TRENDS IN NEUROPHYSIOLOGY OF MOVEMENT DISORDERS

NEUROPHYSIOLOGIC MECHANISM OF NEURAL EFFICIENCY IN HUMANS: CAN IT EXPLAIN PERFORMANCES OF ATHLETES AND PATIENTS WITH NEURODEGENERATIVE DISEASES?

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Problem identification. Purpose of our research is the development and testing of procedures for the study of functional brain organization in elite athletes and patients with cerebral neurodegenerative processes to test "neural efficiency" hypothesis (i.e. selective cortical activity in experts).

Methodology. Cortical activity in elite athletes and patients with Alzheimer's disease (AD) was indexed by the study of

electroencephalographic (EEG) oscillations in the resting state condition and during events.

Results. ATHLETES (Del Percio et al., 2008, 2009, 2010; Babiloni et al., 2009, 2010). More resting state eyes-closed posterior cortical alpha (8-12 Hz) power was observed in elite athletes than in amateur athletes and non-athletes, thus suggesting that athletes' brain is more inhibited in this condition. Furthermore, there was a reduced event-related alpha desynchronization as a sign of less cortical activation in elite athletes than in amateur athletes and non-athletes, during both cognitive and motor events, with some exceptions to be better understood. AD PATIENTS (Babiloni et al., 2004, 2007, 2010, 2013). Less resting state eyes-closed posterior cortical alpha (8-10 Hz) power was observed in prodromic and overt AD than in normal elderly subjects, thus suggesting that patients' brain is less inhibited in this condition. Furthermore, there was a reduced event-related alpha desynchronization as a sign of less cortical activation in the former than in the latter ones during eyes opening.

Conclusions. "Neural efficiency" as a sign of more selectivity and inhibitory capability of brain oscillatory processes may explain at least in part high cognitive-motor performance in athletes and some cognitive-motor abnormalities in AD patients.

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SIMULTANEOUS IMAGING OF THE BRAIN AND SPINAL CORD: ACCOUNTING FOR THE BRAIN-SPINE INTERACTION INTO FUNCTIONAL MODELS OF HUMAN MOTOR SYSTEM

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A large body of neurophysiological work in animals and humans has revealed that the spinal cord is not a simple bystander of the central nervous system or just a bundle of nerves relaying signals from brain to the muscles and from sensory organs back to the brain. Yet, the spinal cord is like a Cinderella for the neuroimaging community at large, which focuses on the brain and mainly ignoring the spine when building and testing models of human motor functions. Thus, the functional models of human motor system proposed based on neuroimaging evidence will always be incomplete as long as they do not include both the brain and the spinal cord in their description. One solution to this problem is the simultaneous functional imaging of the brain and spinal cord in order to assess the brain-spine interaction during various motor tasks. This will allow researchers to partial out the role of each level of the central nervous system in the course of different

motor functions. In my presentation I will first outline the technical challenges of spinal cord imaging, both by itself or simultaneously with the brain. After that, I will present an integrated approach that will address these challenges by using the standard magnetic resonance imaging equipment in combination with a specific slice prescription during acquisition and well-known statistical models during data analysis. Then, I will illustrate the use of this approach in the area of motor skill learning and I will finish with the presentation of possible uses in the study of movement disorders.

CENTRAL PHYSIOLOGY OF DYSTONIA – INSIGHTS FROM DEEP BRAIN RECORDINGS

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The pathophysiology of dystonia is not fully understood, and pathological findings are evident at the cortical, brainstem and basal ganglia levels of the motor and sensory network. Deep brain stimulation (DBS) of the globus pallidus internus is a highly effective treatment in patients with dystonia. However, the mechanism is still not entirely understood. One hypothesis is that DBS suppresses abnormally enhanced synchronized oscillatory activity within the motor cortico – basal ganglia network. Several electrophysiological studies in patients undergoing DBS for movement disorders have revealed evidence for disease-specific oscillatory patterns of neuronal basal ganglia activity that may act as a noisy disruptive signal disturbing both local and distant neuronal network functioning causing characteristic movement disorders. In patients with dystonia, increasing evidence suggests that neuronal activity in the basal ganglia is characterized by enhanced synchronized oscillations in the low frequency band (4 - 12 Hz). Such synchronization correlates and is coherent with EMG activity during involuntary (mainly phasic) dystonic muscle contractions, suggesting that it may contribute to the pathophysiology of dystonia. Pallidal low frequency activity significantly drives EMG of the affected muscles, increases during involuntary movements and correlates with the strength of the muscle spasms.

In my presentation, I will discuss the role of neuronal oscillations in the basal ganglia for the pathophysiology of dystonia. I will show most recent findings from our group in dystonia patients undergoing DBS using a specially designed amplifier allowing simultaneous high frequency stimulation (HFS) at therapeutic parameter settings and neuronal recordings. Here, HFS led to a significant reduction of mean power in

the 4-12 Hz band by 24.8 ± 7.0% in patients with predominantly phasic dystonia. Our findings suggest that HFS may suppress pathologically enhanced low frequency activity in patients with phasic dystonia. These dystonic features are the quickest to respond to HFS and may thus directly relate to modulation of pathological basal ganglia activity, whereas improvement in tonic features may depend on long-term plastic changes within the motor network.

SENSORY FUNCTIONS IN PRIMARY DYSTONIA

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The pathophysiology of primary dystonia is thought to involve dysfunction of the basal ganglia cortico-striatal-thalamo-cortical motor circuits. In the past, emphasis was placed on the role of the basal ganglia in controlling movements; in more recent times, however, it has also become clear that they play an important part in sensory functions. Thus, although the most dramatic symptoms in dystonia seem to be motor in nature, marked somatosensory perceptual deficits are also present in this disease. Recent behavioral studies have shown that these sensory functions are compromised in patients with several forms of primary of primary dystonia. Changes have been found in temporal discrimination and integration of sensory signals, spatial discrimination of tactile stimuli, perception of the vibration-induced illusion of movement, and other illusions (the rubber hand and Aristotele's illusion). The search for abnormalities of sensation was stimulated by the observation in a primate model of dystonia that showed enlarged and overlapped receptive fields of the hand in the S1 after stereotypic movements of the hand. Abnormal representation in S1 of the fingers involved in dystonia characterized by smaller distance between the fingers has been also observed in patients affected by focal hand dystonia using neuroimaging studies. One possible pathophysiological mechanisms for these abnormalities could be a loss of inhibition at multiple levels of the somatosensory system, as documented by somatosensory evoked potentials studies. Consequently, abnormal processing of the somatosensory input may lead to an inefficient sensorimotor integration, thus contributing to the generation of dystonic movements.

This talk focuses on sensory function abnormalities described in primary dystonia using different approaches and techniques and their possible role in the pathophysiology of this syndrome, highlighting potential implications for innovative therapeutic strategies to aid functional recovery.

NEUROPHYSIOLOGY AND TREATMENT OF DYSTONIA: NON-INVASIVE BRAIN STIMULATION STUDIES

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Focal hand dystonia (FHD) is characterized by task-dependent involuntary co-contraction of hand muscles. Functional MRI studies demonstrated excessive activation of primary sensorimotor cortex during dystonic motor action while premotor cortex and supplementary motor area are underactive.

Transcranial magnetic stimulation (TMS) has substantially contributed to our understanding of the cortical pathophysiology underlying these abnormalities. These TMS studies will be reviewed in this presentation. Motor evoked potentials (MEP) are significantly stronger facilitated during voluntary target muscle contraction in FHD compared to healthy controls, indicating hyperexcitability of the corticospinal system. The cortical silent period (CSP), a marker of GABABergic inhibition in motor cortex is shortened during dystonic contractions in FHD, and short-interval intracortical inhibition (SICI), a marker of GABAAergic inhibition in motor cortex is reduced in FHD, indicating significant alteration of inhibitory motor cortical control. The long-latency afferent inhibition (LAI) is reduced in FHD, indicating that central processing of sensory input is abnormal. Finally, surround inhibition is reduced in FHD, supporting the idea that this alteration may be a principal pathophysiological mechanism of activity spillover to antagonist muscles in dystonia.

In addition to measuring motor cortical excitability, repetitive TMS can also be employed for induction of plasticity. It was found that patients with FHD display exaggerated levels of LTP-like plasticity. In addition, while healthy subjects show homeostatic control of plasticity, FHD patients often exhibit non-homeostatic metaplasticity that may lead to non-physiological run-away plasticity. Finally, FHD patients display a failure of depotentiation of LTP-like plasticity, which may contribute to the inability to erase or correct unwanted motor activation patterns once they have been encoded.

In summary, TMS research has provided detailed knowledge on the cortical pathophysiology of dystonia. The data support the notion that hyperexcitability, disturbed inhibition, altered sensorimotor integration and abnormal regulation of synaptic plasticity significantly contribute to the clinical picture of dystonia. In the final part of this presentation, initial studies will be presented that use repetitive TMS as a therapeutic tool for treatment of dystonia aiming at correcting these abnormalities of motor cortex excitability and plasticity.