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Sensory processing during absence seizures

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Absence epilepsies are generalized epilepsies of genetic origin that mainly occur during childhood and adolescence. Absence seizures are characterized by a short and abrupt loss of consciousness accompanied in some cases by very mild automatisms. These seizures are usually inconspicuous and often mistaken for children being inattentive. Most absence epilepsy syndromes are considered to be relatively benign as they respond well to pharmacological treatments and disappear usually after puberty. If absence epilepsy intrigues so many physiologists, it is because absence seizures present two puzzling characteristics: the apparent instantaneous generalization of epileptic activity to the cortex and the thalamus, and the interruption of consciousness during seizures. Indeed, the occurrence of absence seizures is immediately associated in the electroencephalogram (EEG) with a discharge of large amplitude spikes and waves (SWDs), synchronized over the entire cortex. This sudden generalization of epileptic activity to every cortical region supposes the existence of mechanisms capable of quickly synchronizing the activity of the vast majority of cortical neurons. The existence of such a mechanism challenges our current knowledge of cortical neurons' integrative properties and cortical networks' functional connectivity. The second fascinating characteristic of absence seizures (from a physiological point of view) is that the loss of consciousness is most often the unique clinical symptom, suggesting that absence might specifically disrupt the cellular and network mechanisms underpinning conscious perception. The article by Williams and colleagues published in this issue of *The Journal of Physiology* (Williams *et al.* 2016) provides novel insights into the cellular mechanisms underpinning these two intriguing properties of absence seizures.

The sudden synchronization of cortical neurons during absences logically led to the initial hypothesis that SWDs originate from a subcortical pacemaker (presumably the thalamus), the signal of which could not be picked up by surface electrodes. However, analysis of the thalamic and cortical local field potentials in two rat strains constituting well-established genetic models of absence seizures, the GAERS and the WAG/Rij, revealed that SWDs are initiated by a cortical focus located in the somatosensory cortex (Meeren *et al.* 2002; Polack *et al.* 2007). The cortical onset of absence seizures was soon supported in human patients through findings of focal initiation sites in the cortex EEG. Once the focus initiating absence seizures was identified, *in vivo* intracellular recordings performed in GAERS showed that the neurons located in the infragranular layers (layer 5 and 6) of this cortical region were hyperactive during interictal periods (in between seizures) and led cortical and thalamic neuron activity during SWDs (Polack *et al.* 2007). However, this previous study had failed to identify intrinsic (i.e. non-synaptic) properties that could explain a role of pacemaker for those neurons. The present study by Williams and colleagues finally shows that neurons of the GAERS cortical focus present altered integrative properties that could facilitate the initiation of absence seizures. In particular, they identify enhanced excitability during the interictal periods due to a more depolarized membrane potential, and intrinsic properties that could potentially improve the capacity of focus neurons to rebound and burst after hyperpolarization. How these modified integrative properties participate in the initiation of absence seizures remain to be determined.

Williams and colleagues also provide new information on how SWD interacts with sensory inputs. In a previous study, the laboratory of Stéphane Charpier had shown that the occurrence of absence seizures still allowed the transmission of sensory information to the primary sensory cortex in both GAERS and human patients (Chipaux *et al.* 2013). Yet, the impact of SWDs on the capacity of cortical neurons to integrate this sensory information was unknown. Williams and colleagues demonstrate that the integrative properties of neurons from the cortical focus are deeply affected by the alternation of depolarization and hyperpolarization associated with the Spike and the Wave component of the EEG signal, respectively. They show that SWDs lead to an overall hypoexcitability except during a window of relative excitability during the EEG spike. These results in GAERS are reminiscent of the work of Fanselow and Nicolelis, who studied sensory integration in the barrel cortex of Long–Evans rats. These two authors demonstrated that 'whisker twitching', a behavioural state characterized by immobility and low amplitude whisker movements, was also associated with a very low probability of cortical response to mild whisker stimulations, except during a small temporal window in which sensory stimuli would evoke bursts of action potentials. They concluded that 'whisker twitching' was a low level of vigilance optimized for the detection of novel or faint stimuli (Nicolelis & Fanselow, 2002). Interestingly, the 'whisker twitching' behavioural state is associated with the occurrence in the EEG of high-voltage rhythmic activities that share the same morphological and spectral properties with GAERS and WAG/Rij SWDs. They are also underpinned by the same cortical and thalamic neuronal activities (Polack & Charpier, 2006), including the initiation of oscillatory activities in the cortex (Nicolelis & Fanselow, 2002; Polack *et al.* 2007). Despite these important similarities, these two EEG activities have been associated with two completely opposite functions: a physiological state of 'optimized' sensory processing for novel stimuli and a pathological state impeding the conscious processing of sensory information. This dramatic divergence in the interpretation of similar results sheds light on what remains to be known about the cellular mechanisms underpinning conscious sensory processing.

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Additional information

Competing interests

None declared.