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Review

Targeting dynamic interplay among disordered domains or endophenotypes to understand complex neuropsychiatric disorders: Translational lessons from preclinical models

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ABSTRACT

Contemporary biological psychiatry uses clinical and experimental (animal) models to increase our understanding of brain pathogenesis. Modeling psychiatric disorders is currently performed by targeting various key neurobehavioral clusters of phenotypic traits (domains), including affective, cognitive, social, motor and reward. Analyses of such domains and their 'smaller units' – individual endophenotypes – are critical for the study of complex brain disorders and their neural underpinnings. The spectrum nature of brain disorders and the importance of pathogenetic linkage among various disordered domains or endophenotypes have also been recognized as an important strategic direction of translational research. Here, we discuss cross-domain analyses of animal models, and focus on their value for mimicking the clinical overlap between disordered neurobehavioral domains in humans. Based on recent experimental evidence, we argue that understanding of brain pathogenesis requires modeling the clinically relevant inter-relationships between various individual endophenotypes (or their domains).

Contents

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The whole is more than the sum of its parts
Aristotle

1. Introduction

Representing one of the most complex human diseases, neuropsychiatric disorders are serious debilitating illnesses with multiple genetic and environmental causes (Fears et al., 2014; Meyer-Lindenberg and Weinberger, 2006; Nestler and Hyman, 2010; Tsankova et al., 2007). Clinical studies, animal models and mechanistically-driven in-vitro research (Table 1) are critical for studying brain disorders and discovering novel therapies (Cryan and Slattery, 2007; Kalueff et al., 2007; Redei et al., 2001). While the societal impact of psychiatric disorders continues to grow (WHO, 2008), their symptoms, pathogenetic mechanisms and risk factors remain poorly understood (Caspi and Moffitt, 2006; Cowan et al., 2000; Nestler and Hyman, 2010). Psychiatric patients also often do not receive adequate treatment, as many therapies lack specificity and/or have not improved markedly over the last decades (Griebel and Holmes, 2013; McMahon and Insel, 2012).

Because the role of genetic factors in CNS pathogenesis is key, understanding the genetics of brain disorders is necessary for their treatment and prevention (Bernier et al., 2014; Duman et al., 1994; Fears et al., 2014; Flint and Munafo, 2014; Gaugler et al., 2014; Nestler, 2013). However, the majority of brain disorders are complex and polygenic (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Ikeda et al., 2013; Murphy et al., 2003; Uddin et al., 2014). This markedly complicates their genetic analyses, which often not only reveal disorder-specific genes, but also show significant genetic overlap and cross-disorder heritability (Gaugler et al., 2014; Ivleva et al., 2010; Lee et al., 2013). For example, genetic contributions to psychiatric disorders do not always match present diagnostic categories (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013), and may involve complex pleiotropic and epistatic genetic interactions (Gottesman, 1994; Murphy et al., 2003) (Table 1). Therefore, further stratification is needed to link clinical cohorts and phenotypes to specific genetic determinants and associated pathways (Maccarrone et al., 2013). Based on recent experimental evidence, here we parallel cross-domain/cross-endophenotype analyses of clinical and animal neurobehavioral deficits, suggesting that understanding of brain pathogenesis and its genetics requires targeting the clinically relevant inter-relationships between various individual syndromes.

1.1. Endophenotypes of CNS disorders

In the early 1970s, Gottesman and Shields introduced an important concept that addresses the genes-to-behavior pathways by deconstructing complex disorder symptoms into smaller units, termed 'endophenotypes' (Gottesman and Gould, 2003; Gould and Gottesman, 2006). As explained in Table 1, endophenotypes represent objective quantifiable and inheritable biological or behavioral components of a disorder (Gould and Gottesman, 2006), which are present regardless of whether a specific disorder is active, and can be found in non-affected relatives of the patient at a higher rate than the general population (Cannon and Keller, 2006; LaPorte et al., 2008). This term is also related to (but different from) the term 'intermediate phenotype', often used to describe a quantitative trait that is between the genes and the disorder (Flint et al., 2014; Kas et al., 2007; Walters and Owen, 2007).

In both humans and animals, psychiatric endophenotypes can be used as measurable and heritable behavioral or physiological biomarkers for phenotypic traits (Gottesman and Gould, 2003; Gould and Gottesman, 2006; Lenzenweger, 2013b), and can be grouped into distinct 'bigger' clusters (domains), such as affective, cognitive, social, motor and reward domains (see Table 1 for a glossary of terms, and Table 2 for specific criteria defining endophenotypes). In the last decades, the endophenotype concept has emerged as a key paradigm in biological psychiatry (Braff, 2015; Cannon and Keller, 2006; Flint et al., 2014; Glahn et al., 2012, 2014; Hasler et al., 2006). Revealing both overlapping and unique candidate genes of various complex CNS disorders (Courtet et al., 2011; Crossley et al., 2014; Dick et al., 2006; Flint et al., 2014; Ikeda et al., 2013; Ivleva et al., 2010), this concept has also become an important part of computational psychiatry (Wang and Krystal, 2014).

1.2. Diagnostic criteria and current challenges

In general, human brain disorders can be described and diagnosed using categorical or dimensional approaches (Table 1). Conventional diagnostic criteria for brain disorders are outlined in the fifth edition of the diagnostic and statistical manual of mental disorders (DSM-5), recently revised by the American Psychiatric Association (APA, 2013). DSM-5 uses symptoms' categorization based on a consensus about clusters of clinical symptoms—an approach that has been recently criticized from both practical and conceptual points of view (Casey et al., 2013; Stankovic et al., 2012).

Proposed by the US National Institute of Mental Health (NIMH) to address this gap, the research domain criteria (RDOCs; Table 1) approach differs from DSM-5 by applying a functional dimensional system. This approach relies on spectral phenotypes (that range from norm to pathology) and includes biologically-relevant symptoms that may expand beyond the traditional categorical diagnoses (NIMH, 2015). RDOCs can be examined across multiple levels of analysis, from genes and circuits to psychology and behavior (Casey et al., 2013; London, 2014; NIMH, 2015), and may also be applied to preclinical models (de Mooij-van Malsen et al., 2015; Kas et al., 2014; Stewart and Kalueff, 2013).

The endophenotype concept is consistent with the recent emphasis on RDOCs (Casey et al., 2013; Cuthbert and Insel, 2010; Insel et al., 2010; Insel, 2014; NIMH, 2015) as they both target phenotypic dimensions, rather than categories, of psychiatric diagnoses (Gottesman and McGue, 2015), Table 1. Nevertheless, one of the main challenges is that the focus of contemporary biological psychiatry, including both DSM-5 and RDOCs, largely remains [endo]phenotype-centered. Specifically, they mainly target neurobiological mechanisms responsible for specific endophenotypes, their domains or individual disorders (Ditzen et al., 2012; Filiou et al., 2011; Gormanns et al., 2011; Kalueff et al., 2008; Maccarrone et al., 2013), rather than overlap between them. Here, we argue that further attention needs to be paid to studying the dynamic interplay among different endophenotypes—a pathogenetically critical process that can occur either within, or between, different disordered domains, and, respectively, may impact a single poly-domain CNS disorder, or link domains/endophenotypes belonging to several different psychiatric disorders.

1.3. Case in focus: Obsessive-compulsive disorder (OCD)

Consider, for example, obsessive-compulsive disorder (OCD), which includes both repetitive behaviors and increased anxiety (Pigott et al., 1994; Welkowitz et al., 2000). Multiple clinical and animal studies have established the neurochemical, genetic and physiological correlates of these two OCD behavioral domains (McGrath et al., 1999; Schneier et al., 2008; Sturm et al., 2003). Nevertheless, the growing recognition of the 'spectrum' nature of brain disorders (Gratten et al., 2014; Myhr, 1998; Stamou et al., 2013; Stankovic et al., 2012, Fig. 1) necessitates more integrative approaches to modeling brain pathogenesis (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Kalueff and Stewart,