Psychiatria Danubina, 2021; Vol. 33, Suppl. 9, pp 26-29 *Conference paper*

ENDOPHENOTYPE AND PSYCHIATRY: AN INTERESTING COMBINATION

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SUMMARY

The endophenotype is a measurable component which is characterized as an intermediate part of the path existing between the genotype and phenotype of a disease. In the context of psychiatric pathologies, an endophenotype is such if it shares inheritable variations with it, if it is evident both during the active and inactive phases of the pathology, if it is co-transmitted in the family, and if it is evident in both affected family members from pathology, and in healthy people. This review reports the available literature data of the interesting combination between endophenotype and psychiatry.

Key words: *endophenotype – psychiatry - genetics of psychiatry*

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INTRODUCTION

It has long been known that psychiatric diseases are strongly influenced by the genetic background of an organism. Several disorders such as addictions, sleep disorders, bipolar disorders and eating disorders showed an hereditary component (Juli et al. 2012, 2014, 2015, 2018), but identifying how genetic variants contribute to the disease has been a major challenge.

Classical genetics basically studies the so-called "simple Mendelian traits", those in which a certain trait of the phenotype is directly produced by the activity of a specific gene. But the role of complex genes that regulate individual susceptibility to develop a complex trait must also be considered. Genetic susceptibility is linked to modifications in the sequence of the genes considered, which are defined as "gene variants" or "gene polymorphisms". In the case of complex traits we do not have gene mutations, but only gene variants, that is, assets of certain genes that have a greater or lesser efficiency, but not a total loss of function. These gene variants are not capable of directly causing a disease, but they create the conditions for which an individual is more or less susceptible to the disease under consideration. The genetic background of an individual is stable over the years, as the sequences of genes do not change and, although during the course of life, variations in the functional capabilities of some genes may occur, the genetic component of susceptibility to a pathology with which an individual is born remains the same throughout life. On the opposite site, the environmental component of a multifactorial trait is variable over the course of existence, and is closely linked to an individual's lifestyle. The individual can change exposure to environmental risk factors and the use of environmental protection factors over the course of his life. In this way, its genetic risk can produce completely different effects based on the environmental components to which the individual is exposed. Therefore, in the presence of a predisposing genetic background, specific social and psychological factors represent the environmental components that can determine the development of the pathological condition.

THE ENDOPHENOTYPE

In the genetics of complex traits, the concept "endophenotype" or intermediate phenotype has been introduced, and it represents an intermediate point in the journey from genotype to phenotype. It was described in the psychiatric literature for the first time by Gottesman and Shields (1972, 1973), and it can be defined as familial and heritable quantitative trait associated with a complex disease. Since it occupies an intermediate position between genotype and behavior both in affected and in unaffected family members, it offers the potential to bridge the gap between complex disease phenotypes, and underlying genetic mechanisms (Cerullo et al. 2012). An endophenotype may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological. In particular, endophenotypes for psychiatric disorders have to meet certain criteria, such as association with a candidate gene or gene region, heritability that is inferred from relative risk for the disorder in relatives, and disease association parameters (Gottesman & Gould 2003). More in detail, the accepted criteria considered for endophenotype include: a) the endophenotype is associated with illness in the population, it means that in a certain endophenotype it must, as a rule, always be present in individuals affected by a certain pathology; b) the endophenotype is heritable, that is, it must be transmissible to the offspring; c) the endophenotype is primarily state-independent (manifests in an individual whether or not

illness is active), this means that the endophenotype must also be present in moments in which a subject is in a phase of remission from the disease (as happens, for example, in bipolar disorders or in schizophrenia, where there are phases in which patients may not show signs of the disease, but will show the permanence of the endophenotype); d) within families, endophenotype and illness co-segregate, that is, it must be transmitted to all people in a family who develop the disease; e) the endophenotype found in affected family members is found in nonaffected family members at a higher rate than in the general population (Gottesman & Gould 2003). This is a very important point: since having inherited an endophenotype will lead to a greater susceptibility to develop a certain pathology, but not the certainty of developing it; there will be subjects who will present the endophenotype but will not develop the full-blown pathology. The frequency of these subjects will obviously be higher in a family in which there are some cases of the disease in question, rather than within the general population. A schizophrenic parent, for example, will be able to pass on endophenotypes of schizophrenia to their children, even though the children may never become schizophrenic. The possibility of inheriting an endophenotype of schizophrenia, therefore, will be higher in families in which there are already one or more overt cases than in the general population. A further widely supported criterion is that an endophenotype should have good psychometric properties, especially reliability and validity, and be sufficiently sensitive to detect individual differences (Walters & Owen 2007).

ENDOPHENOTYPES AND PSYCHIATRIC DISORDERS

There is growing interest in the use of endophenotypes in the study of the etiology of complex disorders such as developmental dyslexia, schizophrenia, bipolar disorder, autism spectrum disorders, suicide, alcool dependence, substance abuse and addiction. The use of endophenotypes in the study of the etiology of complex disorders, in fact, is considered a useful approach to increase the power of analysis and the identification of candidate genes.

Autism Spectrum Disorder

The definition and description of endophenotypes in Autism Spectrum Disorder (ASD) were described by Cerullo and colleagues. They showed that siblings of individuals with autism displayed a 25-fold increase in autism risk compared to the general population; parents and unaffected siblings showed subthreshold traits qualitatively similar to those found in their autistic family members. This underscores the importance of genetic liability to ASD, which nonetheless has polygenic, heterogeneous and complex underpinnings. They considered that this approach can contribute not only to clarify the significance of genotype and phenotype associations in autism research, but also to dissect clinical subgroups of ASD patients with relatively homogeneous underlying pathophysiological mechanisms. On the other hand, they think that this method will also foster the identification of biomarkers able to aid clinicians in early diagnoses and prognostic predictions regarding developmental trajectories and treatment response, especially in very young children (Cerullo et al. 2012).

Developmental dyslexia

To date, the studies carried out on developmental dyslexia show how the functioning of the magnocellular-dorsal pathway, cross-modal mapping, rapid auditory processing and visual and auditory spatial attention, can be considered as endophenotypes and they represent solid alternatives to clinical phenotypes. To examine the genetic effects and to better understand the pathogenetic pathways underlying this pathology, some candidate genes for developmental dyslexia have been associated with structural and functional alterations in brain areas underlying visual and attentional pathways (Darki et al. 2012, Marino et al. 2014, Eicher 2015).

Schizophrenia

In the case of schizophrenia, the obvious symptom may be psychosis, but the underlying phenotypes are, for example, a deficit in sensory motor gating and a decline in working memory. Both of these traits have a clear genetic component and can therefore be called endophenotypes (Gottesman & Gould 2003). In particular, a good endophenotype candidate for schizophrenia, is the prepulse inhibition that represents the ability to inhibit the reaction to surprising stimuli. It has been shown that if a weaker prestimulus is provided before the startling stimulus, the subsequent startle response is generally diminished (Gottesman & Gould 2003). Other studies have identified gene and chromosomal regions possibly involved in working memory. A study of Finnish twins by Gasperoni and colleagues, which used an endophenotype-based strategy, suggested linkage and association to a region of chromosome 1 (Gasperoni et al 2003). Egan and colleagues, using the functional magnetic resonance imaging (fMRI), analyzed a functional polymorphism (val108/158met) for the enzyme catechol O-methyltransferase (COMT), that assists in the catabolism of dopamine and it has also been linked to performance on a working memory task. Their studies lead to the conclusion that fMRI analysis of subjects undergoing working memory tasks may be a more sensitive endophenotype than working memory performance

alone as measured by neuropsychological testing (Egan et al. 2001, Gottesman & Gould 2003). There was also the development of multisite initiatives such as the Consortium on the Genetics of Endophenotypes in Schizophrenia. Such projects represent an advance in this field in aiming to address reliability concerns by standardizing methodologies for electrophysiological and neurocognitive measures with regular monitoring of procedures, training and reliability (Walters & Owen 2007).

Bipolar disorder

In bipolar disorder, a commonly identified endophenotype is a deficit in facial emotion labeling, found in both individuals with bipolar disorder and in individuals who are "at risk" (i.e., have a first degree relative with bipolar disorder). Using functional magnetic resonance imaging, this endophenotype has been linked to dysfunction in the dorsolateral and ventrolateral prefrontal cortex, anterior cingulate cortex, striatum, and amygdala. A polymorphism in the CACNA1C gene encoding the voltage-dependent calcium channel Cav1.2 was found associated with deficits in facial emotion recognition (Gottesman & Gould 2003).

Suicide

The concept of endophenotype has also been used in suicide studies. Personality characteristics can be seen as endophenotypes that can exert a diathesis effect on the individual's susceptibility to suicidal behavior. Although the exact identification of these endophenotypes is controversial, some traits such as impulsivity and aggression are commonly cited as risk factors. One of these genetic bases for one of these at-risk endophenotypes has been suggested as a gene encoding for the serotonin 5-HT1B receptor, known to be relevant in aggressive behavior (Gottesman & Gould 2003).

Alcool dependence

For alcool dependence, a series of studies by the Collaborative Study of the Genetics of Alcoholism (COGA) are available, in which electrophysiological endophenotypes were considered in addition to clinical diagnoses (Walters & Owen 2007). Here the use of endophenotypes substantially improved both the strength and localization of linkage findings and allowed the identification of GABRA2 and CHRM2 as genes associated with predisposition to alcohol dependence (Walters & Owen 2007). In this case, the utility of analysing electrophysiological data seems to have been that it allowed broad linkage signals reflecting linkage to more than one locus to be decomposed into constituent signals reflecting variation in individual genes; gains in power resulted from a combination of greater genetic homogeneity and the use of quantitative phenotypes.

Substance abuse and addiction

Over the years, there have been several attempts to identify, through brain signal recording techniques, footprints - hidden in neural activity - that could act as an endophenotype for substance abuse and addiction. This technique, called evoked potentials (or event related potential, ERP) allows the identification of peaks in the electroencephalogram (EEG) trace, of the variations in the electroencephalographic signal that reflect the activation of a neuronal population in response to a stimulus. These peaks are usually identified by a letter, which indicates their polarity (P for positive, N for negative) and a number, which indicates the time (in milliseconds) between the stimulus and the peak under examination. Lower numbers indicate immediate responses of the nervous system, and identify peaks (such as N100) that reflect more primitive sensory responses; peaks with higher latency (such as P300, one of the most studied evoked potentials) are instead correlated to more complex cognitive processing. The P300 and its breadth have been the subject of study for some years as part of the search for an endophenotype linked to the propensity to abuse of substances. P300 is evoked by the presentation of a stimulus, typically visual or auditory, rare or unexpected; although the neurological systems underlying this physiological response are not entirely clear, it seems that the P300 reflects the activation of circuits that connect the frontal and time/parietal regions, and which are involved in the processes of attention, in decision-making behaviors and in memory. According to the most accredited theories (Polich, 2007), P300 reflects a neural inhibition mechanism capable of facilitating the transmission of the salient stimulus (rare, or expected) to the detriment of others, considered of lesser importance.

The P300, and in particular the reduction in its amplitude, has several points of contact with the definition of endophenotype for pathologies related to substance abuse: a reduced P300 is associated, first of all, with abusive behavior; the amplitude of this wave is then inheritable from generation to generation and has genetic traits that can also be found in the phenotype that characterizes pathological situations; furthermore, a reduced amplitude of the P300 is evident after a period of abstinence, but also in children - who had never used drugs - of patients with abuse disorders. Finally, a reduced P300 recorded during childhood / early adolescence can predict a high risk of developing pathological situations related to substance use in adulthood, as well as other behavioral disorders (Iacono & McGue 2006).

CONCLUSIONS

The concept of intermediate phenotype or endophenotype represents a fundamental turning point in the genetics of complex traits, and therefore also in the genetics of behavior. In fact, identifying exactly which biological process is influenced by the presence of variants of specific genes allows us to understand which are the ways through which genes regulate susceptibility to multifactorial diseases, to understand which environmental factors are most relevant in determining the phenotype. final and to lay the foundations for a targeted therapy that is no longer based on the treatment of the symptom, but which is aimed at the normalization of altered biological processes. Above all, this type of studies will allow to build personalized therapies that are based on the knowledge of the molecular defects caused by the presence of specific gene variants.

Acknowledgements: *None.*

Conflict of interest: *None to declare.*

Contribution of individual authors:

Giada Juli: writing original draft, editing;
Rebecca Juli: writing original draft,
Luigi Juli: resources.

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