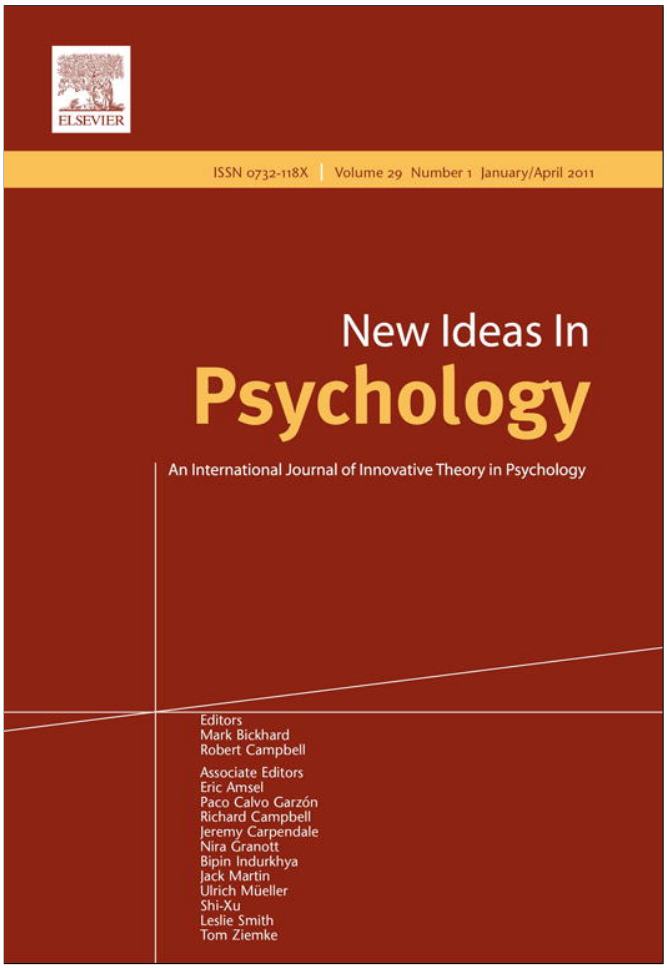

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Domain interplay in mice and men: New possibilities for the "natural kinds" theory of emotion

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ABSTRACT

The recent challenge to the long-held assumption that emotions are natural kinds (i.e., discreet naturally-distinguishable phenomena) has raised the necessity for a closer look into the nature of affective research. If emotions are not natural kinds, there will be widespread consequences for the theoretical foundations of behavioral neuroscience and grave implications for the validity of animal models of emotion and affective disorders. This paper presents the evidence against the hypothesis of emotions as natural kinds, and offers the "domain-interplay" concept as a novel and effective experimental method for establishing the theoretical rationale of non-human animal research in the neurosciences.

1. Introduction: emotions as "natural kinds"

Research studies on emotion and affective disorders are plagued with a critical question: What is an emotion? This definitional obscurity has taken a variety of forms and been supplied with countless answers (Ekman & Davidson, 1994; Griffiths, 1998; Solomon, 2003). However, the defining characteristics of emotional states must be known before an adequate examination of these emotions can be completed. Without this definition, there is no solid foundation on which to build an empirical body of evidence to support any theory of emotion.

One long-standing and intuitive assumption is that emotions are "natural kinds", meaning that they are *recognized* rather than *defined* by humans (e.g., Darwin, 1965; Ekman, 1972; MacLean, 1952; Papez,

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1937). Therefore, under this assumption emotions such as fear should be conglomerations of objective, observable, and natural occurrences. If an emotion is a natural kind, this may be ascertained by observing its characteristics or identifying the natural causal mechanisms. For example, a natural kind emotion in a human being should involve numerous physiological characteristics. Thus, fear will be associated with pupil dilation, sweating, accelerated heart rate, and commonly a fearful facial display. Anger should also elicit a spectrum of physiolological correlates that are observably unique from the correlates of fear. In some cases, one emotion may have numerous physiological manifestations, some which may not be demonstrated in every instance. A reaction arising from the fear circuits in the brain is then classified as fear, though they may be phenotypically visible in many different forms. Here, the causal mechanisms can also serve to establish the emotion as a natural kind.

Despite the apparent plausibility of emotions as natural kinds, this assumption has faced recent criticism (Barrett, 2006a, 2006b; Barrett et al., 2007; Griffiths, 2004; Russell & Barrett, 1999), with potentially ominous implications for neuroscience. If the natural kinds assumption is false and cannot be adequately addressed, then this poses severe obstacles for neurobehavioral research on affective disorders.

The evidence supporting the claim against the natural kinds assumption arises from inconsistent findings used in traditional testing methods such as self-reports of emotion, peripheral nervous system responses, facial and vocal signals, and neural circuit/emotion correspondence (for reviews see: Barrett, 2006a, 2006b). The lack of studies elucidating the distinct causal mechanisms for individual emotions, and the difficulty in defining the specific neural properties of the brain that are associated with specific emotions have led some to suggest that the problem may not lie with the methods being utilized, but rather in the direction of research (Izard, 2007; Panksepp, 2007). An alternative explanation for the inability to firmly establish emotions as natural kinds is that they are, indeed, *not* natural kinds (Barrett, 2006a, 2006b; Barrett et al., 2007).

As a substitute for human subjects, behavioral neuroscience commonly employs the use of animal models in their research due to cost, time and ethical considerations. The bulk of this behavioral research is based on the theoretical foundation that emotions are natural kinds, and therefore that observation of those physiological markers is an experimentally valid way to learn about the neural mechanisms of an emotion or affective disorder (Willner, 1991). This is critically important for the extrapolation of results from animal data to human data in translational research. If it is true that emotions are not natural kinds, then the neurobehavioral science of emotions becomes a very challenging enterprise.

2. Refutation of the "natural kind" theory and the effect on animal modeling

While there are many ways in which non-human animals can be utilized in biobehavioral research (e.g., screening pharmacological agents or genetic effects), investigations of affective processes and neuropsychiatric disorders typically rely on employing simulations of human conditions (Willner, 1986, 1991). These animal models usually attempt to reflect one or more behavioral or neurobiological aspect of the human disorder (Kalueff, Wheaton, & Murphy, 2007). Similar to any other psychological instrument, an assessment of a simulation is necessary to ensure it is being implemented appropriately. Is the simulation measuring the construct of interest? Are there any critical flaws in its performance?

Non-human simulations are typically assessed on three dimensions: face, predictive and construct validity (Willner, 1986, 1991). Face validity refers to the similarities between the animal model and the human psychopathology. Predictive validity assesses the performance of a model with regards to the expected results. This has been historically assessed through the similarity in pharmacological treatment efficacy between an animal model and the human clinical condition (Willner, 1991). Construct validity is a measure of the theoretical rationale of the animal model (i.e., an evaluation of the degree of homology between the simulation and the human condition of interest; Willner, 1991).

If the natural kind theory of emotion is refuted, there could be considerable consequences for the validation of animal model simulations. Recognized as a potential outcome of moving away from this putatively outmoded theory, this criticism admits that animal models may still provide "part of the story for understanding human emotional life" (Barrett et al., 2007, p. 303). However, the arguments

raised against the natural kind theory make it difficult to establish an animal model's construct validity. Without a theoretical rationale, it is unclear how a model would be able to provide even *part* of the story of human affective states or psychological disorders.

For example, one of the arguments against the natural kind theory is that a measured behavior of the animal simulation may not necessarily be linked to a single emotional category (Barrett, 2006b, Barrett et al., 2007). This is a long-standing problem in the field of animal modeling: How do we know that an organism's behavior corresponds with an internal state that is analogous to that state in humans (Kalueff et al., 2007; Willner, 1991)? Animal models that rely on a limited number of measured behaviors have to assess whether the behaviors are produced in a context theoretically similar to the clinical condition (Willner, 1991). In order to use this as the method of establishing a simulation's construct validity, one runs the risk of succumbing to a theoretical rationale based on anthropomorphic reasoning. This is an option often viewed as heretical by behavioral researchers and offers a weak foundation to validate an animal model.

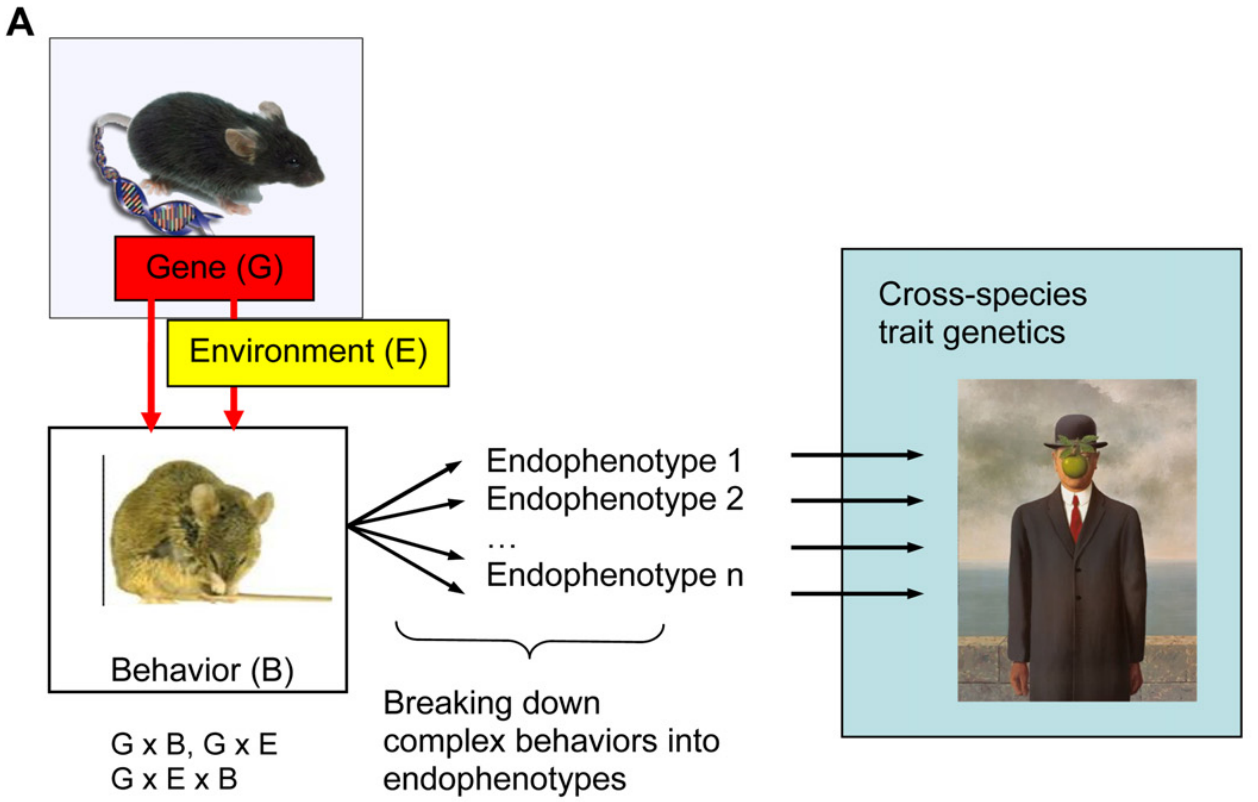
Another argument against the natural kind theory of emotion is the lack of apparent homology between humans and non-humans in regards to the neurobiological underpinnings of affective states (Barrett et al., 2007). Many, if not most, simulations of affective processes and psychological disorders rely on the putative inter-species conservation of core biobehavioral characteristics to account for the construct validity of the animal model. However, there is compelling evidence that there is a great amount of inter-species differences in brain structure–function relationships (Barrett et al., 2007). This leaves researchers with the question of whether their animal models are truly measuring their psychological construct of interest. Further, researchers can question whether the simulation has any translational value, which is normally the ultimate goal of animal modeling research.

Together, these arguments against the natural kind theory of emotion raise serious concerns about the ability to establish the construct validity of animal models of affective processes and psychological conditions. Here we will outline a novel method of utilizing animal models in biobehavioral research and demonstrate how this approach can address the concerns of establishing a simulation's construct validity.

3. Domain-oriented behavioral research

It is clear that the field of affective studies could benefit from a new perspective to establish the validity of animal models, and the solution to the above problem may be more practical than theoretical. The experimental technique that may help is embodied in the "domain-interplay concept" (Kalueff, Ren-Patterson, LaPorte, & Murphy, 2008). Previously, there have been limited techniques available for the study of emotional states in humans and animals. Behavioral neurophenotyping, which seeks to observe the behavioral characteristics of a given model, has been one of the field's most familiar tools. In fact, only four basic approaches (Fig. 1A) have been consistently utilized until recently, which may account for the putative deficiencies in establishing animal model validity (Kalueff, Ren-Patterson, et al., 2008).

While not the exclusive use of this technique, one traditional approach to validate simulations is to study the interaction between genes and environment (Mackay & Anholt, 2007). In the field of mood disorder research this often appears as genetic correlational studies that are focused on a single domain, such as susceptibility to a depressive episode (Caspi & Moffitt, 2006). A second concept examines the interactions between genes and behaviors (Kas & Van Ree, 2004). This method is similarly problematic in that it concentrates on modeling the domains in isolation, thereby neglecting the rich complexity of interplay that occurs between many aspects of genetically modulated behavior. Thirdly, animal model validation has employed endophenotyping in an attempt to distinguish a set of genetic, physiological, or behavioral biomarkers present in the animal that represents an emotion or disorder (Gould & Gottesman, 2006). One problem with this method is that it is very difficult to ensure the endophenotype in an animal model is a proper model of human endophenotypes. Fourthly, the cross-species trait genetics approach seeks to model a disordered domain across numerous species in an attempt at greater validity (Kas, Fernandes, Schalkwyk, & Collier, 2007). This also faces the challenge of ensuring that surface similarities are not interpreted as *real* homologies indicative of model validity. Much fruitful research has been accomplished using these four approaches, though none offer a way to



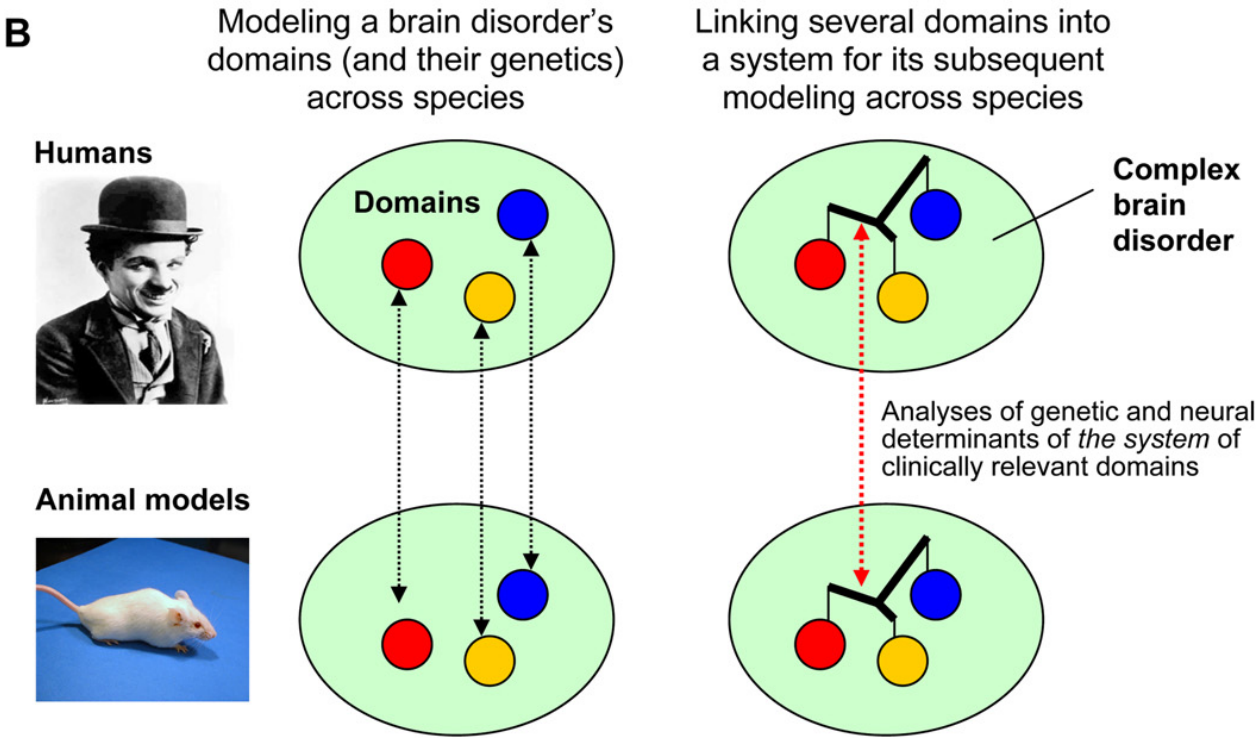


Fig. 1. A brief summary of traditional approaches to experimental modeling of neuropsychiatric disorders (A) and a graphic illustration of the domain-interplay concept and its application to translational biopsychology and integrative modeling of affective disorders (B).

establish simulation's validity if emotions are not natural kinds. This is due to each approach's reliance on assuming phenotype similarities between the simulation and the human affective state or homologous neurobiological underpinnings.

The domain-interplay concept (Fig. 1B) offers a novel way to carry out experiments that may provide a method of establishing animal model validity without necessitating emotions be natural kinds (Kalueff, Ren-Patterson, et al., 2008). The concept of domain-interplay shifts the focus away from singular phenotypes or interactions, and focuses on modeling numerous separate phenotypes, the interface between them when functioning as a system, and the similarities of these systems between species. This provides a design for models that exploit the interplay of phenotypes in basic and clinical brain research. For example, measuring anxiety responses, fear responses, and their interactions in multiple species will greatly enhance knowledge of the homologous neurobiological foundations and the phenotypical behavioral profile that correlates to human affective processes.

This methodological approach is particularly relevant considering the interrelatedness of different neuropsychiatric and mood disorders, as it is becoming increasingly recognized that disorders of mood and emotion can affect each other in a variety of ways. By modeling these phenotypical systems, researchers can represent an extended conglomeration of interactions that serve as a potential indicator of the neurobiological basis of emotive states. Further, these interactions can be modeled across-species and used as a tool for effective translational research. This will widen the extent of phenotypical characteristics that can be investigated and encourages a refocusing of research efforts away from the narrow single-domain approaches. This will likely help alleviate some of the guesswork inherent in endophenotying and cross-species techniques (Kalueff, Ren-Patterson, et al., 2008). The limitations of the previous four methods can benefit greatly through the supplementation of this new concept.

4. Utilizing the domain-interplay concept to establish models' construct validity

The domain-interplay strategy is uniquely positioned to answer the problems raised by the refutation of the natural kind theory of emotion. In fact, this animal modeling concept was created specifically to overcome difficulties in establishing behavioral phenotypic similarities with humans and to account for species differences in the biological substrates of behavior (Kalueff, Ren-Patterson, et al., 2008).

It is true that a single behavioral measure is difficult to interpret because it could be a manifestation of a variety of affective states (Barrett, 2006b; Barrett et al., 2007). Instead of relying on anthropomorphism, the domain-interplay concept looks at an entire aggregate of behavior (see Fig. 1B). This allows for researchers to examine the multiple similarities and differences between the animal model and the human clinical disorder. This empirical assessment of cross-species affective system homology can allow researchers to develop animal-based simulations of human conditions with known similarities. Further, as this domain-interplay approach is looking at the interconnections and inter-related functioning of multiple phenotypic processes, integrating this method will help supply the sophisticated modeling required for the complexities of human emotional states. Specifically, the domain-interplay concept promotes correct data interpretation in behavioral paradigms and supports the construct validity of the animal model by harnessing this inherent emotional complexity. Moreover, it removes the need to rely on anthropomorphic rationales for establishing construct validity. Together, these novel approaches are able to establish the validity of simulations without needing to assume that emotions are natural kinds.

The investigation of the interplay of behavioral domains can provide additional evidence of the animal model's construct validity. Evaluating several domains simultaneously (e.g., Kalueff, Ishikawa, & Griffith, 2008; Kalueff, Laporte, Murphy, & Sufka, 2008; Sufka et al., 2006; Sufka, Warnick, Slauson, Kim, & Rimoldi, 2009; Warnick, Huang, Acevedo, & Sufka, 2009) may distinctly improve the ability of the models to mimic the entire pathway of the disorder, instead of a single point along the continuum. Thus, the clinically-relevant aspects of mood disorders, such as comorbidity and disorder pathogenesis, can now be realistically achieved with this concept, opening new paths of research into neurological substrates of human emotion.

Consider the application of domain-interplay concept to the cases of two complex psychiatric disorders – anxiety and autism. Each of these disorders has been investigated through the use of animal

models that measure social interaction behavior (e.g., Brodkin, 2007; Carola, Scalera, Brunamonti, Gross, & D'Amato, 2008; Crawley, 2004, 2007; File, 1980; Kantor, Anheuer, & Bagdy, 2000). However, since anxiety and autism have a high comorbidity, common genetic determinants, some clinical similarity and overlapping pharmacotherapy, there is a strong possibility that these disorders may overlap in the "social interaction" domain (Bolivar, Walters, & Pheonix, 2007; Brodkin, 2007; Crawley et al., 2007; Moy, Nadler, Magnuson, & Crawley, 2006). Thus, if a simulation singularly mimicked social deficits, it would be difficult for that model to establish construct validity as it is not possible to reliably differentiate anxiety and autism in experiments. Conversely, the investigation of multiple domains allows us to further define and validate social-deficit models. For example, if a model that focuses on social interaction deficits is shown to possess global behavioral inhibition, reduced exploration and/or increased emotionality, it could be considered to possess construct validity as an anxiety simulation (Kalueff, Ren-Patterson, et al., 2008). A model with impaired social interaction behavior and increased behavioral perseverations could be thought to possess construct validity as a simulation of autism (Bolivar et al., 2007; Crawley et al., 2007).

Another example that well illustrates the domain-interplay concept is research into the relationship between anxiety and depression. Most clinicians approach anxiety disorders and major depression as distinct, separate entities (i.e., see DSM-IV-TR). As such, most animal simulations have modeled each illness individually. However, one novel model (Sufka et al., 2006, 2009; Warnick et al., 2009), was developed to simulate both anxiety and depression sequentially within a test session. This model is based on the recent conceptualization of anxiety and depression as a single disorder existing on a continuum, with anxiety disorders as the prelude to depression and depression comprising severe, prolonged anxiety (Baldwin, Evans, Hirschfeld, & Kasper, 2002; Boyer, 2000; Liebowitz et al., 1990; Merikangas et al., 2003; Paul, 1988; Polani, 2004; Tafet & Smolovich, 2004). The ability to model multiple domains (i.e., anxiety and depressive states) allows this simulation the unique capacity to investigate the pathogenesis of depression and the relationship of anxiety and depression. Additionally, modeling multiple inter-related domains makes it much easier to achieve construct validity than modeling each domain separately.

The domain-interplay concept is also able to meet the challenge raised by the claim that the neurobiological basis of affective processes is so distinct between species that it is too difficult to establish homologous relationships. While this concern could be great when utilizing single behaviors, similarity of entire affective systems domains across species is less likely to be the result of spurious neurobiological coincidences. Moreover, both cross-species similarities in domains (Kas et al., 2007) and patterns of their interplay (Kalueff, Ren-Patterson, et al., 2008) could help reveal homologies that are central characteristics of affective states and psychological disorders. These findings could be helpful in the development and validation of new simulations, such as genetic models, biobehavioral assays, and screening psychotropic drugs.

5. Conclusions

It should be noted that we do not seek to use this paper to endorse support or rejection of the natural kind theory of emotion. Rather, we want to introduce a method in which construct validity can be established for simulations in light of this debate. Many of these issues are critically important topics that biopsychologists need to consider, regardless of what they believe about the epistemological issues surrounding the nature of emotion.

The domain-interplay concept developed here emerges as a useful framework that researchers can employ to take into account species differences in behavioral phenotypes and endophenotypes. While it is interesting that this concept can provide a response to issues raised by critics of the natural kind theory of emotion, it also has other strengths that make a compelling case for its use. For example, the domain-interplay concept can increase the relevance of animal models by directly appealing to cross-species comparisons of multiple interlinked domains, and thus, increasing an animal model's translational value (Kalueff et al., 2007; Kalueff, Ren-Patterson, et al., 2008). Second, by focusing on multiple domains instead of an individual behavior (which is typical in animal research today), this strategy reduces the possibility of misinterpreting an animal's behavior by missing the "big picture", including environmental or genetic influences and interactions. Finally, the domain-interplay concept appears to

offer a unique approach in investigating the commonalities and differences, risk factors, comorbidity and pathogenesis of various psychological disorders.

Addressing many challenges in experimental and theoretical biopsychology, the domain-interplay concept will likely be employed by those interested in furthering the understanding of neuropsychiatric disorders (see Fig. 1). However, as outlined above, this concept may also interest both human and animal researchers studying fundamental psychological problems, such as the long-held debate on whether emotions are natural kinds.

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