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This Week's Citation Classic ®

Leao A A P. Spreading depression of activity in the cerebral cortex.
J. Neurophysiol, 7:359-90, 1944.
[Department of Physiology. Harvard Medical School. Boston. MA]

Local electrical or mechanical stimulation of the rabbit's dorsolateral cortex elicits a reaction characterized by a depression of all neuronal electrical activity, maximally deep for one to two minutes. The reaction slowly spreads in all directions from the stimulated site, and within three to six minutes involves all of the dorsolateral cortex, except the retrosplenial area. [The *SCI*® indicates that this paper has been cited in more than 565 publications since 1945.]

Remarkable Reaction of the Brain Gray Matter

Aristides Azevedo Pacheco Leao
Academia Brasileira de Ciencias
Caixa Postal 229
20001 Rio de Janeiro, RJ
Brazil

This paper reports the main results of the research carried out at the Department of Physiology, Harvard Medical School, to obtain my PhD in 1943. At the time of my arrival, in 1941, a study undertaken in the department, on the responses of the cerebral cortex to electric stimulation, was in progress.[1] Among these responses, the electric epileptiform afterdischarges seemed to me particularly interesting, and it was agreed that a further study of them be the subject of my thesis. Thus, I began with experiments on rabbits, using a six-channel ink-writing oscillograph, with capacity-coupled amplification, built in the department. At first, the recordings were exceedingly variable, and I was completely baffled. It took some time to ascertain that the variability was due to an utterly unexpected reaction of the dorsolateral neocortex to electric or mechanical stimuli applied to its surface. It was a reaction, which as Wade Marshall said later, had "confused experiments on the physiology of the cerebral cortex for many years."[2] The subject of my thesis turned to an extensive description of this reaction and its definition as a specific entity, which was given the name *spreading depression.*

I owed the satisfactory completion of the research to the highly favorable circumstances that the department provided, reflecting the harmonious combination of the personalities of Walter Cannon and his long-time associates Alexander Forbes and Hallowell Davis. Davis was my supervisor, and though he became deeply involved in classified war research, I always found him attentive and enlightening. I am also indebted to him for my appointment, in 1942, after obtaining my AM, as Austin Teaching Fellow in physiology, an appointment which, besides the opportune pecuniary aid, was for me a precious enrichment of experience. I must add that throughout my work, I had most profitable discussions with Arturo Rosenblueth, who was then an assistant professor in the department. And, as regards electron tube circuits, I learned much from the departmental electrical engineer, who was no less a person than Albert Grass, of the widely known and reputed Grass Instrument Co. I remember the cordiality of Cannon and Forbes with the utmost pleasure, but I did not have then as much contact as I would have liked with either of them. Cannon, because he retired in 1942, and Forbes, because his participation in the war effort took him far away from Boston (and from physiology). In fact, it was land-surveying that took him to Labrador and farther north into the Arctic—a task that he recounted in an enjoyable little book.[3]

One of the readers of my thesis, Robert Morison, of the neighboring Department of Anatomy, became greatly interested in the *spreading depression* and saw to it that we had six months to undertake together some follow-up experiments. This done,[4] I returned in 1944 to my native land, Brazil.

As for the high level of citation of the paper, I think there can be no doubt that the main reason is the fact that the *spreading depression,* which belongs in the domain of the pathophysiology of the brain and can also be provoked in other nonneocortical brain centers, is of immediate interest to a wide range of investigators, from those concerned with the basic mechanisms of some clinical disorders, such as migraine and cerebral concussion, to those who just use it as a tool in establishing relations between brain centers, or in behavioral research (see, e.g., references 5 and 6).

1 **Rosenblueth A & Cannon W B.** Cortical responses to electric stimulation.*Amer.J.Physiol.*135:690-741,1942 {Cited 130 times since 1945 .)
2. **Marshall W H.** Spreading cortical depression of Leao. *Physiol. Rev.* 39:239-79,1959.(Cited 235 times.).
3. **Forbes A.** *Quest for a northern air route.* Cambridge. MA: Harvard University Press. 1953.
4 **Leao A A P & Morison R S.** Propagation of spreading cortical depression. *J. Neurophysiol.* 8:33-46. 1945.(Cited 115 times.)
5. **Lauritzen M.** Links between conical spreading depression and migraine—clinical and experimental aspects. (Olesen J. ed.) *Migraine and other headaches—the vascular-mechanisms.* New York:: Raven Press. 1991. Vol. 1. p. 143-52.
6. **Albe-Fessard D. Sanderson P & Mavoungou R.** The influence ot striatum on the substantia nigra: a study using the spreading depression technique. *Brain Res. Bull.* 24:213-9. 1990.

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