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Main

The perturbational complexity index (PCI) measures the spatiotemporal dynamics of transcranial magnetic stimulation (TMS)-evoked electroencephalography (EEG) potentials (TEPs) [1]. High PCI values reflect the joint presence of integration and differentiation in thalamocortical networks of conscious brains [1]. Low PCI values have been reported during natural non-rapid eye movement sleep, in disorders of consciousness, and during unresponsiveness caused by general anesthetics [2,3]. The PCI can reliably dissociate different states of unconsciousness in a graded fashion [1,3]. In contrary to the widely accepted existence of distinct levels of unconsciousness (e.g., coma, unresponsive wakefulness syndrome, minimally conscious state, and emerging consciousness), the question of whether a conscious brain has distinct measurable states has remained elusive. When investigating pharmacophysiological factors influencing the PCI during wakefulness, we surprisingly found this to be the case.

We investigated the effects of three antiepileptic drugs (AEDs) on the PCI in 15 healthy awake human volunteers. Study drugs included 1) carbamazepine (CBZ), a voltage-gated sodium channel blocker, 2) brivaracetam (BRV), a modulator of GABAergic neurotransmission through binding to the presynaptic vesicle protein SV2A, and 3) tiagabine (TGB), a selective GABA reuptake inhibitor. The standard TMS–EEG and TMS–electromyography metrics of this sample have already been analyzed and published [4]. Subjects received 600 mg CBZ, 100 mg BRV, or 15 mg TGB in the corresponding drug session. All 15 subjects participated in four sessions (including a placebo control session), however, only a subset of 12 subjects was able to complete the experimental session after intake of TGB due to adverse drug reactions in the other three participants. Using a neuronavigation system, TMS pulses (at 100% resting motor threshold intensity) were applied over the left primary motor cortex while brain responses were recorded using 64-channel EEG. We analyzed the PCI^{LZ} which is the original algorithm for calculating the PCI values [5] (see Supplementary Information for details). As depicted in Fig. 1A, out of the three AEDs tested, only TGB significantly reduced the average PCI^{LZ} in the subject sample from 0.57 ± 0.03 to 0.41 ± 0.03 (mean ± SEM, $p < 0.001$, Wilcoxon signed-rank test), equating a 28% loss of complexity. This was confirmed by using a more recent PCI algorithm (PCI^{ST}, see Supplementary Information). During all measurements we continuously checked that subject had their eyes open and did not fall asleep. Furthermore, offline sleep scoring of the resting-state EEG data according to the American Academy of Sleep Medicine scoring manual [6] confirmed that there were no wake–sleep transitions during the recordings.

A previous study with a large sample of alert healthy subjects has reported 0.39–0.70 as the range of the PCI^{LZ} during wakefulness and identified $PCI^{LZ} = 0.31$ as a reliable cut-off threshold between consciousness and unconsciousness [2]. Our pre-TGB PCI^{LZ} values are within this range. Furthermore, very drowsy but still responsive and conscious subjects who had undergone mild sedation with propofol have also been shown to express an

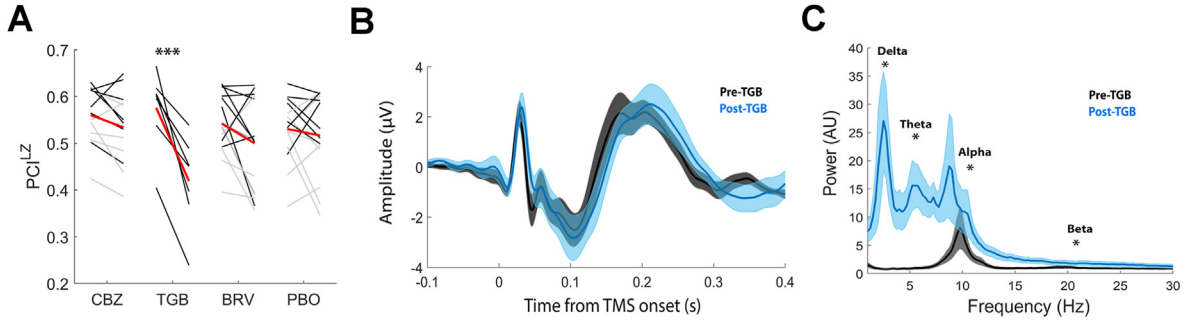

Fig. 1. (A) Effects of antiepileptic drugs on the perturbational complexity index. Only tiagabine (TGB) significantly decreased the complexity of brain responses to TMS measured by PCI^{LZ}. The left and right endpoints of each line segment represent pre- and post-drug values, respectively. The data for the subjects which were excluded from the TGB condition (n = 5 subjects were excluded in the TGB condition, see Supplementary Information) are shown in grey in the other three conditions. *** denotes $p < 0.001$, Wilcoxon signed-rank test. Carbamazepine (CBZ), brivaracetam (BRV) or placebo (PBO) had no significant effect on PCI^{LZ} (all $p > 0.05$, Wilcoxon signed-rank tests) **(B) Effects of tiagabine on TEPs.** Population average of the TEPs pre- and post-tiagabine (TGB) intake plotted for channel Cz (shadings: ±1 *SEM*). TGB had no significant effect on TEPs. **(C) Effects of tiagabine on the spontaneous oscillations.** Grand-average power spectra (shadings: ±1 *SEM*) are plotted for the eyes-open resting-state EEG recording for pre-TGB (black) and post-TGB (blue) measures. Asterisks indicate significant TGB-related changes in the delta, theta, alpha and beta frequency bands ($p < 0.05$, cluster-based permutation tests). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

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intermediate range of PCI^{LZ} values (between 0.34 and 0.42) [1]. Considering 0.41 as the average post-TGB PCI^{LZ} in our study reveals that increasing GABAergic inhibition by TGB reduced brain complexity to a level very close to mild sedation, i.e., below the typical range observed in wakefulness but above the values corresponding to unconscious states. It further suggests that the transition to unconsciousness can be continuous rather than an abrupt state shift and that intermediate brain states exist, i.e., a degraded conscious state during wakefulness. The present findings raise the caveat that AEDs, which are sometimes administered to patients with disorders of consciousness, may actually interfere with the level of consciousness and its detection.

How does TGB degrade the emergence of complex spatiotemporal dynamics in the brain response to TMS that are typically seen in wakefulness? One possible explanation could be a reduction in cortical excitability due to the anticonvulsant effects of the drug, however, our previous study showed no significant cortical or corticospinal excitability changes following TGB intake when tested with TMS–EEG and TMS–electromyography [4]. As also depicted in Fig. 1B, TEPs in pre- and post-TGB were not different while the PCI^{LZ} values dropped significantly following TGB intake (see also Fig. S1A for an example subject's TEPs).

Since highly specific patterns of spontaneous oscillatory activity have been found to reflect the functional architecture of neural networks, we investigated whether drug-induced effects on resting-state EEG oscillations, specially delta and theta oscillations, explain the observed changes in the PCI^{LZ} values.

TGB, and to a lesser degree CBZ, enhanced low-frequency oscillations at rest (see Fig. 1C and Supplementary Information). Hitherto, high-amplitude slow oscillations, especially delta, have been mainly associated with unconscious states. Nevertheless, there is ample evidence that high-amplitude delta oscillations can be observed in special circumstances during consciousness such as in Rett syndrome, Angelman syndrome, schizophrenia and seizure-like EEG events without convulsions or clouding of consciousness [7]. Our results expand the previous body of literature showing that elevated delta and theta oscillations can be observed in healthy awake humans during (slightly degraded levels of) consciousness after TGB and CBZ intake. The fact that only TGB but not CBZ decreased the PCI^{LZ} also highlight the notion that elevated low-frequency oscillations *per se* are not sufficient to degrade consciousness as indexed by PCI^{LZ}.

While this study was not initially designed to assess the cognitive state of the subjects quantitatively, several subjects reported vertigo, spatial disorientation, headache, and confusion after TGB intake. These observations suggest that the degraded state of consciousness during wakefulness can be manifested in abnormal cognitive and spatial orientation functions, yet all of our participants had volitional control over their behavior.

In vitro experiments have revealed that both excess and lack of inhibition result in decreased complexity of neural activity, suggesting that an optimal excitation/inhibition balance is critical for reaching maximum complexity [8]. TGB enhances low-frequency oscillations in the thalamus through activation of GABA receptors [9], hence altering overall excitatory/inhibitory balance in thalamocortical networks profoundly. Our results corroborate this notion, suggesting that a widespread low-frequency oscillatory regime may impede effective communication between brain areas and degrade consciousness during wakefulness.

In light of pathologic oscillations, such as in epileptic seizures, in which a slow rhythm hypersynchronizes a large number of brain areas, leading to loss of consciousness, the degraded consciousness in our study is reminiscent of mild nonconvulsive cases of status epilepticus which are similarly accompanied by rhythmic slow waves [10]. Altogether, our findings suggest that the transition from consciousness to unconsciousness can be continuous rather than an abrupt state shift and that intermediate brain states exist in conscious mind even though without universally accepted clinical definitions.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2021.04.012.

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