

Information Sharing in the Brain Indexes Consciousness in Noncommunicative Patients

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Summary

Neuronal theories of conscious access tentatively relate conscious perception to the integration and global broadcasting of information across distant cortical and thalamic areas [1–6]. Experiments contrasting visible and invisible stimuli support this view and suggest that global neuronal communication may be detectable using scalp electroencephalography (EEG) [3, 5–11]. However, whether global information sharing across brain areas also provides a specific signature of conscious state in awake but noncommunicating patients remains an active topic of research [12–15]. We designed a novel measure termed “weighted symbolic mutual information” (wSMI) and applied it to 181 high-density EEG recordings of awake patients recovering from coma and diagnosed in various states of consciousness. The results demonstrate that this measure of information sharing systematically increases with consciousness state, particularly across distant sites. This effect sharply distinguishes patients in vegetative state (VS), minimally conscious state (MCS), and conscious state (CS) and is observed regardless of etiology and delay since insult. The present findings support distributed theories of conscious processing and open up the possibility of an automatic detection of conscious states, which may be particularly important for the diagnosis of awake but noncommunicating patients.

Results

We evaluated whether measures of brain-scale information sharing, derived from 181 high-density electroencephalography (EEG) recordings, could discriminate, within awake

patients, those showing clinical signs of consciousness from those who do not. Our research capitalizes on experimental studies in normal subjects showing that consciously perceived stimuli, relative to subliminal stimuli, lead to a late ignition of frontoparietal networks and to an increased sharing of information in the brain [3]. Several theories share the hypothesis that this global communication between distant cortical areas defines what we experience as a conscious content [1–6, 16–18].

To quantify global information sharing, we introduced a novel measure, weighted symbolic mutual information (wSMI), which evaluates the extent to which two EEG signals present nonrandom joint fluctuations, suggesting that they share information (Figure 1). This method presents three main advantages. First, it looks for qualitative or “symbolic” patterns of increase or decrease in the signal, which allows a fast and robust estimation of the signals’ entropies. The symbolic transformation depends on the length of the symbols (here, $k = 3$) and their temporal separation (here, $\tau = 4, 8, 16$ or 32 ms; see Supplemental Experimental Procedures and [19]). Second, wSMI makes few hypotheses on the type of interactions and provides an efficient way to detect nonlinear coupling. Third, the wSMI weights discard the spurious correlations between EEG signals arising from common sources and favor nontrivial pairs of symbols, as confirmed by simulations (see Figure S1 available online).

We focused our analyses on patients with preserved arousal abilities. Within this category, vegetative state (VS) patients present no clinical signs of conscious behavior, whereas minimally conscious state (MCS) patients demonstrate fluctuating but consistent deliberate responses [20].

wSMI Indexes the State of Consciousness

When considering the median wSMI across all channel pairs, analyses with $\tau = 32$ ms revealed that VS patients ($n = 75$) presented significantly lower information sharing than MCS patients ($n = 68$; $U = 3737$, $p < 10^{-5}$, area under the curve [AUC] = 0.73), conscious (CS) patients ($n = 24$; $U = 1445$, $p < 10^{-5}$, AUC = 0.80), and healthy (H) controls ($n = 14$; $U = 890$, $p < 10^{-4}$, AUC = 0.85) (Figure 2A). A robust regression confirmed that median wSMI predicted the clinical group to which the subjects belonged (1: VS, 2: MCS, 3: CS, 4: healthy; $p < 10^{-6}$). These effects were observed for all temporal separation parameters τ , except the shortest value of $\tau = 4$ ms (Figure S2A).

wSMI Is Consistent across Etiologies and Delay since Insult

We tested the robustness of wSMI to variability in etiologies and delay since the initial insult. An ANOVA across patients, consciousness states and etiologies showed a main effect of consciousness state [$F(2,119) = 11.96$, $p < 10^{-4}$] but no main effect of etiology [$F(3,119) = 1.83$, $p = 0.145$]. The difference in median wSMI between VS and MCS patients remained significant within cases of anoxia [$n = (23$ VS, 9 MCS); $U = 181$, $p = 0.001$, AUC = 0.87], traumatic brain injury [$n = (21, 27)$; $U = 126$, $p = 0.001$, AUC = 0.78] and stroke [$n = (18, 20)$; $U = 102$, $p = 0.024$, AUC = 0.72] (Figure 2B).

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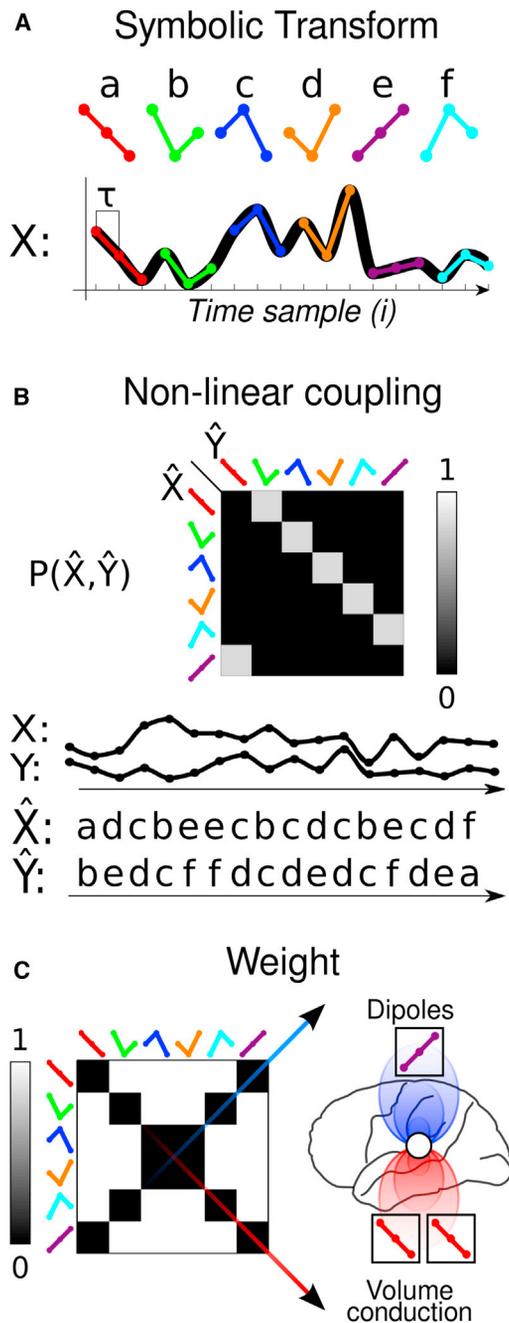


Figure 1. Weighted Symbolic Mutual Information

(A) The transformation of continuous signals (X) into sequences (\hat{X}) of discrete symbols (A, B, ... F) enables an easy and robust estimation of the mutual information shared between two signals. The τ parameter refers to the temporal separation of the elements that constitute a symbol, composed of three elements.

(B) By computing the joint probability of each pair of symbols, we can estimate the symbolic mutual information (SMI) shared across two signals.

(C) To compute weighted symbolic mutual information (wSMI), the SMI is weighted to disregard conjunctions of identical or opposite-sign symbols, which could potentially arise from common-source artifacts.

Similarly, when we categorized the patients according to the time delay between disorder onset and EEG recording [acute (<25 days), intermediate (25–50 days), or chronic (>50 days)], we again found a main effect of consciousness state

[$F(2,132) = 10.01, p < 10^{-4}$] but no main effect of delay [$F(2,132) = 2.24, p = 0.110$]. The difference in median wSMI between VS and MCS patients remained significant within chronic [$n = (23 \text{ VS}, 18 \text{ MCS}); U = 295, p = 0.022, \text{AUC} = 0.71$] and intermediate [$n = (25, 25); U = 98, p < 10^{-4}, \text{AUC} = 0.84$] patients and was marginal in acute subjects [$n = (28, 24); U = 443, p = 0.054, \text{AUC} = 0.66$] (Figure 2D). Patients tested just after the insult (<10 days) presented a significant effect as well [$n = (6, 6); U = 36, p = 0.002, \text{AUC} = 1.00$; Figure 2C].

Relationship between wSMI and Other Entropy or Spectral Measures

Does wSMI merely detect a difference that is also present in simpler measures? First, mutual information need not covary with the entropies of the two signals but is bounded by them. Empirically, we found that permutation entropy significantly increased with consciousness states (Figure S2I). Crucially, the differences in wSMI between VS and MCS patients remained significant after normalizing the symbolic mutual information by local permutation entropy (Figure S2J). Thus, wSMI did not simply reflect changes in local entropies.

Similarly, the power in various frequency bands correlated partially with wSMI (Table S2) and was informative about the patients' state of consciousness (Figure S2G). Nevertheless, in a stepwise regression, median wSMI at $\tau = 16$ and 32 ms systematically outperformed power spectrum measures in discriminating VS and MCS patients. Furthermore, once wSMI was entered in the model, spectral differences were no longer predictive. At shorter τ (4 or 8 ms), the converse pattern was observed: power spectrum measures contributed to the prediction of consciousness state whereas wSMI did not (Table S3). Therefore, for long τ , wSMI provides robust information about consciousness over and above power spectral densities.

A distinct question is which frequency bands carry the effects detected by wSMI. Each selection of a τ value sensitizes wSMI to a different frequency range ($\sim 4\text{--}10$ Hz for $\tau = 32$ ms; $\sim 8\text{--}20$ Hz for $\tau = 16$ ms; Figure S2H). Further band-pass filtering prior to wSMI computation suggested that the difference between VS and MCS was particularly driven by events in the θ band (4–8 Hz). However, no consistent group differences were found in phase-locking value or phase-locking index at 4Hz or above, and phase locking alone did not suffice to explain the difference in wSMI (Tables S4 and S5).

wSMI Impairments Predominate over Centroposterior Regions

Topographies summarizing the amount of information that each EEG channel shares with others suggest that the information sharing deficit in VS patients was present over most scalp regions ($p_{\text{FDR}} < 0.05$ in more than 97% of the current sources, Figure 3A). When comparing VS to MCS patients, the median wSMI over frontal areas was less impaired than it was over the posterior regions (Fz versus Pz EEG channels; $U = 2035, p = 0.038, \text{AUC} = 0.60$).

To facilitate the interpretation of the very large number of channel pairs (Figures S3C–S3E), we reduced our data to 16 clusters composed of ~ 16 current sources each. The results confirmed that VS patients exhibited an overall reduction of information sharing mainly with centroposterior areas (Figure 3B): 48% of the 120 cluster pairs showed significantly smaller wSMI in VS than in MCS or in CS patients ($p_{\text{FDR}} < 0.05$).

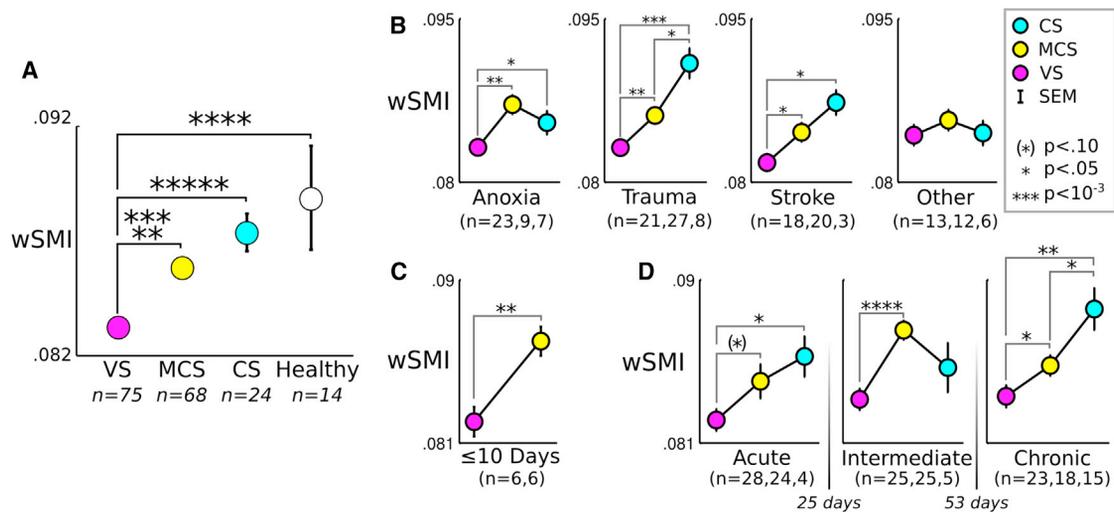


Figure 2. wSMI Indexes Consciousness Independently of Etiology and Delay since Insult

The median wSMI across current sources is depicted for each state of consciousness (A). Error bars represent SEM. Significant pairwise comparisons are denoted with asterisks. Analyses were reproduced for each etiology (B) and delay since insult (C and D). The results showed that median wSMI is mainly affected by the state of consciousness and does not vary significantly across etiology or delays.

Variations with Interchannel Distance

To test the hypothesis of a change in brain-scale information sharing, we investigated the relationship between wSMI and the Euclidian distance separating the channels. For distances below 5 cm, wSMI quickly dropped toward zero, as expected given that this measure was designed to eliminate common source artifacts (Figures 4A and S4A). We therefore avoided these short distances and restricted our analyses to five equally spaced distances for which the median wSMI values were comparable at $\tau = 32$ ms. wSMI discriminated VS from MCS at all but the shortest interchannel distance (Figure 4C). The interaction of distance with consciousness state (VS versus MCS) was significant when pitting the shortest distance against any of the longer ones (all $p < 0.028$). Thus, wSMI is robust to variations in interchannel distance except in the very short range, suggesting that loss of consciousness is associated with an impairment in information sharing over medium-to-long distances. With nonweighted SMI, the difference between VS and MCS was weaker and was invariant to interchannel distance (Figures S4C and S4D).

Discussion

Several theoretical models of consciousness predict that brain-scale information sharing should provide a consistent signature of conscious processing [1–6, 16–18, 21]. In agreement with this prediction, we show that wSMI, which estimates the amount of information shared by two EEG signals, increases as a function of consciousness state and separates vegetative state (VS) from minimally conscious state (MCS) patients. This increase appears particularly prominent across centroposterior areas and across medium and long interchannel distances.

These results supplement recent EEG studies investigating the relationship between information sharing and loss of consciousness using spectral-based functional connectivity measures [13, 22]. The present work relies on a large group of patients, which allowed us to demonstrate the independence of our findings from etiology and delay since insult.

Moreover, our measure, unlike several traditional synchrony measures, minimizes common-source artifacts and improves the discriminability of consciousness states. Finally, we show that its changes cannot be simply reduced to local changes in entropy or power spectrum but reflects a genuine change in information sharing particularly detectable over medium and long distances across the scalp. A similar change may also exist at shorter distances, but, due to common-source artifacts, scalp EEG is unlikely to provide conclusive information on this point.

The observed change in brain-scale information sharing fits with earlier observations showing that the state of consciousness can be affected by diffuse anatomical lesions to the cortex and the underlying white matter as well as to the thalamic and brain stem nuclei. In particular, several studies have underlined the prominent role of diffuse white matter lesions in persistent VS [23–26]. These anatomical lesions may lead to functional deficits in thalamocortical [27, 28] as well as corticocortical communication [15, 29–31] and to abnormal default mode network activity in VS patients [23, 30–34], all of which would result in reduced mutual information over long corticocortical distances, as observed here.

wSMI could be computed after cortical source modeling, but this step remains fraught with inaccuracies, particularly given the patients' frequent brain and skull damage [35]. Instead, our analyses were performed after applying a current-source-density transform to EEG recordings, which coarsely focalizes the effects over the corresponding cortical regions. Topographically, the largest differences in information sharing between VS and MCS patients were found over centroposterior regions. Although this effect may appear at odds with the preponderant role of the prefrontal cortex in conscious processing [3, 6, 36], it fits with the recent identification of posterior cingulate and precuneus as essential hubs of cortical networks [3] and the correlation of mesoparietal activity with the state of consciousness [37]. In particular, numerous studies have highlighted a frequent hypoactivation of the precuneus and posterior cingulate in VS patients [38]. These areas participate in the default mode network and

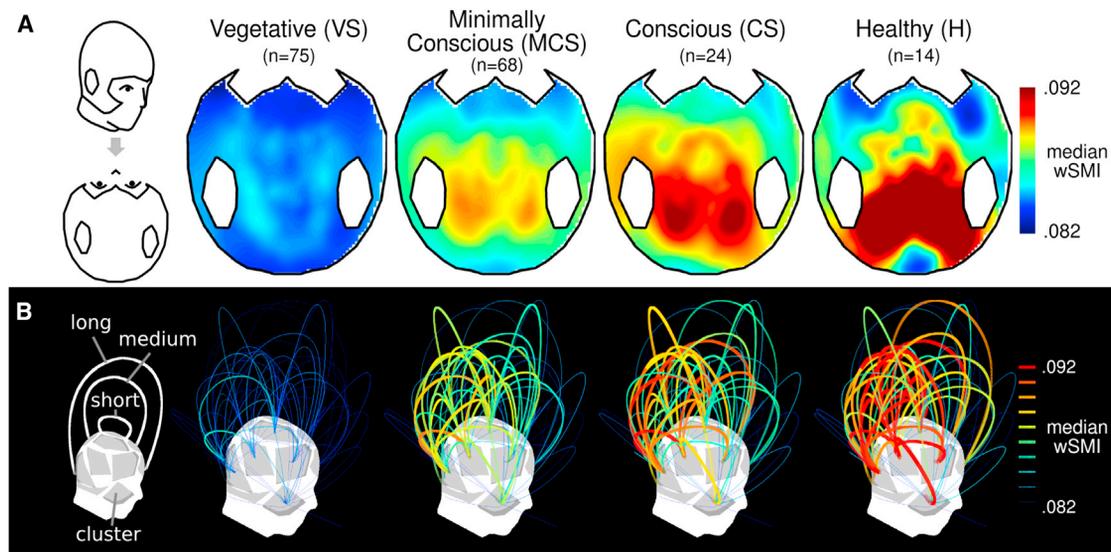


Figure 3. wSMI Increases with Consciousness, Primarily over Centroposterior Regions

(A) The median wSMI that each EEG channel shares with all other channels is depicted for each state of consciousness.

(B) 120 pairs formed by 16 clusters of EEG channels are depicted as 3D arcs whose height is proportional to the Euclidian distance separating the two clusters. Line color and thickness are proportional to the mean wSMI shared by the corresponding cluster pair.

have been repeatedly associated with the representation of self and others, episodic memory, and mental imagery [39, 40], i.e., processes that are characteristic of the conscious brain.

Our study could be criticized for pooling over a group of VS patients, while recent fMRI results suggest that some of them may actually show preserved consciousness undetectable by classical clinical examination [41, 42]. However, recent estimates suggest that this may concern ~15%–20% of VS patients [42]. Although their presence in our data cannot be excluded, it would minimally affect our conclusions and only reduce our effect sizes. Nevertheless, it would be interesting to measure wSMI separately in VS patients with as well as without a capacity for fMRI-based communication. In the former, we predict that wSMI should remain quantitatively unimpaired.

Our findings are compatible with theories that associate consciousness with recurrent loops in posterior networks [4], a distributed brain-scale global workspace [3, 6], or a “dynamic core” [2]. They add to the panoply of behavioral and neuroimaging tools available to diagnose disorders of consciousness [38]. Our measure has the advantage of using EEG, a measure available in all clinics, rather than the complex and costly method of fMRI combined with instructions such as imagining playing tennis [41] or answering a spoken question [42]. In a recent fMRI study [42], 28 out of 33 MCS patients with consistent behavioral signs of consciousness showed no fMRI markers of deliberate communication. Future research should investigate whether the present technique, which may detect any residual brain-scale information sharing, proves more sensitive. Ultimately, a combination of neuroimaging and behavioral measures is likely to prove most useful in the clinic.

Experimental Procedures

This study has been approved by the ethical committee of the Salpêtrière Hospital (Paris). Detailed experimental procedures and clinical details are provided in the [Supplemental Experimental Procedures](#) and [Table S1](#).

Participants

181 EEG recordings (75 VS, 68 MCS, and 24 CS patients, as well as 14 healthy controls) were obtained from 126 subjects (age: $M = 47$ years old, $SD = 18$ years, males: 72%) who performed an auditory paradigm for clinical purposes [43]. All patients had been without sedation for at least 24 hr prior to the recording session, which was performed to help assess their diagnosis and their state of consciousness. Before each EEG recording, trained neurologists (F.F., B.R., and L.N.) performed a clinical evaluation of the patients with the Coma Recovery Scale-Revised (CRS-R) from which patients’ arousal and state of consciousness was derived [44]. Note that CS patients differed from healthy subjects as they presented important brain lesions, were often recovering from a VS or an MCS, and were recorded at bedside. Data from healthy subjects were only used to verify the consistency of the proposed measure of consciousness.

Experimental Design and EEG Preprocessing

Analyses were based on 800 ms time periods, during which subjects were presented to four consecutive identical tones. EEG preprocessing is described in [Supplemental Experimental Procedures](#).

Weighted Symbolic Mutual Information

EEG signals were first transformed in a series of discrete symbols defined by the ordering of k time samples separated by a temporal separation τ (Figure 1). Analysis was restricted to a fixed symbol size ($k = 3$) and four different values of τ ($\tau = 4, 8, 16, \text{ or } 32$ ms between time samples). Signals were low-pass filtered at corresponding frequencies (40, 20, and 10 Hz for $\tau = 8, 16, \text{ and } 32$ ms respectively) to avoid aliasing artifacts. Then wSMI was estimated for each pair of transformed EEG signals by estimating the joint probability of each pair of symbols. The joint probability matrix was multiplied by binary weights to reduce spurious correlations between signals. The weights were set to zero for pairs of identical symbols, which could be elicited by a unique common source, and for opposed symbols, which could reflect the two sides of a single electric dipole.

Cluster analyses were performed by averaging wSMI obtained across the $256 \times (256 - 1) / 2$ channel pairs within $16 \times (16 - 1) / 2$ manually selected regions. The distance separating EEG channels was calculated along a straight line using default electrode coordinates.

Statistics

Except if stated otherwise, statistical analyses were performed with R and MATLAB (2009b) and nonparametric two-tail tests (Wilcoxon, Mann-Whitney U tests, and MATLAB’s robust and stepwise regressions). Effect sizes are reported using receiver operating curve (ROC) and AUC analyses.

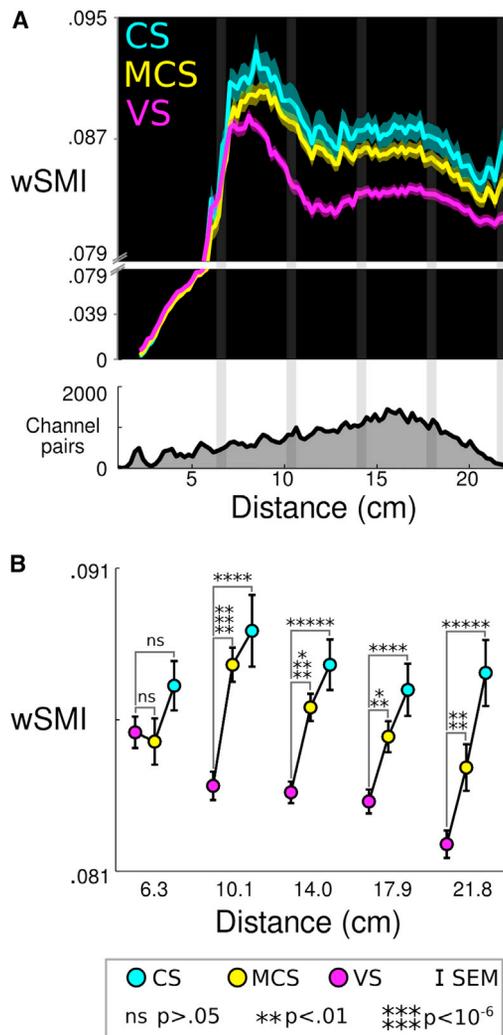


Figure 4. wSMI as Function of Interchannel Distance

(A) wSMI is plotted as a function of the Euclidian distance separating each pair of EEG channels. While wSMI is relatively stable between 8 and 23 cm, it drops toward zero as interchannel distances diminish, which thus confirms its robustness to common source artifacts.

(B) Histogram plotting the density of channel pairs as a function of interchannel distance.

(C) VS patients presented lower wSMI than MCS and CS patients, particularly over medium and long interchannel distances (>10 cm).

False discovery rate (FDR) was used to control for multiple comparisons (noted as p_{FDR}).

Supplemental Information

Supplemental Information includes four figures, five tables, Supplemental Experimental Procedures, and Supplemental Results and can be found with this article online at <http://dx.doi.org/10.1016/j.cub.2013.07.075>.

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