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Evidence of cortical learning in vegetative state

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Sirs: Vegetative state (VS) is the complete lack of coherent behavior despite the presence of a sleep-wakefulness cycle and normal or even exaggerated reflexes [3]. The same clinical condition was previously described as apallic syndrome [4]. Recent imaging studies repeatedly report remaining cortical functions in some patients [2, 7, 10]. These reports, however, mostly concern small patient samples. Given the difficulty of the differential diagnosis of VS [1], a sceptic might suggest that the described patients presented diagnostic errors, borderline cases, or otherwise exceptions from the VS population.

A learning process in form of the habituation of blink reflex has been reported [11, 12] in a selected subgroup of VS patients with better behavioral responsiveness. However, blink reflex is a simple brain stem reflex which persists even in decorticated preparations. A study of a large group of VS patients [12] mentioned that the habituation of the cortical component N1 of auditory evoked potentials (EPs) was also examined; however, the authors did not report whether the habituation process was really observed in VS.

We examined thirty-three VS patients (14 females), aged 19–62 years (mean 42.1). The clinical diagnosis was based on the complete absence of goal-directed behavioral responses. Patients with apparent but inconsistent responses (in whom a diagnosis of minimally conscious state might be suggested) were excluded, as were patients younger than 14 years and those with severely disturbed brain stem auditory EPs. The Disability Rating Scale [9] was > 21. Disease duration ranged from 2–70 months (mean 6.8). Etiological factors were head injury (16 patients), subarachnoidal hemorrhage (8), or brain anoxia (9).

Ten runs of 50-ms 800-Hz sine frequencies were presented, one per 400 ms, with the intervals between runs being 5 s. An additional, 11th run contained tones of 1500 Hz. Auditory EPs were recorded from Fz and Cz sites, referred to mastoids. The electrooculogram was recorded using electrodes attached to the left and right orbital rim, and above and below the right eye. Ocular artifacts were removed by means of a regression technique [6]. EPs were averaged, firstly, across trials in each run (resulting in 11 averages, the last of them to the deviant 1500 Hz tone), and secondly, across the ten 800 Hz runs for each trial number (i.e., 10 first trials, 10 second trials, etc.). Thus each average contained 10 trials. The amplitude of the N1 component was measured, and the rate of its change across trials and runs was taken as a measure of short-term and long-term habituation, respectively (Fig. 1).

The N1 amplitude decreased with repetition across trials with a rate of 0.13 μV/trial ($t = 2.05$, $p < 0.05$) and 0.24 μV/trial ($t = 3.60$, $p < 0.001$), for Cz and Fz, respectively (Fig. 2, top). The amplitude decrement across runs was less steep (0.07 to 0.15 μV/run) and attained significance at Fz only ($t = 2.59$, $p < .02$). Given the short interstimulus interval, the amplitude decrease across trials might be accounted for by refractoriness, rather than habituation as a central learning process. However, refractoriness should have an even stronger effect on P2 (due to its larger latency), but the P2 amplitude did not change with stimulus repetition, which is in line with habituation data [5]. Further, the refractoriness hypothesis predicts that patients with a faster N1 decrement (i.e., unstable responses) would have a smaller N1 averaged across all 100 trials. Exactly the opposite was the case: patients with a faster N1 decrement had a higher N1 across all trials ($p < 0.001$).

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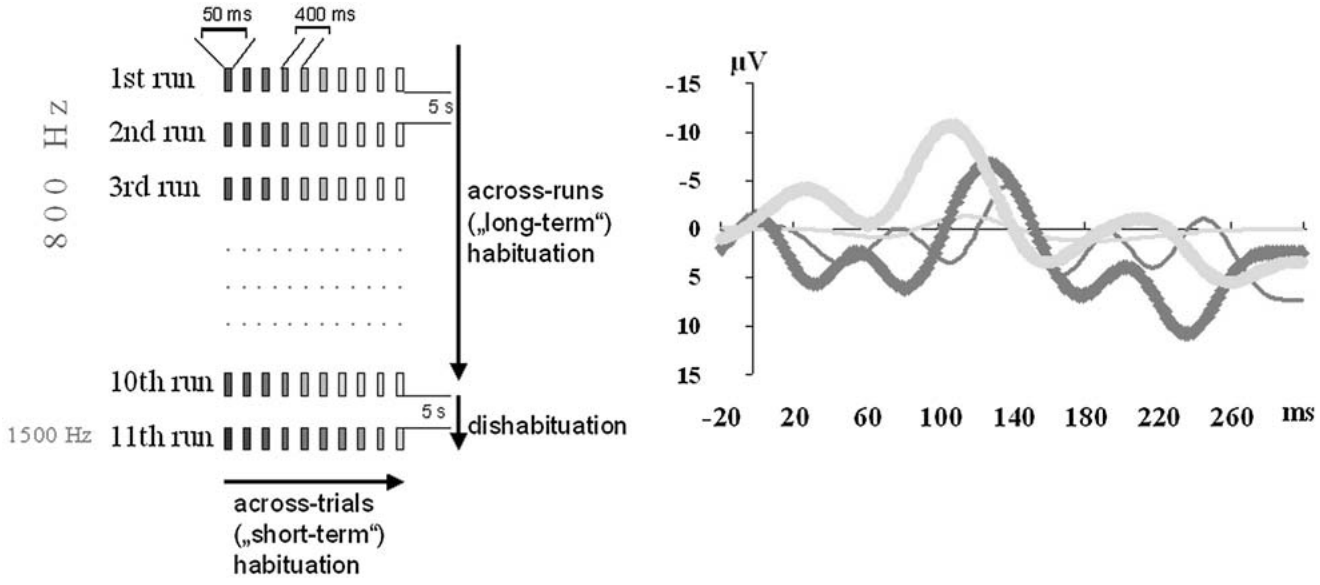

Fig. 1 Left panel: Schema of stimulus presentation: ten runs of ten 800-Hz tones were followed by a run of ten 1500-Hz tones. Evoked potential (EP) changes across trials within runs indicated "short-term" habituation. EP changes across runs indicated "long-term" habituation. EP changes between the 10th and the 11th run indicated dishabituation. Right panel: Examples of EPs in two vegetative state patients (light and dark lines respectively). Bold lines: EP in the first run. Thin lines: EP in the 10th run. The N1 peak was defined as the largest negativity between 90 and 150 ms, and the P2 peak, as the largest positivity between 150 and 300 ms. The amplitudes of these components were measured as the mean amplitude within an interval of ± 30 ms around the peak. Habituation rate was calculated as the term b (i.e., the slope) in the equation (Amp) = a + bN, where (Amp) was the component amplitude, and N was the trial number or run number, in both instances N running from 1 to 10

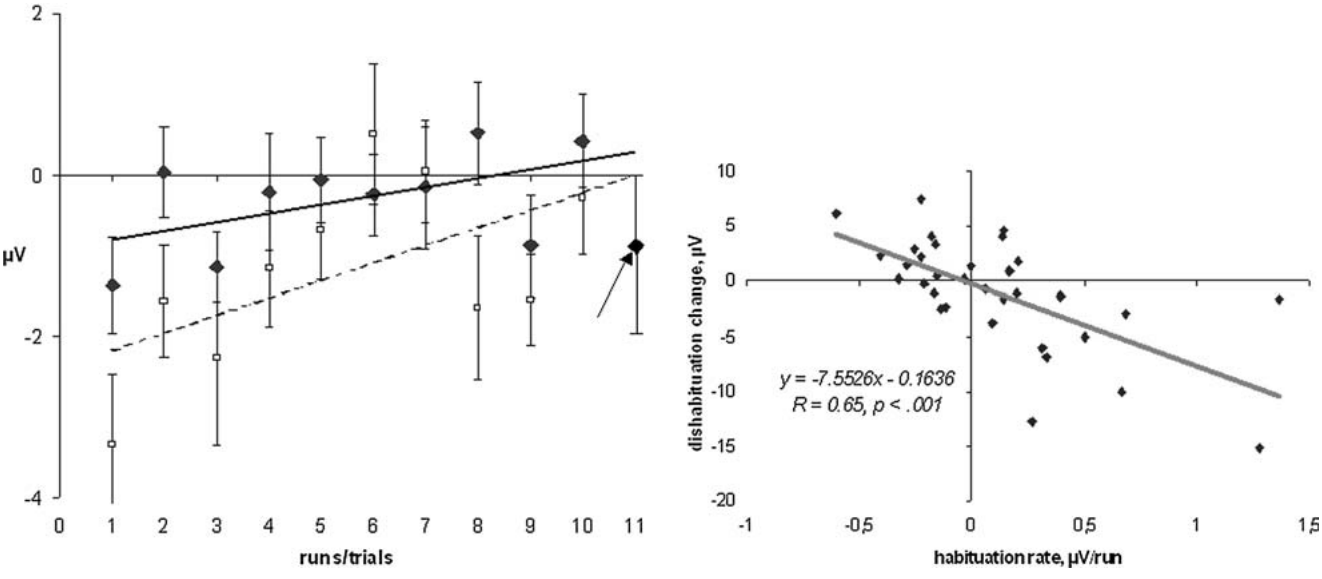

Fig. 2 Left panel: Changes of the N1 amplitude across trials (empty squares, linear approximation shown by the dashed line) and across runs (filled diamonds, linear approximation shown by the solid line), averaged over thirty-three patients with persistent vegetative state (Cz lead). The rightmost diamond pointed by the arrow indicates the reinstatement of the EP amplitude after stimulus change (dishabituation). Right panel: The relationship between the rate of interrun habituation and the magnitude of the following dishabituation of the EP, across all PVS patients

The change of tone pitch in the 11th run yielded an increase of N1 by 1.1 μV as compared with the 10th run, but due to a broad variance this increment was not significant. However, the rate of amplitude decrement from the 1st to the 10th run strongly correlated ($p < 0.001$) with the sub-

sequent restitution of the amplitude after stimulus change (Fig. 2, bottom). The fact, that the two changes shared more than 42% variance, indicates that they cannot be attributed to random variation.

Thus habituation of the N1 amplitude was observed in a group of VS patients, indicating an elementary learning process. In contrast, most cortical processes previously observed in PVS were static and they did not include a learning component. Also, this finding is different from habituation of blink reflex previously reported in a selected group of patients [11, 12]. Whereas blink reflex is a simple brain stem response, the sources of the N1 component are in the superior temporal gyrus and, additionally, in the frontal lobe [8]. Therefore the N1 amplitude decrement indicates that cortex learns to selectively ignore repeated irrelevant stimuli. Never before has cortical learning been described in VS. This significant learning characterised a large non-selected sample of VS patients, thereby making implausible any account on this finding as a consequence of a diagnostic error.

Declaration

The study was a part of the project approved by the Ethical Committee of the University of Tübingen, Medical Faculty.

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