Functional Neurodissection in the First Episode of Schizophrenia: Time to Do It

Fidias E. Leon-Sarmiento[1]
Jaime Bayona-Prieto[2]
Hernán G. Hernández[3]

Abstract

Introduction: Current available knowledge does not delineate the relative contribution of cortical and/or subcortical mechanisms in the development of the various symptoms of schizophrenia. *Methods*: We propose here to employ a battery of functional neurological studies to be done in the earliest phase of manifest schizophrenia combining transcranial magnetic stimulation and brainstem reflex studies. The proposed battery would examine both cortical and subcortical mechanisms reasonably well-correlated with neurotransmitter abnormalities to differentiate GABAergic, cholinergic, and dopaminergic subgroups of patients and healthy controls. *Conclusion*: These investigations would lead towards a better neurophysiological subcategorization and could guide towards a more focused pharmacological intervention in early schizophrenia symptoms.

Key words: Schizophrenia, transcranial magnetic stimulation, gamma-aminobutyric acid, acetylcholine, dopamine.

Título: Neurodisección funcional en el primer episodio de esquizofrenia: es hora de hacerla

Resumen

Introducción: El conocimiento actual que tenemos de la esquizofrenia no permite conocer la contribución de los mecanismos corticales o subcorticales que llevan al establecimiento clínico de los diferentes síntomas de la esquizofrenia. *Métodos*: Se propone emplear una batería de evaluaciones neurológicas funcionales que se deberán hacer en la fase más temprana de la enfermedad, y así combinar la estimulación magnética transcraneal y los reflejos del tallo cerebral. Esta batería de estudios permitiría investigar el funcionamiento de los mecanismos

[1] Médico neurólogo. PhD. Unidad de Movimientos Anormales & Neuromagnetismo, Sección de Neurología Clínica, Departamento de Medicina Interna, Fundación Santa Fe, Bogotá, Colombia. Uni.ciencias Research Group, Universidad Nacional de Colombia, Bogotá, Colombia.
[2] PhT y NRh. Uni. Ciencias Research Group, Universidad Nacional de Colombia, Bogotá, Colombia.
[3] MD. PhD(e). Uni. Ciencias Research Group, Universidad Nacional de Colombia, Bogotá, Colombia.

corticales y subcorticales y su correlación con anormalidades en diferentes neurotransmisores, incluidos los gabaérgicos, los colinérgicos y los dopaminérgicos. Este último hecho llevaría a diferenciar clínicamente los diferentes subgrupos de pacientes y entre estos e individuos normales. *Conclusión*: Estas evaluaciones llevarían hacia una mejor subcategorización neurofisiológica clínica y guiaría hacia una intervención más efectiva en los estados iniciales de la esquizofrenia.

Palabras clave: esquizofrenia, estimulación magnética transcraneal, ácido gammaaminobutírico, acetilcolina, dopamina.

Introduction

Schizophrenia's heterogeneity has confounded its neurobiological research underpinnings, symptoms, course, and response to treatment for decades (1,2). Much effort has been expended on elucidating the different subtypes of the disorder and has concentrated mainly on symptom clustering. Functional studies of schizophrenia show cortico-striato-pallido-thalamic dysregulation suggesting both cortical and subcortical abnormalities (1). However, currently available knowledge does not delineate the relative contribution of cortical and/or subcortical mechanisms in the development of the various symptoms of schizophrenia. Moreover, it is not known whether the degree of contribution of cortical and/or subcortical mechanisms is similar among all or the majority of schizophrenia patients. Most of the neurophysiological investigations have been done in small samples of chronic patients with different pathological stages who have been receiving miscellaneous treatments. First episode of antipsychotic naive (FEAN) schizophrenia patients offer a unique opportunity of avoiding possible confounding clinical and farmacological cofactors (2) and allow elucidating the effects of primary illness processes.

Current Status

Some advances have been made in neuroimaging and in neuropsychological as well as in some limited neurophysiological investigations in FEAN schizophrenia patients. In this latter regard, a deficient inhibitory sensorimotor circuit as measured by single and paired-pulse transcranial magnetic stimulation (TMS) has been found in schizophrenia with contradictory results (3,4). Motor threshold (MT), thought to reflect ion channel conductivity and hence membrane excitability in pyramidal neurons (5), is considered a measure of the excitability of the facilitatory circuits (6,7). Decreased resting MT was found in some FEAN patients paralleling ketamine effects on cortical excitability while chronic patients have normal or increased MT values. Likewise, TMS applied to primary motor cortex induces a transitory suppression of the EMG-activity in contracting muscles after eliciting MEP, referred to as the cortical silent period (CSP) (7). The CSP has been proposed as a mea-

sure of the excitability of the cortical inhibitory circuits (7); it has been found shortened in chronic patients with schizophrenia paralleling the intensity of stimuli applied to motor cortex. Elicitation of the MT utilizing different stimulus strengths is used to develop Stimulus-Response curves (S-R), and they have been shown to be an additional useful measure of cortical excitation/inhibition states. The typical characteristics of the MEP S-R curve are motor threshold, slope and plateau (8). It covers the full range of low- and high-threshold corticospinal neurons, and also I1-waves which are predominant in the low-intensity range, and later I-waves that are predominant with high stimulus intensities (9). Despite the fact that the neurotransmitter system strongly influences the MEP amplitude (10), the S-R curve has never been investigated in FEAN. On the other hand, pairs of magnetic stimuli delivered to the motor cortex have been used to examine cortical excitatory/inhibitory mechanisms as well. The effects of a sub-threshold conditioning stimulus on the amplitude of a suprathreshold testing stimulus presented within a very short interval (1-5 msec) is the classic paradigm used for examining intracortical inhibition (ICI) (11). ICI has been found normal in FEAN schizophrenia patients but decreased in chronic disease stages (3,4). With the aforementioned available studies it is difficult to explain the large array of symptoms, particularly positive symptoms, which are considered by some authors as a result of subcortical deafferentation.

In this sense, abnormal inhibitory mechanisms may be the consequence of an aberrantly modulated subcortical input that could be tested by brainstem evaluation, that is, by blink reflexes (BR). The electrically elicited BR at supraorbital nerves generates three neural responses recorded in the orbiculari oculi muscles. R1 is an ipsilateral monosynaptic response to the stimulation side; R2 is a bilateral oligosynaptic response and R3, also bilateral, follows multisynaptic synapses (11,12). Curiously enough, only one limited study done in medicated patients with first episode schizophrenia looked for habituation of any of the three responses of the BR (13). 47% of patients had deficient habituation of R3 response investigated with single stimulation which is indicative of cholinergic dysfunction (14).

Proposal

The decision to begin treatment in patients with first episode schizophrenia is a challenge and most of the time they are medicated without clear rationale. Neurotransmitter subgroups may differentiate patients and healthy controls. These subgroups can be characterized by cortical and subcortical excitability deviations and by inference to the neurotransmitters mediating these measures by means of single and

paired-pulse TMS and single and paired BR studies. The study of the three responses of the BR which are GABA-related (R1) (15), dopamine-related (R2) (16) and cholinergic-related (R3) (14) obtained by paired electrical stimuli could give a more complete picture of subcortical neurotransmitter abnormalities in FEAN schizophrenia patients. Likewise, TMS yields the detailed knowledge of cortical GABA, glutamate and cholinergic brain activity (17). Neurotransmitter activity detected by TMS correlates inversely with some brainstem responses, namely BR, in normal people (18). Thus, the combination of the largely noninvasive and relatively in-expensive tests commented above could shed significant light on the pathophysiology of this disorder, similar to the way other neuropsychiatric disorders characterized by aberrant cortical and subcortical neural plasticity have been described recently (19).

Conclusion

Dissecting neurophsyiological subtypes in FEAN schizophrenia patients would increase the likelihood of predicting the clinical response to pharmacological intervention which would have a significant impact on the management of these patients by improving the use of health care resources and preventing the exposure of potential non-responder FEAN schizophrenic patients to the risk of side effects.

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Correspondence
Fidias E. Leon-Sarmiento
Calle 74 Nº 15-15 (201)
Bogotá, Colombia
feleones@gmail.com