious processing of the stimuli, while nonconscious P300/N400-like ERP responses have been reported with simpler paradigms in controls and patients.[6–9] Therefore, the positivity of this ERP test is a strong argument to correct the clinical diagnosis in these 2 patients, and to classify them as conscious in spite of the negative behavioral assessment. In both patients, the negativity of clinical examination and of CRS scoring could not be explained by motor impairments. These 2 cases are reminiscent of recent reports of the few patients clinically assessed as VS who showed evidence of consciousness in active fMRI paradigms.[10,11]

Our test, however, presents several limitations: the high rate of data rejection is inherent to EEG recording in awake and nonsedated patients. Moreover, our test lacks sensitivity in as much as it requires the patient not only to be conscious, but also to understand task instructions, to keep them in working memory, to continuously keep attention focused on the stimuli, and to mentally count global deviants.

The second objective of our study was to explore value of the ERP global effect for the prognosis of patients in VS. Interestingly, in terms of consciousness, the early outcome was much better in patients with a rule violation effect than in those lacking it. This differential outcome was less pronounced on a longer time scale. This is compatible with our proposal that the rule violation effect is a neural signature of consciousness per se rather than a predictor of consciousness recovery. Long-term (≥2 years) follow-up will be addressed in a dedicated study.

The auditory rule violation ERP test can be used to probe consciousness, and its positivity in patients who meet clinical criteria of VS therefore questions the clinical diagnosis.

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DISCLOSURE

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