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Animal models in psychiatric research: The RDoC system as a new framework for endophenotype-oriented translational neuroscience

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A B S T R A C T

The recently proposed Research Domain Criteria (RDoC) system defines psychopathologies as phenomena of multilevel neurobiological existence and assigns them to 5 behavioural domains characterizing a brain in action. We performed an analysis on this contemporary concept of psychopathologies in respect to a brain phylogeny and biological substrates of psychiatric diseases. We found that the RDoC system uses biological determinism to explain the pathogenesis of distinct psychiatric symptoms and emphasises exploration of endophenotypes but not of complex diseases. Therefore, as a possible framework for experimental studies it allows one to evade a major challenge of translational studies of strict disease-to-model correspondence. The system conforms with the concept of a normality and pathology continuum, therefore, supports basic studies. The units of analysis of the RDoC system appear as a novel matrix for model validation. The general regulation and arousal, positive valence, negative valence, and social interactions behavioural domains of the RDoC system show basic construct, network, and phenomenological homologies between human and experimental animals. The nature and complexity of the cognitive behavioural domain of the RDoC system deserve further clarification. These homologies in the 4 domains justifies the validity, reliably and translatability of animal models appearing as endophenotypes of the negative and positive affect, social interaction and general regulation and arousal systems' dysfunction.

Contents

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1. Nosological entity problem in psychiatry

A fundamental problem of clinical diagnosis in psychiatry is the identification of disease as an objective and unique entity. Emil Kraepelin established the basis for modern nosology of psychiatric diseases (Kraepelin, 1893, 1896). The contemporary International Statistical Classification of Diseases and Related Health Problems (ICD-10, 1989, http://www.who.int/classifications/icd/en/) and the Diagnostics and Statistics Manual of Mental Disorders (DSM-5, 2013, http://www.dsm5.org/Pages/Default.aspx) imply a clear distinction of nosological entities from normality and from each other. Diagnosis of psychopathologies is mostly based on the presence of deviant behaviour, self-evaluated discontent, behavioural maladaptation and danger posed to the patient or others. The categorical assignment of illnesses is justified by practical needs, such as unification of data across medical institutions, statistics, on default diagnostic efforts and treatment and on official grounds of reimbursement for a diagnostic means and therapeutic interventions by health insurance companies. However, diagnostic complexity and the lack of confidence in the final diagnosis often result in a formal use of contemporary nosological classifications (Maj, 2015).

Nosological entities imply the existence of specific causations. As a result, major efforts have been made to try to identify specific hallmarks of pathogenesis or associated genes using objective measurements in order to gain a high level of diagnostic reliability. Despite this effort, no clear markers have been identified that are indicative for existing psychiatric nosological entities. On a morphological level, volume reduction of cortical areas and the hippocampal formation has been reported for major depression and schizophrenia (Bremner et al., 2000; Meisenzahl et al., 2010; Nelson et al., 1998). Complex changes in molecular factors such as receptors expression, transporters and secondary messengers (Nikolaus et al., 2012; Scarr et al., 2015) contribute to a deterioration in neuroplasticity and synaptogenesis and are seen throughout the brain without clear nosological distinction (Bernardinelli et al., 2014; Kassem et al., 2013). Specificity of genetic signatures will only be possible with a tremendous increase in sample size, which will correspond ironically to lower nosological precision (Hyde et al., 2016; Ripke et al., 2014).

The failure to identify specific markers can be explained as follows: (1) A linear and finite relationship between the cause and outcome is a rare in psychiatric disease (Fig. 1, left). Instead, there are many reciprocal interactions between the biological background, its functional expression and numerous exogenous factors (Fig. 1, right). (2) The theory of allostatic load introduces preceding experience as a factor that may recalibrate the behavioural and physiological reactions and change the adaptation potential (Ellis and Del Giudice, 2014; McEwen, 1998; Nederhof and Schmidt, 2012). Environmental stress is considered as a pathogenetic element of a high importance in psychiatry (De Kloet et al., 2005; McEwen and Stellar, 1993; McEwen, 2008; Millan et al., 2012; Peyrot et al., 2015). (3) The interaction between the genome and the environment has a strong context limiting/permitting component (Notaras et al., 2016). Mechanisms that evolved over millions of years to protect individuals from a life-threatening environment have become maladaptive in respect to contemporary sociocultural demands (Del Giudice, 2016; Ellis and Del Giudice, 2014; First and Wakefield, 2013). (4) This research approach is problematic as it keeps the nosological entity as the focus. Jaspers (1913) insisted that a nosological entity is a goal for study, but not an objectively existing phenomenon. Thus, any nosological approach to stratify disease should be viewed as a diagnostic strategy rather than approach to research distinct pathogenesis.

2. Evolutional and neurobiological understanding of psychopathology

MacLean (1970, 1985, and 1990) first recognized the importance of an evolutionary concept to understand the regulation of mental function and proposed The Triune Brain Model (Fig. 2, left). According to MacLean, the phylogenetically oldest *Protoreptilian* brain provides instinctive actions, which are the basis of essential behaviours necessary for survival (e.g., exploration, escape behaviour, foraging, feeding, aggression, domination and reproductive behaviour). The *Paleomammalian* formation comprises parts of the brain that are conventionally assigned to the limbic system (or Papez circuit, Papez, 1937). It is responsible for emotions and motivation and transforms a primary response to more adaptive ones, based on previous experience and instincts. The neocortical *Neomammalian* formation provides actual declarative knowledge of all incoming sensory information.

The Triune Brain Model was followed by The Affective Neuroscience Scale system (Davis and Panksepp, 2011; Panksepp, 1998, 2005). According to Panksepp's theory, core emotional affects and defensive behaviours are represented by the diencephalic action systems of “Panic”, “Fear”, Rage”, “Lust”, “Seeking”, Care” and “Play” (Fig. 2, middle). Genetically determined neuronal networks are considered as neurobiological substrates of these behaviours (Panksepp, 1998) and appear to be conserved throughout the mammalian evolution (Berridge, 2000; Saudino, 2005; Rutter et al., 1997). Emotions and defence behaviours serve focused and distinguished behavioural goals, and, therefore, can be controlled with specific stimuli and operate relatively independently (e.g., Anderson and Adolphs, 2014). Three reference points were suggested to specify the network, responsible for 1 of the behaviour characteristics selected by Pankseep: (1) similar neuronal circuits maintain coherent functions; (2) artificial stimulation of the particular network (with a pharmacological, electrophysiological, and opto-/chemo-genetic means) generates predicted responses; and (3) changes in the carriers of the network activity (neurotransmitters and other substances with messenger activity) predict the behavioural changes (Panksepp, 1998). A lot of research aims to decipher the circuitries that predominantly control (1) arousal and sleep (Herrera et al., 2016; Kim et al., 2012; Landgraf et al., 2016), (2) fear, (3) anxiety, (4) aversive memories (Bravo-Rivera et al., 2014; Kim et al., 2013; McCullough et al., 2016; Tovote et al., 2015), (5) reward (Kelley, 2004; Kelley and Berridge, 2002; Smith et al., 2011), (6) attention and motivation (Berthet et al., 2016; Carli and Invernizzi, 2014; Kim, 2013), (7) goal-oriented behaviour and habits (Burguière et al., 2015; Chersi et al., 2013; Frank, 2011; Gremel and Costa, 2013; Medendorp et al., 2011) and (8) social functions (Konopka and Roberts, 2016; Kragel et al., 2015; Sladky et al., 2015; Zikopoulos and Barbas, 2013).

The objective partition of the networks is nonetheless neither a physical nor functional segregation. Thus, emotional affect networks are integrated into the limbic system of the brain. In turn, the emotional homeostasis provided by the limbic system defines the efficacy of both the phylogenetically old defence systems and more advanced cognitive functions (de Waal, 2011; Panksepp, 2005; Park et al., 2016; Vermunt et al., 2016). In turn, the refined cortical functions favour better top-down control over the affective behaviours and provide more efficient adaptation strategies (Adhikari et al., 2015; Comte et al., 2016; Parikh et al., 2016; Rajasethupathy et al., 2015). For instance, recent fMRI findings on activity in the prefrontal cortex and anterior/posterior cingulate cortex have shown that these cortical structures exert inhibitory top-down control of emotional responses. This results in suppression of the context-irrelevant behavioural activity (Fair et al., 2008; Jaffard