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The nociferous influence of interictal discharges on memory

This scientific commentary refers to 'Interictal epileptiform activity outside the seizure onset zone impacts cognition', by Ung *et al.* (doi:10.1093/brain/awx143).

Cognitive impairment is common among people with epilepsy, and the contribution of abnormal interictal ('between seizure') brain activity is often overlooked. In this issue of *Brain*, Ung and colleagues elegantly dissect how interictal discharges affect memory function (Ung *et al.*, 2017).

Interictal discharges (spikes) are brief 'blips' of focal pathological electrical activity on EEG. Often occurring within or around the epileptogenic zone, these spikes can also have distributed network effects (Gelinas *et al.*, 2016). The patient is usually asymptomatic when they occur, despite thousands of local neurons firing in synchrony. However, there is accumulating evidence of subtle, brief lapses in cognitive function during spikes (Fig. 1).

This phenomenon was dubbed transient cognitive impairment (TCI) by Aarts *et al.* (1984), though it had been described previously by many other investigators (see Binnie, 2003). Studies with scalp EEG and electrocorticography (ECoG) (Rausch *et al.*, 1978) had reported inverse correlations between spike rates and test scores. However, these analyses yielded mixed results, and may have overlooked critical spike-related impairments (Kleen *et al.*, 2013; Horak *et al.*, 2017). The key attribute of TCI is an interictal discharge that is time-locked with disruption of a cognitive or memory process attributable to the anatomical structure where the discharge occurs.

Research on TCI has ebbed and flowed for several decades. More recently, advances in digital signal conversion and electrode coverage stimulated a slew of ECoG investigations (Krauss *et al.*, 1997; Kleen *et al.*, 2013; Horak *et al.*, 2017), and even a cross-species validation of TCI in rats (Kleen *et al.*, 2010). These studies expanded the spatial specificity and applicability of TCI, though the magnitude of its effects and their interplay with underlying epileptic networks required better definition.

Ung *et al.* leveraged an impressive database of 67 subjects, each of whom had performed a memory task while their brain activity was monitored intracranially as part of a presurgical work-up for medically-refractory epilepsy. The task invoked delayed recall, with subjects asked to memorize a list of 15 random nouns per trial. This was followed by a brief distractor task (mathematical problems), after which the subjects were asked to recall aloud as many of the words as possible. Meanwhile grid and depth electrode arrays continuously monitored activity from cortical and deep anatomical structures with distinct (sometimes overlapping) roles in cognitive processing.

Spikes were automatically detected in ECoG data using an algorithm with modest accuracy (~72% detections verified as spikes), but importantly, free from bias. Spikes occurring during word presentations were considered in the memory encoding period, and spikes occurring during recall were considered in the memory retrieval period. Ung *et al.* used a generalized logistic mixed model, given the necessity of a statistical approach suited to adjusting for variability between different subjects, sessions, and other influences of task performance.

Ung *et al.* distinguished between spikes in or outside of the seizure onset zone (SOZ), finding a significant effect of the latter while patients were encoding the word lists. This was observed in patients who had a

Glossary

Interictal spike: A brief (<70 ms) large amplitude waveform (epileptiform discharge) followed by a slow wave observed on EEG or ECoG during periods between seizures. They are caused by transient focal bursts of pathological neural activity in the underlying brain tissue in patients with epilepsy, and can be seen within or outside the seizure-onset zone.

Seizure-onset zone (SOZ): The brain region thought to be the primary source from which seizures are generated in a given patient, due to focal pathological neural circuits. The region varies between patients, and can usually be resected for the purposes of treating medication-refractory seizures without major detriment to cognition (though in some individuals it can still harbour important functional circuits).

Transient cognitive impairment (TCI): A phenomenon describing a brief lapse in cognitive or memory function around the time of an interictal spike, which typically goes unnoticed unless specialized testing is used (Fig. 1). The specific process affected is usually characteristic of the structure in which the spike occurs, and therefore the mechanism is thought to reflect transient disruption of local neural circuits.

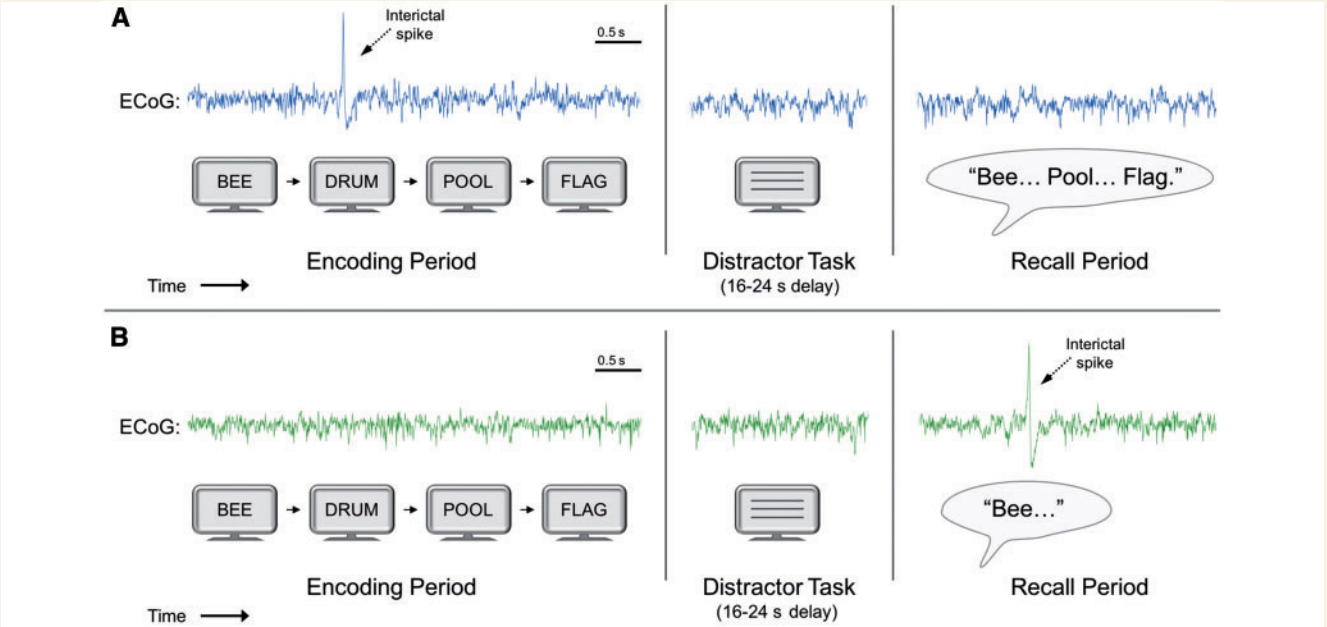

Figure 1 Schematic of TCI phenomena during a delayed recall memory task, similar to that used by Ung and colleagues. (**A**) Example portraying spike-related disruption of memory encoding. Continuous ECoG (in blue) is recorded while the subject views words sequentially displayed on a screen, followed by a distractor task (mathematical calculations), and finally by a period when the subject must recall any words they remember. Note the impaired recall of the word that occurred around the same time as the spike (DRUM). (**B**) Example portraying spike-related disruption of memory retrieval, with continuous ECoG in green. This is similar to **A**, except here a spike in the recall period is associated with impaired recall of further words. These examples are simplified for conceptual clarity.

seizure-onset zone in the left hemisphere (predominantly temporal localizations), but not the right hemisphere. The structures accounting most strongly for this spike-related effect on memory encoding were the fusiform, inferior temporal, middle temporal, and superior temporal gyri. These findings are in accordance with Horak *et al.* (2017) who also described this effect of spikes in inferior temporal areas, though Ung *et al.* have further defined the distinct anatomical structures, and weighed the importance of the SOZ. Of note, it is not entirely clear whether this effect is due to disruption of actual memory encoding, or the requisite sensory processing of linguistic and visual information (subserved in part by these cortical structures).

Next, Ung *et al.* determined the effect of spikes during the retrieval phase. Similar to previous studies (Kleen *et al.*, 2013; Horak *et al.*, 2017), spikes occurring while subjects attempted to recall words tended to decrease the total number recalled. The authors again distinguished between spikes inside and outside of SOZs, showing that the latter, in either hemisphere, disrupted retrieval. Contrary to results for memory encoding, spikes within left-sided SOZs affected retrieval (though spikes in right-sided SOZs did not). This might suggest that complex function of language-associated cortices (predominantly left-sided) in combination with the intricate dynamics of memory retrieval may render even pathological circuits necessary to some degree.

A caveat worth mentioning in TCI investigations is the difficulty of

showing causation, since analyses are largely based on retrospective relations between the timing of spikes and task errors. Alternative explanations are possible: for instance, spikes can become more frequent during drowsy or distracted states (Leung, 1988). Subjects would therefore have both poor recall (due to lack of engagement) and more frequent spikes, thus relation but not causation. Ung *et al.* have added a task feature to mitigate this (mathematical calculations to engage attention), but future researchers could also verify subject engagement using neurophysiological means. In addition, broadening the choice of memory and cognitive tasks would increase the generalizability of the conclusions.

As a final point, Ung *et al.* also attempted to quantify TCI by modelling their results structure by structure. They showed that in this task a single spike in the fusiform gyrus could reduce the odds of accurate memory recall by 19%, and a spike in the inferior temporal gyrus by approximately 8%. Furthermore, they found additive influences of additional spikes, suggesting that increased spike burdens can contribute cumulatively to cognitive dysfunction.

This latter result begs the recurrent clinical question: should we 'treat the EEG'? Certainly we have pharmacological means to decrease spike burden in patients with epilepsy who have cognitive impairments. For example, medications such as lamotrigine and levetiracetam have been shown to decrease interictal spike rates (Binnie, 2003) and could be considered strategically. A central issue, as in seizure management, is the need to walk the fine line between symptom control and side effects. Further research is clearly still warranted. However, the evidence, like the influence of spikes, continues to accumulate.

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Cortex-wide optical imaging and network analysis of antidepressant effects

This scientific commentary refers to 'Cortical functional hyperconnectivity in a mouse model of depression and selective network effects of ketamine', by McGirr *et al.* (doi:10.1093/brain/awx142).

Worldwide, more than 300 million people suffer from major depressive disorder. Conventional antidepressants relieve depressive symptoms slowly over a period of up to 4 months and are not effective in all patients (Trivedi *et al.*, 2006). Efforts to develop more effective treatments will require new insights into both the neural underpinnings of depression and the therapeutic mechanisms of existing antidepressants. One obstacle to deciphering the pathophysiology of depression stems from the highly complex, multi-level, and interconnected network structure of the brain (Fig. 1). It is unclear whether specific brain regions or cell types are selectively vulnerable, and to what extent brain-wide network alterations play a role. Likewise, systemic delivery of antidepressants may either affect the whole brain indiscriminately or preferentially act upon particular cells or circuits. Another obstacle hindering understanding is the long time-lag required for conventional antidepressants to take effect, which complicates efforts to pinpoint key therapeutic processes. In contrast, ketamine, when infused intravenously at subanaesthetic doses, relieves depressive symptoms rapidly, providing a new opportunity to overcome this obstacle (Zarate