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LETTER TO THE EDITOR

Neural detection of complex sound sequences or of statistical regularities in the absence of consciousness?

Lionel Naccache,[1,2,3,4,5] Jean-Rémi King,[3,6] Jacobo Sitt,[3,6] Denis Engemann,[3,6] Imen El Karoui,[3] Benjamin Rohaut,[1,3] Frédéric Faugeras,[3] Srivas Chennu,[7] Mélanie Strauss,[6] Tristan Bekinschtein[8] and Stanislas Dehaene[6,9]

1 AP-HP, Groupe hospitalier Pitié-Salpêtrière, Department of Neurology, Paris, France
2 AP-HP, Groupe hospitalier Pitié-Salpêtrière, Department of Neurophysiology, Paris, France
3 INSERM, U 1127, F-75013, Paris, France
4 Institut du Cerveau et de la Moelle épinière, ICM, PICNIC Lab, F-75013, Paris, France
5 Sorbonne Universités, UPMC Univ Paris 06, Faculté de Médecine Pitié-Salpêtrière, Paris, France
6 INSERM-CEA Cognitive Neuroimaging unit | CEA/SAC/DSV/DRM/Neurospin center, Gif/Yvette cedex, France
7 MRC-Cognition and Brain Sciences Unit, Cambridge, UK
8 Department of Psychology, University of Cambridge, Cambridge, UK
9 Collège de France, 75005 Paris, France

Correspondence to: Lionel Naccache
AP-HP, Groupe hospitalier Pitié-Salpêtrière,
Department of Neurology, Paris, France
E-mail: lionel.naccache@psl.aphp.fr

Sir,
We read with interest the article by Tzovara *et al.* (2015), recently published in *Brain*. In this study the authors adapted a paradigm we previously designed (Bekinschtein *et al.*, 2009) to probe the EEG of comatose patients in response to two types of violations of auditory regularities. Unfortunately, several important problems mitigate the reliability of their conclusions.

In the local-global paradigm, local auditory irregularities correspond to a change of sound within a trial, whereas global irregularities correspond to a change of sound sequence across trials.

The authors showed with a decoding algorithm a significant difference in EEG responses to global violations in 10 of 24 comatose patients. Observing such a global effect in unconscious subjects challenges our previous conclusion that this global effect can only be observed in conscious and attentive subjects (Bekinschtein *et al.*, 2009; Wacongne *et al.*, 2012; El Karoui *et al.*, 2014) and systematically disappears in inattentive subjects (Bekinschtein *et al.*, 2009; King *et al.*, 2013), sleeping subjects (Strauss *et al.*, 2015), and clinically unconscious patients in vegetative state (Faugeras *et al.*, 2011, 2012). Converging findings from multiple functional brain imaging tools [high-density EEG, magnetoencephalography (MEG), intracranial stereoelectroencephalography (SEEG), functional MRI] demonstrated that the global effect is characterized by a late (> 300 ms after violation onset) and sustained brain response (King *et al.*, 2014) typical of conscious access (Dehaene and Naccache 2001; Dehaene *et al.*, 2011). In our data, the only two patients in a vegetative state showing a late global effect recovered clinical signs of minimally conscious state within the next 3 to 4 days (Faugeras *et al.*, 2011), suggesting that EEG could be more sensitive to conscious processing than clinical examination.

In this context, the conflicting results of Tzovara *et al.* call for an explanation. Two main aspects may account for the discrepancy between Tzovara *et al.*'s study and our original findings: differences in the type of patients being recorded, and differences in the analyses conducted on the EEG signals.

First, the patients recorded by Tzovara *et al.*, were not in a vegetative or minimally conscious state, but in post-anoxic comatose state under mild therapeutic hypothermia (33°C)

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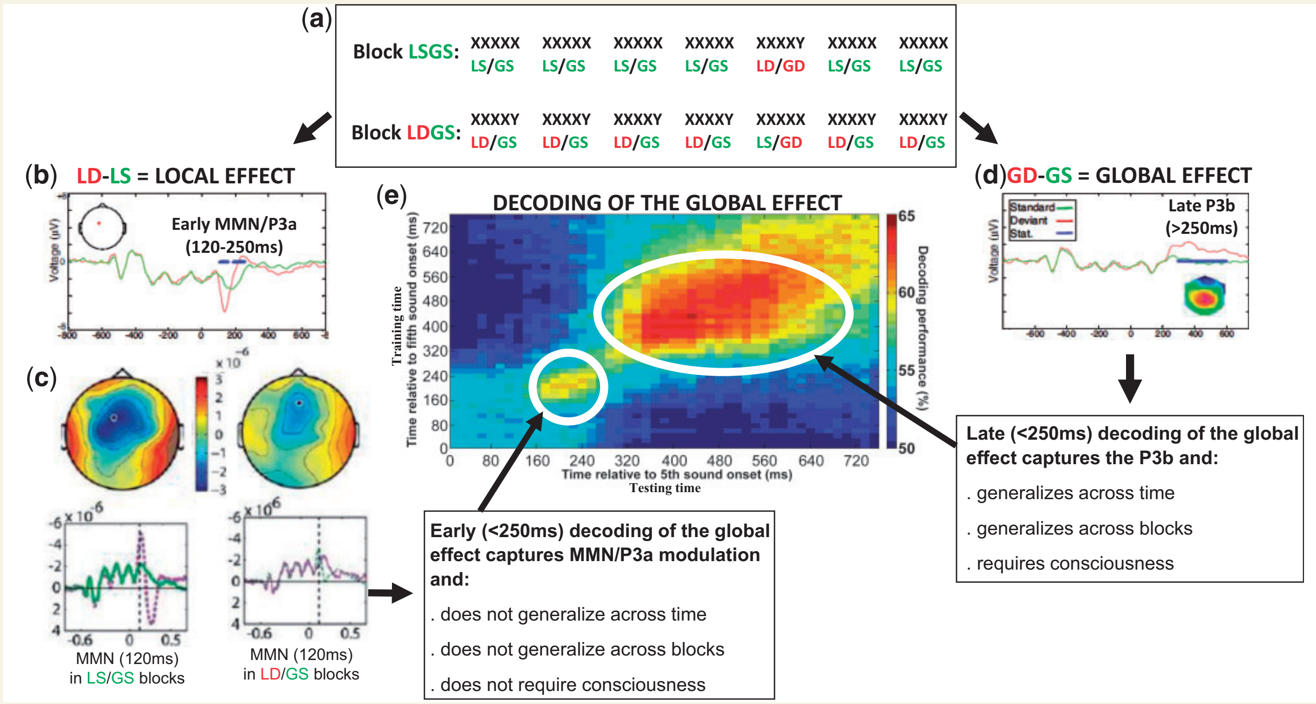

Figure 1 Two distinct time windows for the global effect: separating an early, transient and unconscious effect from a late, sustained and conscious effect. (**A**) The local-global paradigm crosses orthogonally two levels or regularities with local standard or deviant (LS, LD) trials that can be either global standard or deviant (GS, GD) trials according to the block rule (LSGS versus LDGS). (**B**) The local effect corresponds to an early (120–250 ms) event-related potential complex combining a MMN component followed by a P3a (adapted from Bekinschtein *et al*., 2009). (**C**) Crucially, the MMN is affected by the frequency of local deviant trials (adapted from Wacongne *et al*., 2012). (**D**) The global effect corresponds to a late (250–700 ms) sustained P3b event-related potential component independent from the physical attributes of the stimuli (adapted from Bekinschtein *et al*., 2009). (**E**) Multivariate algorithmic technics can decode the global effect at two time windows corresponding to two distinct processes: an early (120–250 ms) transient and low-level perceptual process only sensitive to statistical regularities of the stimuli, which does not require conscious processing, followed by a late (250–700 ms) sustained abstract cognitive process sensitive to the abstract rule and which requires a minimal level of consciousness.

or normothermia. Therapeutic hypothermia is usually associated with curare administration (vecuronium was used by Tzovara *et al*.; see Supplementary material) which obviously limits the behavioural assessment of conscious state. While this point is not discussed by Tzovara *et al*., it would inevitably lower the confidence in the diagnosis of comatose state, especially for those patients who showed a reactive EEG. If such patients were actually conscious but paralysed, the interpretation of the findings would be very different. In addition, the report of a significant global effect in one hypothermic patient with a burst suppression EEG pattern, which corresponds to severely impaired cortical processing, and in three normothermic patients with non-reactive EEG, raises doubts as no late event-related responses would be expected under such conditions. In comparison, surprisingly, Tzovara *et al*. managed to decode the global effect above chance level in only 6 of 21 control subjects. This lack of results in control subjects sharply contrasts with our own studies, in which all attentive subjects demonstrated a strongly significant P3b global effect (Bekinschtein *et al*., 2009; Faugeras *et al*., 2011, 2012; King *et al*., 2013).

Second, a major problem is that the vast majority of results reported by the authors occurred during the early time-period (0–250 ms) following the onset of the irregular sound. This early time-window obviously misses the late P3b component (~300—700 ms), and thus fails to provide a legitimate test of our proposal that this component relates to consciousness. In an extensive multivariate decoding study of four experiments (high-density EEG, MEG, SEEG) performed in conscious controls and in 165 vegetative–minimally conscious state patient recordings, we (King *et al*., 2013) previously reported important points that Tzovara *et al*. failed to take into account (Fig. 1). When decoding the global effect at the single-trial level, two temporal windows contain relevant information about global violations: an early (< 250 ms) modulation of the mismatch negativity (MMN) and P3a complex, followed by a late (> 250 ms) and sustained P3b component. Major differences exist between these two event-related potentials: the early global effect contemporary of the MMN-P3a reflects an unconscious appraisal of statistical regularities inherent in our paradigm, rather than a genuine abstract processing of global violations (Wacongne *et al*., 2012; Chennu *et al*., 2013; King *et al*., 2013). Conversely, the late brain responses to global violations relate to the updating of a rule representation in conscious working memory.

This conclusion is supported by additional decoding analyses applied to different subsets of the trials. Specifically, the local–glocal paradigm uses two blocks to orthogonalize local and global violations in such a way that a global deviant can be either a local standard trial (XXXXX) or a local deviant trial (XXXXY). When half of trials (XXXXX or XXXXY trials) are used to train a decoder to distinguish global standard from global deviant trials, and that this decoder is then tested on the second half of trials (XXXXY or XXXXX trials), the decoding performance in the early time window drops considerably, whereas the decoding performance of the late time windows remains unchanged (King *et al*., 2013).

Together, these results suggest that a global effect can be taken as an index of conscious access only if it is significant during the late time-window (>250 ms) (Faugeras *et al*., 2011, 2012). By contrast, the results reported by Tzovara *et al*. may correspond to an unconscious modulation of the early MMN by statistical regularities, rather than to a classic P3b effect associated with conscious access. This interpretation could explain why Tzovara *et al*. still detected a modulation of the MMN in comatose patients with a non-reactive EEG or under burst-suppression regime. It would also be coherent with the prognosis value of this effect: it is long known that the presence of the MMN is a predictor of clinical recovery from coma (Kane *et al*., 1993; Fischer *et al*., 1999, 2004; Naccache *et al*., 2005), and Tzovara *et al*.'s paper further suggests that patients with improved decoding of the early global effect have a better prognosis of consciousness recovery, as previously shown by the same group for the dynamics of the MMN (Tzovara *et al*., 2013).

We end by regretfully noting that the authors refused to share with us their published data, although this would have allowed us to test the above interpretation by re-analysing separately the early and late global effects.

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