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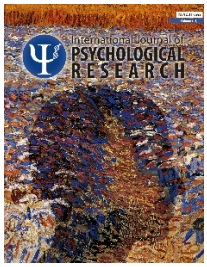
Endofenotipos Neurocognitivos: una actualización en el área



Editorial

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The endophenotype construct, initially formulated by Lewis and Gottesman in the 1960s, referred to an indicator of vulnerability not necessarily expressed as a clinical marker of status. However, this subclinical marker was established in the phenotype as a component that co-segregated with the genetic disease background, not only determining both potential and differentiated types within the same phenotype of interest, but also related to changes in the prognosis and evolution of the syndrome or disorder, increasing or decreasing the risk and outlining the pathogenesis of the syndrome itself at the molecular level, since it would be more associated with causes than the effects of the disease while exhibiting a continuous variation in the general population. (Gottesman & Gould 2003).

Every endophenotypes must fulfill various criteria to be validated as an intermediate phenotype involved in a syndrome: Must be close related to disease, independent of its state as well as heritable and stable over the time. Therefore, endophenotypes contribute to the discrimination in complex diseases such as mental illness or psychopathology, of molecular pathways underlying genetic effects that allow us to recognize patterns of specific susceptibility (Cuartas, 2011)

In this regard, different approaches on the search for endophenotypes have used neuroimaging, neurophysiology, allelic variants and neurochemistry. With these approaches, neurocognitive findings and their potential as candidates endophenotypes are at this moment a novel approach in the clinical treatment of mental or psychopathological syndromes. Therefore, changes in executive function have been studied recently as candidates endophenotypes since the executive functioning is a constituent component of human development of adaptive cognitive and behavioral patterns to favor the success as a species; in fact, aspects such as problems solving, decisions making, flexible behavior and self-regulation before the reward according to their working memory and attentional performance, allows us to successfully evolve in response to the stressor.

Showing all these efficient behaviors as a species, demonstrate the great evolution that we had in the front of Rolando' fissure, the frontal lobes which are organized hierarchically and comprise 20% of the neocortex shows the prefrontal cortex as the main structure to explain human behavior and that has enabled our species to colonize this evolutionary time called by Steven Pinker as the "cognitive niche" referring to the use of abstraction and social cohesion as an evolutionary and intelligent way that favors human problem solving and self-regulated behavior (Pinker, 1999).

Taken into account the phylogenetic heritage of cognitive function, to delineate the temporary architecture of behaviour it is helpful to evaluate the differents executive domains, which allows to include the whole neuropsychological network operated in three regions of the prefrontal cortex: prefrontal dorsolateral cortex, prefrontal cortex, medial or paralimbic and orbital prefrontal cortex. This cortical topology is formed of a large network of cortico-subcorticales interconnections that supports the operating mode. Today, various studies have nominated individual executive domains that together with genetic factors explains percentages greater than 40% of the variance (González-Giraldo, et al. 2015), although, for mental disorders there is a high

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heritability, is not clear yet what genes are directly responsible, due to the large pre-existing genetic heterogeneity and not consistently replicated in association studies to specific allelic variants.

In this context, the variant genes that are closely related to mental disorders, affect multiple cortical and subcortical neural systems, i.e., networks such as dopaminergic, serotonergic, and glutamatergic among others, which regulate the expression of neurocognitive processes thereby, reshaping the phenotypic expression in the functions of language, attention, memory, learning, self-appreciation and emotional activation, inhibitory control and social cognition such as neuropsychological domains and executive functions which are seen from a differential way in the clinical dimension of the disorder.

To this regard, Halford and collaborators in 2010, had previously deepened in the relational knowledge as a cognitive process of higher-order that underlies the goal-directed behaviors and that correspond to the skills of reasoning, categorization, planning and language expression (Halford, et al. 2010). From this perspective, Han and his group proposed an approach to what we can call a cognitive complexity metric and that conceptualized as relational processing, which is consistent with the approaches of Halford and is potentially sensitive to changes in brain activation in the prefrontal cortex which have been frequently associated with psychopathological, neurological and psychiatric problems (Christoff, et al. 2001). Not only the prefrontal cortex is associated with the ability of complex processes at the relational level, they are also the ways of connectivity, since there are frontoparietal networks established and girdle-opercular which underlies all the genetics architecture which corresponds to the variable expression of performance and activation of these cortical areas. In this sense, the work of Hansell found a robust partnership as potential neurocognitive endophenotypes processing relational, cognitive function essential and core of reasoning and working memory (Hansell, et al. 2015), these findings are consistent with findings reported by Ragland JD et al. in 2012, determining a high heritability (67%), this means that 67% for the trait of relational population variation of processing can be explained by genetic factors (Ragland, et al. 2012).

Therefore, the limitations in handling and interpreting complex relationships suggest a central axis in the general cognitive processing, which in turn operates through genetic factors shaping neurobiological ways of molecular expressions, particularly in the prefrontal cortex. Now, a measure that raises the cognitive construct is the processing speed, however much of the neuropsychological batteries incorporated the variable of time in seconds; but in order to increase the sensitivity and the effectiveness of the measures in reaction times of the cognitive responses, they should be evaluated in milliseconds.

It is likely that some findings related to executive performance and their potential as a candidate endophenotypes for subdomains, have been influenced by the lack of sensitivity about the processing speed; Accordingly, one of the main variable in the neurocognitive assessment of the syndromes is reaction times. (Nikolas & Nigg, 2015).

As an example, to evaluate the motor impulsiveness with a self-reported scale, or with some Neuropsychological test that does not discriminate reaction times, the circumscribed changes in the inhibitory control could not be effectively determined. Instead, we could choose to assess prepulse inhibition (PPI or startle reflex), that is, the presence of sub-threshold stimuli prior to the startle stimulus which manage to decrease the magnitude of the response, and that activates inhibitory mechanisms and processes of filtering sensory information. This alternative would allow us to infer the phenotype of the impulsivity as response behavior that emerges from deficits in inhibitory control with more sensitivity.

The neural basis of PPI is the hippocampal response which currently constitutes one of the best evaluated endophenotypes in schizophrenia, autism and some neurodevelopmental disorders and its high heritability observed through robust experimental designs, have allowed to explore its genetics structure and to discriminate different etiopathogenic within the same syndrome, which will impact the clinical and pharmacological intervention of the disease in the future. (Greenwood, et to al. 2015; Osumi, et to al. 2015; Roussos, et al. 2015).

For now, the challenge is to sensitize the neuropsychological measures to refine the cognitive metrics using tools that allow to determine reaction times and processing speed (from seconds to milliseconds), in the executive function tasks. This will allow to explore in more detail the scope of variation to brain and cognitive level. With this type of methodologies and also with the incorporation of neuroimaging and psychophysiological measures, improve the sample sizes, controlling population stratification, using designs based on families or couples of brothers, and homogenize the clinical

criteria; It is the progress in identifying or validate neurocognitive endophenotypes which outlining the pathogenesis of mental disorders and the therapeutic targets in the future.

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