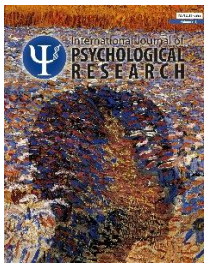
Neurocognitive Endophenotypes: an update on the field

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. The endophenotype not only determined 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. It increased or decreased the risk and outlined the pathogenesis of the syndrome itself at the molecular level while exhibiting a continuous variation in the general population.

Every endophenotypes must fulfill various criteria to be validated as an intermediate phenotype involved in a syndrome. It must be closely related to disease, independent of its state and heritable and stable over the time. Therefore, endophenotypes may contribute to the discrimination of complex diseases such as mental illness or psychopathology as well as of molecular pathways underlying genetic effects (Cuartas, 2011).

Different approaches to searching for endophenotypes have used neuroimaging, neurophysiology, allelic variants and neurochemistry. Neurocognitive findings and their potential as candidate endophenotypes are a novel approach to the clinical treatment of mental or psychopathological syndromes. Recently, changes in executive function have been studied as candidate endophenotypes. Executive functioning is an integral component for 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 conducts as a species, determine the great evolution that we have had in the frontal lobes. These lobes are organized hierarchically and comprise 20% of the neocortex. The prefrontal cortex is the main structure that accounts for human behavior and that has enabled our species to colonize the current evolutionary time called by Steven Pinker as the "cognitive niche" (Pinker 1999). This term refers to the use of abstraction and social cohesion as an evolutionary and intelligent way that favors human's problem solving and self-regulated behavior.

Taken into account the phylogenetic heritage of cognitive function, to delineate the temporary architecture of behavior it is helpful to evaluate the different executive domains. This allows circumscription of the neuropsychological network operating in three regions of the prefrontal cortex: dorsolateral prefrontal cortex, medial or paralimbic prefrontal cortex and orbital prefrontal cortex. This cortical topology is formed of a large network of cortico-subcorticales interconnections that supports the operating mode.

Today, different studies have identified candidate executive domains that, together with genetic factors, explain greater than 40% of the phenotype variance (González-Giraldo, et al. 2015). Even though for mental disorders there is a high heritability, is not clear yet what genes are directly responsible. This is mainly due to both the large pre-existing genetic heterogeneity and lack of consistent replication of specific allelic variants in association studies.

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In this context, the underlying genetic causes of mental disorders affect multiple cortical and subcortical neural systems. That is, networks such as dopaminergic, serotonergic, and glutamatergic among others. They regulate the expression of neurocognitive processes thereby reshaping the phenotypic expression in language, attention, memory, learning, self-appreciation and emotional activation. Also, they regulate inhibitory control and social cognition such as neuropsychological domains and executive functions which are differentially seen in the clinical features of the disorder.

In this context, Halford and collaborators (Halford et al. 2010) focused on 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. From this perspective, Hansell and his group proposed an approach to what can be called a 'cognitive complexity metric' that can be conceptualized as relational processing. This approach is consistent with that of Halford et al. and potentially sensitive to changes in brain activation in the prefrontal cortex. Such changes 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, it is also the connectivity system from which the frontoparietal and girdle-opercular networks are established. Here underlies all the genetic architecture corresponding to the variable expression of performance and activation of the cortical areas. The work of Hansell found the relational processing to be a strong potential neurocognitive endophenotypes. The relational processing is essential for both reasoning and working memory (Hansell, et al. 2015). These findings are consistent with those reported by Ragland JD and co-authors (Ragland, et al. 2012), who reported a high heritability (67%). That is, 67% for the trait of relational population variation of processing can be explained by genetic factors. The limitations in handling and interpreting complex relationships suggest a central axis in the general cognitive processing. This axis, in turn, operates through genetic factors shaping neurobiological ways of molecular expressions, particularly in the prefrontal cortex.

A measure that raises the cognitive construct is the processing speed. However, many of the neuropsychological tests incorporate the variable time in seconds. Still, in order to increase the sensitivity of measuring reaction time of the cognitive responses, time should be recorded in milliseconds. It is likely that some findings related to executive performance and their potential as candidate endophenotypes for subdomains, have been influenced by the lack of sensitivity regarding the processing speed. Accordingly, one of the main variables when evaluating neurocognitive assessment of a syndrome should be reaction times. (Nikolas & Nigg 2015).

As an example, evaluating motor impulsiveness with either a self-reported scale or a neuropsychological test that does not discriminate reaction times, would not allow determination of changes in the inhibitory control. Instead, we could choose to assess prepulse inhibition (PPI or startle reflex): the presence of sub-threshold stimuli prior to the startle stimulus which manage to decrease the magnitude of the response. PPI activates inhibitory mechanisms and processes of filtering sensory information. Assessing PPI could allow us to infer the phenotype of the impulsivity as response behavior that emerges from deficits in inhibitory control with higher 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. Its high heritability observed through robust experimental designs (Greenwood, et al. 2015; Osumi, et al. 2015; Russos, et al. 2015), have allowed the exploration of its genetics structure and the discrimination of different etiopathogenic within the same syndrome. This, in turn, will impact the clinical and pharmacological intervention of the disease in the future.

For now, the challenge is to develop more sensitive neuropsychological measures to refine the cognitive metrics using tools that determine reaction times and processing speed (from seconds to milliseconds), in tasks related to the executive function. This will allow the exploration of 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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