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Discharges in ventromedial frontal cortex during absence spells

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Abstract

Neural mechanisms of conscious attention require thalamic control of widespread cortical networks. Absence spells involve a momentary loss of voluntary control of attention, during which the person is inactive and unresponsive. The spike–wave seizure discharges of these spells rapidly engage both cerebral hemispheres in the classic sign of a "generalized" seizure. Animal evidence suggests that spike–wave seizures are caused by a disruption of thalamic circuitry, with extensive spread to cortex through thalamocortical propagation. We applied advanced methods of electrical source analysis to dense array (256-channel) electroencephalographic recordings of spike–wave discharges of absence spells. Neither the onset nor the spread of these seizures is generalized. Rather, the slow waves of the discharges are restricted to frontotemporal networks, and the spikes represent a highly localized and stereotyped progression of electrophysiological activity in ventromedial frontal networks. Given the current knowledge of the neurophysiology of absence seizures, this specificity of the frontal cortical discharges suggests the hypothesis that absence spells are associated with pathology in a circuit comprising ventromedial frontal cortex, rostral thalamic reticular nucleus, and limbic nuclei of the thalamus. Disrupted in absence, this circuit appears to regulate important aspects of the voluntary control of conscious attention.

Keywords: Absence; Epilepsy; Seizures; Cortex; Thalamus; Electroencephalography; Consciousness; Attention; Frontal lobe

1. Introduction

Absence spells reflect a localized disruption of attention. Often appearing first in childhood, these spells are identified by brief episodes of profound inattentiveness, during which the EEG shows large characteristic spike–wave discharges [1]. There appears to be a momentary impairment in voluntary control of consciousness, including both the capacity to organize action and the capacity to respond to environmental events. Even with the disruption of conscious attention, however, absence spells are unique among seizures in producing remarkably little impairment in the continuity of experience and orientation to context. After an absence discharge has completed, the patient may continue with behavior in the context of recent events, such as by finishing the writing of a sentence that was begun before the absence spell [2].

1.1. Neural activation in generalized spike–wave seizures

Although the neuropsychological impairment in absence thus appears to be quite restricted, in clinical neurology it has been assumed that the spike–wave discharges of absence seizures are "generalized" in that they engage the entire cerebral mantles of both hemispheres simultaneously. This assumption seems to have arisen because generalized onset of the pathological cerebral activity (rather than origination in one cerebral hemisphere) is

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implied by the rapid appearance of large, bilateral spike–wave discharges on the EEG [1,2].

In recent years, several investigators have examined functional MRI (fMRI) scans during generalized spike–wave seizures, scanning during the period of the seizure indicated by EEG recorded during the MRI procedure. In many cases, the patients with these seizures exhibit the typical absence syndrome; in other cases, the spike–wave seizures are associated with more complex symptoms including secondary generalization. In this research, the blood oxygen level-dependent (BOLD) index of cerebral activation was typically synchronized to an episode of the spike–wave discharges, with the apparent expectation that the fMRI activation would indicate the neural mechanism of the seizure. However, none of these fMRI studies found hemodynamic increases that would be expected from the conventional assumption that spike–wave seizures cause generalized activation of both hemispheres. Several studies did find increased BOLD responses in the thalamus (consistent with the notion of thalamic control of widespread generalized seizures) during spike–wave discharges [3–5]. However, the most consistent changes in the cortex have been decreases in cortical activity during spike–wave discharges [3–8].

Furthermore, there is a consistent pattern to the cortical decreases during spike–wave discharges, in that the deactivations are localized to the posterior cingulate, to the parietal lobes, and to both lateral frontal and ventromedial frontal cortices. Archer et al. [7] observed decreases in the posterior cingulate and in bilateral temporal and parietal cortex. Aghakhani et al. [9] observed variable fMRI changes, with hemodynamic activation decreases more common than increases in cortex, particularly in frontal and parietal regions. Salek-Haddadi et al. [5] also observed bilateral decreases in frontal and parietal regions, and, consistent with Archer and colleagues [7], they also observed decreases in posterior cingulate (retrosplenial) cortex.

Generally consistent results were observed by Laufs et al. [4], who examined hemodynamic changes that correlated with the occurrence of spike–wave discharges during the fMRI recording of a patient with absence seizures. With both 1.5- and 3.0-T scans of this patient, the fMRI responses predicting the presence of spike–wave seizures were deactivations in bilateral posterior cingulate, parietal, and frontal areas including ventromedial frontal cortex. Laufs and colleagues [4] recognized that this pattern of deactivations is similar to that seen during cognitive tasks in many PET and fMRI studies, leading to the interpretation that activity in these regions reflects a "default mode" of cerebral activity during the resting condition of neuroimaging studies [10], pointing out that deactivation of this posterior cingulate and dorsal cortical network is also seen in sleep [11].

Laufs et al. [4] proposed that the default mode network deactivation during spike–wave discharges may explain the deficit of conscious awareness during the absence seizure. Extending the joint EEG–fMRI approach to a group of 46 patients who showed generalized spike–wave seizures, Hamandi et al. [3] confirmed that thalamic changes are most often activations, and cortical changes are most often deactivations, with the pattern of cortical deactivation typically consistent with the default mode of conscious rest.

Gotman et al. [6] also discovered deactivation of the dorsal cortical pathway of the default mode. BOLD fMRI recordings were made during spike–wave discharges of 15 patients with a variety of generalized epilepsy syndromes. Activations were observed in the thalamus bilaterally, in the insula, midcingulate cortex, and cerebellum. Deactivations were seen in ventromedial prefrontal cortex and throughout dorsolateral and parietal frontal cortex. Gotman et al. [6] propose, in a manner similar to Laufs and colleagues [4], that the suppression of the normal cerebral pattern of the default state of consciousness may explain the symptomatology of generalized spike–wave seizures.

1.2. Electrophysiological analyses of generalized spike–wave seizures

Although the concept of "generalized" seizures has persisted in clinical practice, both traditional EEG observation [12] and more recent EEG source analysis [13] have shown that, although it is bilateral from the outset, the spike–wave pattern is not generalized, but remains localized to frontal cortex. In applying dense array (256-channel) EEG to examine a patient's absence seizures, we found that, although seizure onset appeared to develop rapidly, both the wave and the spike features of the pathological discharges could be localized to midline frontal regions, during both the onset of the seizure and the propagation of stereotyped spike–wave patterns. Particularly striking was the transition over the frontal pole, as the positive spike abruptly displaced the diffuse anterior-negative slow wave. Analysis of multiple absence discharges in four additional patients with absence seizures confirmed this midline frontal localization in each case [14].

These dense array EEG findings suggest that generalized seizures may not be generalized, in the commonly accepted sense of engaging the entire cortex simultaneously [15]. Rather, the stereotyped and localized pattern of the spike–wave progression suggests a specific neurophysiological disorder, engaging cortical networks of the midline frontal lobe. Because the pathological, high-amplitude discharges of the spike–wave seizures would be expected to increase, rather than decrease, cerebral metabolism and hemodynamic response, the localization to frontal midline appears to contradict the fMRI studies reviewed above, where decreases have been reported for ventromedial frontal cortex as well as other regions of the "default mode" during spike–wave seizures [3–8].

1.3. Implications of ventromedial frontal cortex discharges for thalamic control

Although difficult to reconcile with what appears to be a consistent set of cortical deactivations in fMRI studies of