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DIALOGUES

Cortex excitability, epilepsy and brain illness: which are their correct relationships?

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In their work Gilio et al. (2008) investigate the mechanisms involved in the regulation of excitability of the cortex in epileptic subjects, and in particular their epileptogenic threshold. Authors propose an experimental strategy established on the following assumptions:
1) Most of the authors consider that epileptogenic foci are expression of cortex hyperexcitability, thus it should be expected that a repetitive stimulus, such as a train of magnetic impulses applied over the primary motor area of an epileptic patient must be associated with an increase of the cMAP evoked from the arm and a decrease of the response's threshold.
2) The response's threshold, expressed in this work as RMT, reflects something like the "amount of activity" of a cortical area, and this concept has been emphasized through a distinction of the motor facio-cheiro excitability. This presents some difference between the two hemispheres (dominant or not) both in a normal and in a pathological population.
With respect to the expected results, authors found an inverse pattern that is a lack of temporal summation of cMAPs amplitude following a 5 Hz repetitive cortical magnetic stimulus, together with a lack of post-synaptic discharge potentiation in the "affected" hemisphere of epileptic patients. According to these results, a final conclusion of the manuscript can be "a decreased excitability within the studied cortical area" suggesting a possible refutation of the current pathophysiological model of epilepsy.
Authors show to have great consciousness about the complexity of the mechanisms involved in the excitability of the cortex, so their last sentence in the manuscript states "our findings probably reflect an altered balance between the excitatory and inhibitory circuits within the primary motor cortex and from distant areas in patients during the interictal phases".
My impression about this study hints several considerations: first the amount of influences that determinate cortex excitability as a main recordable data is too conspicuous and, probably, not yet completely known in order to allow a formulation of a final theory model. For example, recent animal studies in rats suggest a regulatory role of cholinergic septohippocampal-dentate axis in cortical excitability, which is mediated and, at the same time, is a mediator of the glutamate-GABA balance (Frazier et al., 2003). Furthermore, it seems that the plastic remodeling of the inter-cortex circuits, in part mediated by NMDA activity through the induction of dendritic sprouting (Miskevich et al., 2002; Zepeda et al., 2004; Lei et al., 2006; Falo et al., 2008) is not an isolated occurrence (see, for example, models based on recurrent inhibition mechanisms (Medvedev, 1990)), and

so it is not possible to indicate a variation of cortical excitability only as the result of the fast-term excitatory strengthening by NMDA receptors. A second neurophysiological perplexity derives from the general concept of "activity" when this is applied on the cortex functions particularly in epileptic phenomena: for example, it is well known that a hyper-discharge of primary motor cortex in a Jackson-like seizure is expressed in terms of a subsequent myoclonic activity. Thus, the rare but well described epileptic focus delimited in the motor language area does not provoke a vocalization or a fluent speech, but an aphasic outburst whereas vocalizations or other speech' behaviors can be typically the consequences of a more extended temporal cortex lobe crisis. Generally, we consider the concept of activity as something of "positive" opposed to the inactivity as a "lack of presence". Neurophysiologic improvements have been up to demonstrate that a neuronal population can exert a "pure role" of inhibition. About this topic it can be read some interesting works by Inghilleri et al. (1993, 1998) in which the cortical silent period subsequent to a single or combined magnetic stimulations of the primary motor area has been examined. In particular, in these works the increase of the motor threshold has been shown as a response to single transcranial magnetic shock *but not* to electric stimuli.

In my opinion it is no more acceptable a theoretical model of a brain function based on static balances regulated by two opposing instances playing above an "active area". In the studies of movements, first and foremost in cinematic analysis (Piron et al., 2001; Wu et al., 2005; Kazennikov et al., 2007) the fundamental role of a temporal sequence of on-off switching clearly appears in order to represent the correct and flowing reality of the movement. Our imagination, even interpreting the biochemical and physiological data, should be driven in terms of a "movie" sequence of activation and deactivation of the cerebral tissue forward a spatiotemporal pattern. In this context of interpretation, the possibility of an intercritic "hypoexcitability" of the affected epileptic hemisphere is probably less paradoxical. I have recently read a very interesting article about the more prominent activity of sensitive-visual mirror neurons in complex motor tasks in patients with multiple sclerosis compared to the normal population (Rocca et al., 2008). Thus, a simple model of "defective" neuronal functions generally applied on illness of brain seems to be definitively overcome.

Since Gilio et al.'s manuscript (2008) was very interesting and theoretically stimulating, I cannot deny some defect. The first and more serious seems to be the method of population's recruitment: if the experimental focus was on the motor property of the brain (i.e. recording upper limbs cMAP and its motor threshold by magnetic stimulation of the brain), authors should collect an epileptic population affected only by focal motor seizures. Otherwise, the resulting data showing a "hypoexcitability" of the affected hemisphere might be the expression of a plastic remodeling involving remote intercortex circuits, for example from visual cortex areas. A second problem is the rather poor technology used to lead the experiment. With a more focused brain stimulation, i.e. by a stereotactic RM points localization of the affected areas, investigators could have taken in consideration individual differences.

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