Misuse of Cognitive Neuropsychology in Psychiatry Research: The Intoxicating Appeal of Neo-Reductionism

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NEUROPSYCHOLOGICAL DIAGNOSTIC instruments were developed expressly for the detection of and assessment of neurological disorders (e.g., Lezak, Howieson, Bigler, & Tranel, 2012). The historic role of these instruments in locating damage in the central nervous system has diminished with the advent of various imaging technologies. Thus, the prominent role of neuropsychological assessment has been circumscribed predominantly to determining the extent of cognitive, emotional, and behavioral dysfunctions subsequent to brain damage. Nowadays, cognitive neuropsychology, the study of cognitive functioning, is being clinically utilized to demonstrate disability in educational, medical, and forensic settings, and increasingly utilized in psychiatry research. For example, a recent systematic review of neuropsychological investigations into obsessive-compulsive disorder (OCD) noted a fourfold increase in the number of peer-reviewed publications between the years 1990–2000, compared with 2000–2010 (Abramovitch, Dar, Mittelman, & Schweiger, 2013)

The age of the brain invigorated the biomedical model of psychological problems, and virtually transformed psychiatry to a new science that would be more appropriately titled "biological psychiatry" (Guze, 1989). To a considerable extent, this transformation essentially medicalized psychology as well, both in terms of its explanatory models and the search for remediation of psychopathology. Cerebral pathology has begun to take center stage as the primary focus in research on etiology of psychopathology, which is being now conceptualized as the expression of aberrations in brain functions, or "brain disease" (Deacon, 2013). The utilization of the best standardized objective behavioral approach to measure brain pathology, namely, neuropsychological testing, was the logical next step in the arsenal of identifying such diseases.

Although neuropsychological tests are sensitive to behavioral dysfunction, they are inherently nonspecific. For example, a test sensitive to a decline in visual spatial skills cannot distinguish whether this decline is due to brain pathology, peripheral perceptual deficit, or motivational- and effort-related factors on the part of the examinee. As such, neuropsychological tests can speak to the relative difference from normative functioning, thus providing a very useful tool, but not one that speaks directly to the etiology of the deficit. Consequently, the potential for neuropsychological test results of one kind or another to serve as an endophenotypical factor or "cognitive marker" in psychopathology is extremely limited (Caspi et al., 2013). It's no wonder, therefore, that despite years of well-funded research, not a single biological or cognitive marker, or a cluster of markers, have been identified that would predict a specific psychopathology. It is not even clear that a search for such etiological factors could yield theoretically useful fruits.

The ongoing discontent with the DSM classification system, together with the increasing appeal of neuroscience, and the trend toward a more reductionist, biologically based (preferably brain-related) approach to psychiatric disorders, engendered the NIMH RDoC initiative (Lilienfeld, 2014). The RDoC vision emerges from the assumption that "psychiatric disorders" are brain disorders and, as such, could be one day fully explained and treated by unraveling their underlying brain abnormalities. Indeed, the RDoC envisions a time when a patient would come into a clinic, have his/her brain scanned (and may undergo a saliva test or take a few brief cognitive tests), the results of which would indicate whether or not this person presents with the biomarkers that fit into one or another category of pathology (e.g., negative affect). Once identified, the subsequent treatment for such a disorder would be the appropriate biologically based agents, or neurotherapy such as deep brain stimulation (DBS). The work of the RDoC "Unit Work Groups" produced a detailed matrix to be used as a guideline for researchers. This matrix includes specific domains for future research (e.g., positive Valence System, Cognitive Systems), specific constructs (e.g., Reward Learning, and Frustrative Non reward) to be examined using specific units of analysis (e.g., genes, neuronal circuits, molecules, or behavior).

Recent criticism regarding this vision has been leveled concerning different aspects of this approach, including the problems underlying the assumption that psychological conditions are brain disorders associated with a state of chemical imbalance (Lacasse & Leo, 2015), and the difficulties of a narrow, reductionist explanation of psychological entities (Satel & Lilienfeld, 2015) analogous to the attempt to explain "wetness" by referring exclusively to H_2O molecules. Criticism was also directed at the return to a modern version of phrenology (e.g., the relentless attempt to circumscribe psychological phenomena to highly specific brain regions or neuronal networks), sometimes referred to as neophrenology (Satel & Lilienfeld). However, in this article we focus on a specific domain within the RDoC initiative, namely, the domain of cognitive neuropsychology and neuropsychological tests in the context of psychiatry research. This domain, with its allure of objectivity, has been utilized in psychiatry research for a few decades. Recently it becomes increasingly evident that cognitive neuropsychology has been recruited to serve the premises of biological psychiatry, in a similar way to brain imaging.

Specificity

Research into cognitive function in the context of psychopathology aims primarily at identifying diagnostic markers, or to understand the involvement of cognitive functions in the etiology and presentation of psychiatric disorders. The reasoning behind this approach is that neuropsychological test performance reflects brain abnormalities. As such, this view fits nicely with the biomedical model of psychiatric disorders and its premise that psychiatric disorders reflect underlying brain pathologies. Consequently, neurocognitive assessment may be an objective and reliable tool to identify specific abnormalities and thus aid in the diagnosis of specific disorders and increase understanding of specific psychopathological processes. For example, attention-deficit/hyperactivity disorder (ADHD), a disorder characterized by

inattention, impulsivity, and hyperactivity, is associated with deficient response inhibition as measured by continuous performance tests (CPT), and Go-No/Go tests (GNG; Crosbie, Perusse, Barr, & Schachar, 2008). In particular, research indicates that individuals diagnosed with ADHD make more commission errors on these tests when compared with nonpsychiatric controls. This makes intuitive sense, given that these tests of response inhibition assess the ability to inhibit inappropriate responses, which has been traditionally linked to behavioral impulsivity (Logan, Schachar, & Tannock, 1997). Moreover, these results appear to make biomedical sense, and are in line with findings of reduced neuronal activity in the prefrontal cortex, a region associated with higher-order executive functions (Morein-Zamir et al., 2014). Indeed, the prevailing model of ADHD highlights response inhibition as the primary factor accounting for ADHD symptomatology (Barkley, 1997). In fact, this model has been widely accepted, to the extent that CPT and GNG tests are regularly employed around the world in the assessment of ADHD, particularly in educational settings.

This ideal picture, in which response inhibition has been considered a robust cognitive marker of ADHD, led some clinicians, and in particular for-profit clinics, to rely heavily upon the results of CPT and GNG tests to reaffirm, if not establish, a diagnosis of ADHD. However, examination of the data reported in research assessing response inhibition across psychiatric disorders reveals a very different picture. For example, in a comprehensive meta-analysis of GNG test performance across 11 DSM disorders, Wright and colleagues (Wright, Lipszyc, Dupuis, Thayapararajah, & Schachar, 2014) analyzed data from 318 studies and found moderate effect sizes reflecting underperformance on GNG tests in most disorders. The authors reported effect sizes for commission errors (the primary outcome measure for response inhibition) to range between g = 0.2 to 0.5 across ADHD, addiction, autism, bipolar disorder, depression, OCD, personality disorders, schizophrenia, and Tourette's syndrome. These findings are not limited to GNG tests, as the same research group reported very similar results in a meta-analysis assessing performance on another common response inhibition test, the Stop Signal Task (SST; Lipszyc & Schachar, 2010). Accordingly, deficit in response inhibition (as measured by neuropsychological tests) has been suggested as a cognitive diagnostic marker and an endophenotype for different disorders such as OCD (Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005), bipolar disorder (Bora, Yucel, & Pantelis, 2009), borderline personality disorder (McCloskey et al., 2009), schizophrenia (Turetsky et al., 2007), and ADHD (Slaats-Willemse, Swaab-Barneveld, de Sonneville, van der Meulen, & Buitelaar, 2003).

Importantly, some of the foregoing disorders are associated with quite different clinical presentation and neurobiological models. As an illustration, consider the case of OCD, a disorder associated with inhibited temperament, hyper-control, and harm/risk avoidance, as well as with resting state *hyperactive* frontostriatal network (Pauls, Abramovitch, Rauch, & Geller, 2014). In contrast, ADHD is a disorder associated with prominent impulsive behavior, risk taking, hypo-control, and resting state frontostriatal *hypoactivation* (Castellanos & Tannock, 2002). Remarkably, response inhibition has been suggested as a diagnostic cognitive marker and endophenotype for both disorders. In other words, research suggests that underperformance on tests of response inhibition can predict the presence of OCD, but could also predict the presence of ADHD, as well as several other disorders. Taken together, research shows that underperformance on response inhibition tests may predict to some extent the presence of virtually any psychiatric disorder (and a number of neurological and other medical conditions), and thus has no value as a unique marker for any one of them (Caspi et al., 2013; Snyder, Miyake, & Hankin, 2015).

More broadly, it appears that the vast majority of DSM disorders are associated with underperformance on a plethora of cognitive tests, identifiable in most of the primary neuropsychological domains (i.e., executive functions, memory, attention, processing speed, and working memory). These findings have been consistently reported in meta-analytic reviews of neuropsychological test performance among samples of individuals diagnosed with depression (Snyder, 2013), schizophrenia (Fusar-Poli et al., 2012), bipolar depression (Bourne et al., 2013), OCD (Abramovitch, Abramowitz, & Mittelman, 2013; Abramovitch, Abramowitz, et al., 2015), antisocial personality disorder (Morgan & Lilienfeld, 2000), borderline personality disorder (Ruocco, 2005), eating disorders (Van den Eynde et al., 2011), PTSD (Scott et al., 2015), and ADHD (Schoechlin & Engel, 2005). This lack of specificity may indicate that underperformance on neuropsychological tests, assessing virtually any neuropsychological domain, could be associated with any psychopathology. Indeed, in their seminal work, Caspi and colleagues (2013) examined what they termed "the p factor"—a single factor signifying psychopathology—which, as a single-factor model, was found to fare better, compared with a three-factor model (i.e., internalizing, externalizing and thought disorder). In their examination of data from more than 1,000 individuals, they provide evidence that cognitive functions showed weak or no correlations with all three factors. The authors concluded that the p factor is associated with small to moderate degree of cognitive problems in the major neuropsychological domains, such as attention, mental control, working memory, visuospatial functions and visuomotor coordination. The authors concluded, "*researchers should not expect to routinely find single-disorder loyalty in biomarkers (e.g., neuroimaging findings, cognitive task performance, and hypothalamic-pituitary-adrenal axis hormones), consequences (e.g., suicide attempts and impaired relationships), treatments (e.g., psychotherapy and pharmacotherapy), or causes (e.g., maltreatment and genes)*" (Caspi et al., 2013, p. 134).

Impairment

The findings described heretofore challenge the utility of objective neuropsychological tests as disorder-specific markers. Moreover, they lead to a series of equally important questions concerning the definition of the magnitude of underperformance on these tests, namely, what is a cognitive/neuropsychological impairment? What is the operationalization and statistical definition of a neuropsychological deficit or impairment? Do these definitions require the presence of functional impairments outside the realm of neuropsychological tests? Finally, what are the clinical correlates of such impairments?

It is a common practice for neuropsychological studies of psychiatric disorders to conceptualize statistically significant lower test scores as a deficit or impairment. This common practice usually disregards the magnitude of the difference (i.e., effect size), or the clinical sample's standardized score compared with tests' norms. Reviewing the classic neuropsychological literature, a neuropsychological impairment is usually defined as a difference of 2 or 3

standard deviations from the population norm (equivalent to Cohen's *d* effect size of 2.0-3.0; Lezak et al., 2012; Zakzanis, Leach, & Kaplan, 1998). For example, research findings indicate that the cutoff for detecting cognitive decline predicting the conversion from mild cognitive impairment to Alzheimer's disease is at least 1.5 standard deviation difference (García-Herranz, Díaz-Mardomingo, & Peraita, 2015). In fact, one of the more liberal definitions of cognitive impairment on the Wechsler memory and intelligence scales has been suggested to be 1.0 *SD* (Taylor & Heaton, 2001). As noted above, review of neuropsychological meta-analyses across major DSM disorders reveals that most disorders are associated with widespread underperformance on neuropsychological tests that is usually less than 0.5 *SD* below the normative average/control group, and rarely reaches an effect size equivalent to 1.0 *SD*.

Perhaps a more important question would be: What are the clinical, behavioral, and phenomenological correlates of "neuropsychological impairments"? With a vast literature repeatedly concluding that disorders are associated with impairments in verbal memory functions, for example, or deficits in executive function, such as response inhibition—what would be the clinical expression of such a deficit in real life? Finally, assuming an association between functional impairments and neuropsychological impairment exists, is it disorder-specific?

Indeed, the association between neuropsychological test performance and functional indices across some disorders has been subject to empirical investigations. Naturally, the majority of these studies focus on disorders where cognitive deficits are a prominent part of the clinical presentation of these disorders (e.g., schizophrenia, ADHD, Alzheimer's disease, depression), neglecting other conditions such as OCD and anxiety disorders. Despite the prominence of neuropsychological symptoms, these studies are characterized by inconsistent results and most often by a low range of explained variance. Moreover, some studies find that the association between neuropsychological test performance and functional indices may be more clearly observed among control samples or large representative cohorts from the general populations (Miller & Hinshaw, 2010; Sayal, Washbrook, & Propper, 2015).

Importantly, some studies have found that participants' self-report concerning cognitive problems hold a much stronger predictive power for functional indices than actual cognitive tests; the latter, although considered objective, were insignificant as predictors (Barkley & Fischer, 2011; Barkley & Murphy, 2010). Research suggests that cognitive functions in disorders such as schizophrenia predict social functioning, activities of daily living, and general real-life problem solving (Revheim et al., 2006). It has been further suggested that such findings may help in identifying individuals with more severe cognitive impairments in order to tailor more intensive rehabilitation programs for these disorders (for a review see Green, Kern, Braff, & Mintz, 2000). This type of (prevalent) logical inference may be appealing, perhaps even intuitive. However, this type of inference assumes a causal relationship that has yet to be proven: namely, that neuropsychological dysfunction causes such functional impairments. Such an assumption ignores the alternative converse inference, that the symptoms of schizophrenia (or any other disorder, for that matter) may produce neuropsychological problems. Thus, it remains to be ascertained whether inattention predicts social functioning, or that individuals diagnosed with schizophrenia tend to be very associative in conversations, for example, or may use blunt language, both of the latter resulting in impaired social functioning.

Causality

First-year students in psychology learn that correlation does not imply causation. Presently, the question can be stated as follows: Is an underlying brain dysfunction, expressed as underperformance on a neuropsychological test, the cause of a particular psychopathology, or its correlate? It seems quite clear that if a neuropsychological symptom appears in a variety of disorders, it cannot be a specific sign of any one of them. That is, it may be a necessary but not sufficient sign of the disorder. For example, response inhibition cannot uniquely signify the presence of OCD, since it is just as likely to be present in ADHD, the latter presenting behaviorally with quite the opposite symptoms as the former. From our review of the relevant literature, it is quite obvious that most, if not all, neuropsychological signs appear in various combinations in different psychiatric disorders. As such, they may constitute signs of psychopathology in general (and possibly also of neurologic disease, brain injury, endocrine dysfunction, and a host of medical problems), but they lack the necessary specificity to serve as the direct cause of any. That is not to say, of course, that neuropsychological signs may, theoretically at least, reflect a network of symptoms indicative of some underlying brain pathology. However, serving as a cognitive marker requires that a sign should possess the specificity which neuropsychological indicators are lacking.

One consequence of the foregoing systematic and pervasive inferential error is that the recently expressed hope of treating neuropsychological deficits as a means of treating specific psychiatric disorders (e.g., Vandborg, Hartmann, Bennedsen, Pedersen, & Thomsen, 2015) is bound to crash onto the rock of reality. In other words, given that experiencing symptoms of posttraumatic stress disorder, ADHD, depression, schizophrenia, OCD, and so forth, result in underperformance on neuropsychological tests, does not necessarily imply that practicing cognitive skills would alleviate these different symptoms. In fact, research indicates that cognitive training hardly improves the corresponding cognitive functions, let alone generalizes improvement outside the specific targeted cognitive function (Melby-Lervag & Hulme, 2013). Similarly, the search for the underlying sign of psychiatric pathology using brain imaging may be ill conceived. Whereas the clinical and diagnostic utility of imaging research in the context of psychopathology has been extensively criticized (Satel & Lilienfeld, 2015), the use (or, in some cases, even abuse) of cognitive neuropsychology of psychiatric disorders received very little critical scrutiny. One possible reason could be the traditional role of neuropsychological assessment in providing objective information regarding deficient cognitive functions that was used to inform physicians as to the localization of damaged brain regions. A second reason is the appeal of objective tangible data such as response speed, number of errors, number of words remembered correctly, number of categories achieved, etc.

The State of the Field

Hundreds of papers and dozens of meta-analytic reviews indicate repeatedly that various psychiatric disorders are associated with underperformance on neuropsychological tests (Abramovitch & Cooperman, 2015; Abramovitch, Mittelman, Tankersley, Abramowitz, & Schweiger, 2015; Ahmari, Eich, Cebenoyan, Smith, & Blair Simpson, 2014; Caspi et al., 2013; Shin et al., 2010; Snyder

et al., 2015). This is irrespective of the known differences among these conditions in terms of their psychological mechanisms, neurobiological/neurochemical models, and pharmacological and psychological interventions. Only recently did some investigators note that this variability and lack of specificity poses a major problem in the context of the search for cognitive diagnostic markers. In fact, it has recently been articulated that cross-sectional studies comparing clinical and control samples on traditional neuropsychological batteries are no longer required as these do not provide new insight (Abramovitch & Cooperman; Snyder et al.).

The aforementioned difficulties did not hinder the recent development of a freely available neuropsychological battery by the NIMH (i.e., the NIH Toolbox) that comprises the same traditional neuropsychological tests. Moreover, in contrast to the known lack of specificity, it appears that the RDoC initiative in effect brought about prioritization of funding for studies that are set to identify cognitive markers using traditional neuropsychological tests. Proponents of the RDoC vision may justify this prioritization, arguing that the lack of specificity in the context of cognitive diagnostic markers is only associated with research of DSM-defined diagnostic entities. However, review of the literature reveals that underperformance on neuropsychological tests is characteristic of psychopathological mechanisms (outside traditional DSM disorders), which are associated with RDoC domains as well. These include negative valence, behavior disinhibition, acute and potential threat, and habit formation. In a perfect world, the findings discussed in this and other papers ought to inform us that it is not the classification of psychopathology that results in a lack of specific diagnostic cognitive markers. It is the lack of specificity of neuropsychological assessment. Nevertheless, the state of the field is such that labor, resources, and funding continue to be invested in cognitive markers research. This may, in turn, obfuscate reconsideration of the role of classic neuropsychology in psychiatry research and thus hinder progress and innovation in the field.

The dubious belief, reinforced with increasingly more sophisticated technologies used in neuroscience, that the root cause of psychopathology will be found in the assessment arsenal of the neuropsychologist (or the microbiologist or the neuro-radiologist), is unlikely to deliver the desired answers. Psychopathology and brain diseases are of different logical categories that may complement and overlap with each other, but cannot form a reductionist explanatory basis of each other, in the same way, for example, that molecular motion can explain heat. By implication, neuropsychological assessment lacks the necessary specificity to identify and individuate psychopathology. It is better left to its important role of providing increasingly more sensitive and specific information on the cognitive status of various conditions, be they of developmental, medical, or psychiatric etiology.

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