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Toward the Study of Trans-Disease Processes: A Novel Approach With Special Reference to the Study of Co-morbidity

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Abstract

The objective of this article was to propose a novel approach, referred to as the study of trans-disease processes (TDPs), to the neuroscientific study of disease processes in general and to co-morbid diseases in particular. The features of this approach are outlined; one potential TDP—delay discounting, which may help account for the co-morbidity of cigarette smoking and schizophrenia—is explored; and the concept of TDPs is contrasted with the concept of endophenotypes. TDPs have the potential for a variety of positive impacts on science.

Keywords

Trans-disease processes; *co-morbidity*; *scale-free systems*; *delay discounting*; *cigarette smoking*; *schizophrenia*

Psychiatric co-morbidity, such as nicotine dependence among those with mental illness (Williams & Ziedonis, 2004), presents an interesting and complex set of challenges to the scientific understanding of disease processes. Some of the challenges result from the complexity of the disorders themselves, while others result from the paradigms associated with scientific disciplines or the organizational and administrative structure of institutions charged with addressing diseases.

Psychiatric disorders present challenges for study because they are both complex and indeterminate. For example, neither the disorders themselves nor the symptoms that are observable manifestations of those disorders are precisely defined (Williams & Ziedonis, 2004). Moreover, the symptoms of these disorders are often heterogeneous and diffuse; symptoms may overlap across disorders, suggesting either a problem with definition, a problem with with specificity of the symptoms, or that perhaps there is a commonality underlying the symptoms. Problematically, institutions that fund research and treatment of this heterogeneous and diffuse symptomology tend to create functional boundaries between different diseases based largely upon historical artifacts of the institutions' evolution.

An additional factor adding to the challenges is the predominate paradigm undergirding the practice of science. Science as a discipline largely follows the reductionistic approach: studying smaller and smaller phenomena as a means of understanding more complex phenomena (Strange, 2005; Soto & Sonnenschein, 2005; Skurvydas, 2005). Given the remarkable productivity of this approach, it is likely to remain the dominant paradigm for some time. One aspect of reductionism's productivity, a rapid increase in the number of research reports

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published, may be having unintended consequences, however. So as to remain current in and relevant to their field of inquiry, scientists are compelled to learn more and more about progressively finer points regarding their subject matter—to specialize. They can only hope that the "cause" of the disease they wish to abate will become evident at some progressively finer level of analysis (Evans, 2008).

We would caution that the realization of this hope may not be inevitable if the compulsion to specialize deprives scientists of the ability or willingness to communicate across specialties. If we were to take any complex thing, such as a computer, and break it down into its constituent parts, the resultant parts list would do little to indicate how it worked.[1] For that, we require a framework for communication about the processes constituted of the parts. In the sciences addressed to diseases, greater specialization may result in both intellectual silos and failures to recognize important commonalities and relationships across disease processes.

An antidote to these intellectual silos and a contrast to scientific reductionism are provided by the novel approach that we refer to as the analysis of trans-disease processes (TDPs). The goal of this approach is best summarized by the physicist and philosopher of science Ernst Mach, who stated in his classic text, *The Science of Mechanics*, "Thence is imposed the task of everywhere seeking out in the natural phenomena those elements that are the same and that amid all multiplicity are ever present" (Mach & McCormack, 1893, p. 6). Indeed, the goal of analysis of TDPs at multiple analytical levels is to understand the processes that operate in more than one disease and use that information to better understand, in principle, all the diseases in which they operate. For example, addiction, attention deficit disorder, depression, and schizophrenia have all been shown to exhibit executive dysfunction (Bickel & Yi, in press; Bickel et al., 2007; Doyle, 2006; Peuskens, Demily, & Thibaut, 2005; DeBattista, 2005). Understanding the commonalities in executive dysfunction and in its treatment may enhance progress for each of those disorders.

A central theoretical underpinning of TDPs is the recent application of scale-free systems theory to psychopathology (Chambers, Bickel, & Potenza, 2007). Chambers et al. (2007) point out that scale-free system theory, which is well established in the biological and physical sciences, is consistent with the biology of the nervous system, provides a scientific account for the intractability characteristics of addiction and other psychiatric conditions, and suggests novel strategies for intervention. In scale-free systems analysis, the constituents of a disease process are referred to as nodes (or perhaps modules) with connections to one another. Typically, most systematic models for disease analysis have assumed that component disease processes in the system attach randomly or exponentially. This results in a presumed normal distribution of disease-causing factors. In contrast, a scale-free network has a small number of nodes that are preferentially attached to many other nodes, while most nodes are associated via a small number of connections to other nodes. The architectural differences of these systems have functional consequences. First, scale-free systems are more efficient in the transmission of information than are random networks. This suggests the biological plausibility of the former. Second, scale-free systems show less of a decrement in functioning as nodes are randomly eliminated, while random systems show a progressive loss of function as nodes are lost. However, in scale-free systems, deletion of one of the preferentially connected nodes can cause catastrophic failure. As Chambers et al. (2007, p. 1017) note, "According to a scale-free organizational plan, such information management would entail decision making and habit formation capacities as features of motivational processing increasingly implicated in addictive" behavior and also, we would argue, in other psychiatric disease as well.

[1]We thank Robert Chambers for providing this analogy.

This novel approach has important implications for understanding co-morbidity. It would likely suggest that some co-morbidities may have a high frequency of occurrence because the diseases that are co-morbid have some of their nodes (e.g., decision making processes) in common. Indeed, this approach would also likely suggest that for any pair of co-morbid disorders, In at least one of them the common neurobehavioral process or processes are preferentially attached. To encapsulate, application of this approach to co-morbidity would suggest a 5-step process. First, there would be identification of a neurobehavioral process or a quantitative variation in behavior that is well defined, precisely measured, and evident in individuals exhibiting a disorder and not evident in unaffected individuals. Second, that same neurobehavioral process should be demonstrated in other disorders that are typically co-morbid with the first disorder. The third step would be to determine whether the process is evident in individuals with dual diagnosis. The fourth step would be investigation of the factors that account for that neurobehavioral process. The fifth step would be a determination of the causal contribution of that neurobehavioral process to the symptomology of each of the two diseases. An sample determination in the fifth step could be this: can the neurobehavioral process be discerned to function as an enabling cause—necessary but not sufficient for manifestation of the disease—or a threshold cause—a factor that moves the other disease factors to interact, resulting in the manifestation of one, the other, or both diseases?

To show how the TOP approach may operate in a concrete example, we will briefly examine the issue of co-morbidity between smoking and schizophrenia from a TDP perspective. The co-morbidity of these two diseases has been shown to be prevalent (Williams & Ziedonis, 2004). Moreover, we will use delay discounting as our candidate neurobehavioral TDP. Delay discounting has been proposed recently as a component of executive function (Bickel & Yi, in press). Delay discounting refers to the reduction in value of a commodity as a function of temporal delay to its delivery (Rachlin, Ralneri, & Cross, 1991). This process is intuitive in that most individuals would prefer $1,000 today to $1,000 delivered in 1 year (Kirby, Petry, & Bickel, 1999). This preference reveals that we attribute less value to—in other words, discount—the latter, delayed reward. To quantifiably assess the discounting process, experimenters or practitioners present to their participants series of trials, each of which poses a choice between an immediate and delayed outcome. From trial to trial the Immediate outcome decreases, while that of the delayed outcome remains the same, (e.g., receive $990 now versus $1,000 In 1 year, receive $980 now versus $1,000 in 1 year). The value of the immediate outcome in the trial in which the participant first switches away from the immediate outcome is an Indicator of the present subjective value of the delayed amount. If, for example, preference switches from the immediate option when it is worth $800 and the other amount is $1,000 after 1 year, then we can infer that $1,000 dollars is discounted by 20% over a year. If this cholce-trial-presentation process is repeated using the same delayed commodity value but various delays (e.g., 1 day, 1 week, 1 month, 3 months, 6 months, 1 year), then the discount function for that commodity over time can be plotted. The shape of the function is typically hyperbolic and can be quantified with the following equation, originally developed by Mazur (1987):

$$\text{Value}=\text{Mag}/(1+\text{kD})$$

Mag refers to magnitude of a commodity, D is the delay until receipt of the commodity, and k (the free parameter) is the discount rate, that is, the quantitative measure of the participant's discounting of future events involving that commodity.

Research on discounting has repeatedly shown that cigarette smokers discount delayed commodities to a greater extent than matched control nonsmokers (Bickel, Odum, & Madden, 1999; Reynolds, Richards, Horn, & Karraker, 2004; Mitchell, 1999; Bickel & Marsch, 2001; Baker, Johnson, & Bickel, 2003); ex-smokers discount at the same rate as controls (Bickel et

al., 1999). Discount rate increases as cigarette and/or nicotine consumption increases (Bickel et al., 1999; Ohmura, Takahashi, & Kitamura, 2005). Interestingly, it has been shown that the discounting assessment (the procedurally determined k value) can serve as a predictor of treatment outcomes (Yoon et al., 2007; Krishnan-Sarin et al., 2007) and that promoting abstinence among smokers can also decrease their discounting rates (Yi et al, 2008). Excessive discounting of delayed outcomes has also been documented in at least one study of persons with a diagnosis of schizophrenia (Heerey, Robinson, McMahon, & Gold, 2007). In sum, the existing literature indicates that smoking and schizophrenia share the process of excessive discounting.

To use the TDP approach to explore this co-morbidity would require that a number of research questions be addressed. Below, we provide a brief categorized list of questions that would need to be addressed. It is not presumed to be exhaustive.

Environment

Are certain environments (e.g., economically disadvantaged communities) associated with greater prevalence of dual diagnosis?

Do Individuals without either disorder exhibit greater discounting in those same environments?

Interaction

Is the excessive discounting phenomenon more pronounced as a co-morbid factor than as a factor in each disease by itself?

Origins

Is excessive discounting evident prior to expression of either disease?

Is excessive discounting exacerbated by the onset of either disease, or does it begin with the onset of either disease?

What are the genetic bases of excessive discounting, and are those gene signatures evident in both diseases when they occur alone and together, or do they occur in only one of the diseases?

Prevalence

Does everyone with co-morbidity exhibit excessive discounting?

Resolution

Does a reduction in excessive discounting result in a diminution of either or both diseases?

This discussion could raise concerns that TDP is just another term connoting the meaning of endophenotypes. The purpose of the endophenotypes concept is to identify a genetically based stable biobehavioral indicator of a disease (Gottesman & Gould, 2003). The TDP and endophenotypes notions are comparable in that the TDP concept, like endophenotypes, may refer to a genetically based stable component of disease. However, the TDP concept is distinguished from endophenotypes by virtue of the fact that TDP refers to neurobehavioral processes involved in *two or more* diseases, whereas endophenotype implies *one* disease, and TDP refers to *both genetic and nongenetic* components of disease, whereas endophenotye implies only a genetic component. Thus, an endophenotype restricted to one disease process would not be considered a TDP. While a TDP can include an endophentoype that is relevant

to more than one disease, it can also include nongenetic processes that operate in more than one disease.

The goal of this brief paper has been to begin to identify a new tactic for scientific research that crosses multiple disciplinary boundaries. If this approach were to be utilized, the potential benefits are severalfold. First, identifying neurobehavioral processes will likely require more extensive specification of symptoms than current diagnostic descriptors, Second, and as a result of the first benefit, determination of whether two disorders share specific processes needs to be ascertained unequivocally. Third, exploration of whether symptoms play a role in the genesis of the disorder would begin to provide an understanding of the causal processes that result in disease and co-morbidity. Most importantly for the field of psychopathology, TDPs would by definition result in rapid dissemination of knowledge, because once a new finding is characterized as a TDP then that phenomenon can be examined in the context of other diseases that share that process. Hopefully, the study of TDPs not only can lead to the understanding of important disease processes but may provide a new understanding of disease pathogenesis and maintenance and thus suggest novel approaches to treatment. We hope that this paper is a step in that direction.

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