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Mini Review

Endophenotypes in Psychiatry: An overview

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Abstract

As the attempts to identify genetic contributions have met with limited success, the hunt for intermediate characteristic or vulnerability indicators rooted in the neurosciences is ongoing. Such indicators might be useful for identifying persons who are at risk of acquiring the disease, elucidating etiological causes, and identifying new treatments. Recent research indicate that this can be achieved by identifying the 'intermediate phenotypes' or endophenotypes. This review contains a brief coverage of overall idea of an endophenotype and discusses the specific endophenotypes in various psychiatric illnesses like schizophrenia, depression, bipolar disorder, autism spectrum disorder and ADHD.

Keywords: Endophenotypes, Psychiatric Illness, Depression, Schizophrenia, Bipolar Disorder, ASD, ADHD

Introduction

There was a lot of enthusiasm in the psychopathology research community ten years ago, when it was discovered that endophenotypes could lead to significant advancements in genetics of psychiatric illnesses. Gottesman and Gould's work on the potential of endophenotypes has contributed significantly to this confidence. This work introduced the idea of endophenotype, outlined how it could be used in schizophrenia research to locate molecular genetic targets, and highlighted eye-tracking failure and sensorimotor gating as plausible endophenotypes. In their subsequent paper, Gould and Gottesman narrowed the definition of endophenotype to make it more helpful in psychiatric genetics [1]. This concept of endophenotypes challenged Darwin's Theory of natural selection by exophenotypes which could be related to when John and Lewis discovered that grasshopper adaptation to local environments cannot be fully explained by exophenotypic variation, but also by endophenotypic variation [1,2].

Biomarkers vs Endophenotypes

There has been a confusing concept of endophenotypes versus biomarkers which needs to be distinguished. Biomarkers includes parameters that may be measured and assessed objectively as a sign of normal biological processes, pathogenic processes, or pharmacological reactions to a therapeutic intervention as they are directly linked to the illness. Biomarkers can be categorised into distinct types as antecedents, screening, diagnosis, prognosis, and stratification markers respectively based on their functions,

such as risk assessment, early detection, identification, illness progression prediction, and treatment response prediction [3]. Endophenotypes also termed as "Intermediate Phenotypes" are considered to be an important trait marker and subtype of biomarkers [4]. Endophenotypes at present has become an important and emerging topic that needs to be conceptualised in each type of psychiatric illness.

Definition

Gottesman and Shields derived this term 'endophenotypes' from insect biology as internal phenotypes that exist along the gene-disease route. Endophenotypes are "measurable components unseen by the unaided eye along the road between disease and distal genotype," according to Gottesman and Gould. The rationale behind the concept is that variation in an endophenotype is based on fewer genes than variation in a more complicated illness phenotype, making it more tractable to genetic research [5]. Gottesman and Gould's six criterias for defining an endophenotype are that it should be heritable, segregate with the illness in the population and should cosegregate within affected families, must be state -independent meaning that it must manifest in an individual whether the illness is present or in remission, must be present at higher rate in the affected families than the general population and should be specific to the illness of interest and reliably measurable [6].

Other secondary criterias signify that Endophenotypes should be considered as part of the disease-causing process and the pathogenic mechanism involved. It should be quantified on a regular basis and can provide a probabilistic prediction of disorder. Endophenotypes (whether genetic or environmental) should be closer to the site of the primary causative agent thandiagnostic categories. Endophenotypes could be represented as anatomical, developmental, electrophysiological, metabolic, sensory and psychological [7].

Endophenotypes in Psychiatric Disorders

Psychiatry and associated sciences were heavily focused on uncovering pathognomonic signs of psychiatric illness throughout the twentieth century and until recently. Pathognomonic indicators reveal indisputably that a person has a certain illness. These signals are critical in medicine for accurate diagnosis and therapy. They are delicate, explicit, and indicate a thorough understanding of the disease process, allowing for more effective treatment and countermeasures [8]. However, *Insel, et al.* (2010) introduced the RDoC as a framework for integrating genetic and neurological data to build a pathophysiology-based classification system with the goal of improving prevention, early intervention, and treatment results [9]. In order to do this, RDoC substantially abandons the current diagnostic system and favours dimensionally measurable structures and brain circuits linked to upstream genetics and downstream behaviour. Endophenotypes are typically found at the level of the RDoC system's intermediate units of analysis (molecules, cells, circuits, physiology) [10,11].

Endophenotypes in Schizophrenia

The competitor endophenotypes that have been analyzed in schizophrenia range from metabolic and formative measures to underlying brain structural and functional attributes, just as neuropsychological and neurophysiological records. Schizophrenia is one of the most common researched psychiatric disorders for defining endophenotypes. The route for neuronal development is critical as it may be altered by some minor genetic abnormalities.

These genetic mutations can be observed in minority of the patients of schizophrenia and this endophenotypic feature corresponds to a neurodevelopmental hypothesis [12]. Consortium on the Genetics of Schizophrenia (COGS), conducted candidate gene and linkage analyses of many schizophrenia related endophenotypes. Genotyping for 130 families was done using a custom genotyping array that evaluated 94 candidate genes for schizophrenia and 8 candidate genes were identified that were associated with multiple endophenotyes. These genes were CTNNA2, ERBB4, GRID2, GRIK3, GRIK4, NOS1AP, NRG1, and RELN [13,14]. The main psychological endophenotypes includes deficits in working memory an executive functioning observed using Letter number sequencing and difficulty in attention on Continous Performance Test (CPT). Neurophysiological endophenotypic measures incorporate antisaccade oculomotor working, smooth pursuit eye development, P50 concealment, prepulse restraint (PPI) of the frighten reaction, P300 ERPs, and visual in reverse covering. Each of these endophenotypes has gone through a coherent, regular history of movement in logical investigations: schizophrenia patients, their clinically unaffected relatives, and schizotypal character confused subjects have shortfalls contrasted and ordinary subjects [15].

Endophenotypes in Depression

As per International Classification of Disease 10 criteria, depression is characterised by presence of low mood, loss of interest in previously pleasurable activities and feeling of tiredness. Other symptoms include difficulty in concentrating, negative cognitions, sleep disturbances and suicidal ideation, etc. [16]. Thus, these psychopathological features that are biologically and clinically meaningful, fulfilling the defining criteria for endophenotypes were marked as psychopathological endophenotypes of depression. It included depressed mood, anhedonia, impaired learning, memory and executive cognitive function, psychomotor retardation and increased stress sensitivity. Biological endophenotypes includes abnormalities in brain structures and functioning and changes related to neurotransmitters like serotonin, dopamine and norepinephrine. Structural imaging showed reduction in volumes of Anterior Cingulate Cortex and Hippocampus (may be associated with BDNF val66met polymorphism) whereas functioning imaging showed elevation of cerebral blood flow and glucose metabolism in resting amygdala while reduction in both in subgenual prefrontal cortex. There may be alteration in Hypothalamic-Pituitary-Adrenal axis and 5-HT1A receptor binding potential. Decreased levels of

CREB, BDNF, and the TrkB receptor have been reported in suicide victims [17].

Endophenotypes in Bipolar Disorder

Bipolar disorder patient exhibits multiple endophenotypes, of which abnormalities in circadian rhythm one of the most important endophenotype that could lead to abnormal sleep wake cycle, thermoregulation and hormonal secretion. This is commonly observed in recurrent affective disorder. Neurophysiological endophenotypes includes delayed P300 response corresponding to reduced attention and cognitive processing. Behavioural response to psychostimulants and other medications can also an endophenotypic feature. On Magnetic Resonance Imaging (MRI), risk for white matter hyperintensities is three fold higher than the normal population. Biochemical abnormalities in peripheral mononuclear cells can also act as endophenotype for bipolar disorder. However few endophenotypes such as abnormal dexamethasone, tryptophan depletion and alpha-methyl-paratyrosine may be seen commonly in both bipolar disorder and unipolar depression patients [18,19].

Endophenotypes in Autism Spectrum Disorder

Genetics has a significant role in the pathophysiology of ASD. Two decades ago, twin studies concurred on heritability estimates of greater than 90%, with monozygotic twins showing concordance rates of 73-95 percent compared to 0-10 percent in dizygotic twins. Furthermore, first-degree relatives exhibit moderate features that are qualitatively similar to those seen in autistic relatives, validating the term "autism spectrum" or "extended phenotypic." Among biochemical endophenotypes elevated serotonin levels in blood is observed in 30-50% of the cases and presence of altered concentrations of solutes known as oligopeptides is seen 10 to 60% of the individuals. Morphologically, macrocephaly and various minor physical anomalies may be present in ASD patients. Oxytocin playing important role in establishing social bonds is seen to be deficit in these individuals. Similarly, melatonin is secreted in lower quantities. Neuropsychological endophenotypes include gaze abnormalities recorded by eye tracking and deficits in executive functions, such as spatial working memory and strategic planning. Behavioral endophenotypes include several variables like stereotypic behaviors, verbal language, I.Q., and savant skills [20].

Endophenotypes in ADHD

There is limited literature available to describe endophenotypes in ADHD. A subset of these concerns is addressed in ADHD research, which has yielded a few possible endophenotypes. On a few variations that impact dopamine (DA) neurotransmission, hereditary affiliation concentrations consistently generate bigger possibilities proportions for individuals with ADHD versus controls. These traits are strongly transmitted in the striatum, which is downregulated in people with ADHD and hence less responsive to fully anticipating motivating factors. These striatal responding deficits are a major neurological underpinning of hasty direction, which is a symptom of ADHD. Despite the fact that few components of striatal DA activity are inherited, this striatal under-reactivity to compensate is also evident in people who have other troublesome behaviour difficulties, such as conduct issues, utter disrespect for others, and substance-use issues. The high co-morbidities of ADHD with other externalising messes may explain this lack of specificity, but new studies have shown more recalcitrant issues [21].

Attention deficits, the symptom as well as endophenotypic feature of ADHD can be measured by Continous Performance Test (CPT). There may be executive function impairment especially in visual spatial working memory, state regulation difficulties in reaction time and altered reinforcement. Anatomical endophenotypes may include volumetric changes in Dorsolateral prefrontal cortex, Dorsal anterior cingulate gyrus and Caudate nucleus [22].

Utility of Endophenotypes

Molecular genetics have shown that a variety of genetic variants are associated with specific psychiatric illness. Studies based on this approach reveal that mental disorder are polygenic showing different genes being associated with a single psychiatric illness. Endophenotypes are the heritable traits that can be measured using different investigations like neuroimaging, electroencephalographic anomalies, cognitive functions, eye movements, facial expressions, etc. Due to heritability and genetic linkage, endophenotypes features are observed to be present in the affected population and have higher incidence in the first-degree relatives when compared to the normal population. Thus, it may also help to detect the population at risk for developing illness. As, endophenotypes are more proximal to the action of genes than the clinical diagnosis and thus identify the gene associated with the illness. In future, it will help to make confirmation of the diagnosis and may try to elucidate the etiological factor and advances in finding novel treatment of various illnesses [23,24].

Limitations of Endophenotypes

Of all the endophenotypes described, only few fulfil the criteria mentioned in the definition. Certain endophenotypes that fulfil the criteria also can be result of some environmental, social or epigenetic factors thus making it difficult to differentiate between biological predisposition and behavioural manifestations. Also, the act of treating all neurobiological correlates of psychopathology as endophenotypes raises a few questions. Endophenotypes are state dependent, thus contamination can happen by fluctuation in the course of illness and drug treatment. There are lot of uncertainties about reliability as there may be inter-laboratory variation and some chances of interpretation biases. The cost of measuring some endophenotypes, particularly those based on neuroimaging or genetic sequencing, currently prohibits their application to the large samples required for gene-finding studies [10].

Conclusion

Endophenotypes in psychiatry is an emerging topic which needs further exploration to overcome the limitations. It may play an important role in prevention research as they may help in identifying those at risk and may prevent the onset of the illness. However, the implications of these finding is difficult and needs further research.

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