

Updating the research domain criteria: the utility of a motor dimension

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Within the NIMH Research Domain Criteria (RDoC) framework, dimensions of behavior are investigated across diagnoses with the goal of developing a better understanding of their underlying neural substrates. Currently, this framework includes five domains: cognitive, social, arousal/regulatory, negative, and positive valence systems. We argue that the inclusion of a motor systems domain is sorely needed as well. Independent of medication, distinct areas of motor dysfunction (e.g. motor planning/inhibition/learning/coordination, involuntary movements) commonly appear across a number of mental disorders (e.g. schizophrenia, bipolar disorder, autism, attention deficit hyperactivity disorder, Alzheimer's disease, depression) as well as neurological disorders accompanied by significant psychological symptoms (e.g. Parkinson's disease). In addition, motor systems are amenable to study across multiple levels of analysis from the cellular molecular level focusing on cytoarchitectonics and neurotransmitter systems, to networks and circuits measured using neuroimaging, and finally at the level of overt behavioral performance. Critically, the neural systems associated with motor performance have been relatively well defined, and different circuits have been linked to distinct aspects of motor behavior. As such, they may also be differentially associated with symptoms and motor dysfunction across diagnoses, and be uniquely informative about underlying etiology. Importantly, motor signs can change across stages of illness; they are also often present in the prodromal phases of disease and closely linked with course, suggesting that these behaviors represent a core feature reflective of pathogenic processes. The inclusion of a motor domain would allow researchers to better understand psychopathology more broadly, and may also reveal important contributions to disease processes across diagnoses.

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Introduction

The Research Domain Criteria (RDoC) initiative was introduced by the National Institute of Mental Health (NIMH) to provide a cutting edge framework for the study of brain disorders. The principal goal of the RDoC initiative is to combine the study of behavior with neuroscience research, to better understand psychopathology and develop targeted treatment options (Sanislow *et al.* 2010; Cuthbert & Insel, 2013). Within this framework, constructs are investigated dimensionally across diagnoses with the goal of developing a better understanding how respective neural substrates are involved. Ultimately, such an approach stands to increase our understanding of disease processes, particularly given the emphasis on the biological substrates from multiple levels of analysis (e.g. cellular, genetic, brain, behavior). This relatively new initiative has

already proved fruitful in providing new integrated frameworks (e.g. Langenecker *et al.* 2014; Dillon *et al.* 2014), and as current research conducted as part of the RDoC initiative matures, mental health research stands to make great strides.

As it stands currently, there are five domains included in the RDoC initiative: negative valence systems, positive valence systems, cognitive systems, systems for social processes, and arousal/regulatory systems. Noticeably missing, however, are motor systems. Consistent with the other five domains in RDoC, motor behavior also varies greatly among individuals, and there is a plethora of evidence to indicate that there are motor deficits across psychiatric diagnoses including schizophrenia, bipolar disorder, major depression, and Alzheimer's disease, as well as in developmental psychopathology such as autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD), and tic disorder. Motor systems and circuits are amenable to study across levels of analysis, from investigations of cytoarchitectonics, to network investigations using neuroimaging, and with instrumental behavioral measures and self-report

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assessments of performance. Further, given that a number of motor behaviors occur in clinical populations that we have a much more developed etiological conception for (e.g. Huntington's, Parkinson's, stroke), understanding these behaviors in psychiatric populations could potentially allow for us to tap into this sizeable work more directly, and make significant strides in conceptualizing and treating mental illness. Given that motor dysfunction is present in many psychiatric diagnoses across the lifespan (Quinn *et al.* 2001), inclusion of such a category stands to provide key insights into the underlying biology associated with psychopathology. Although the nature of the motor deficits varies to some degree across disorders, there are also cases of overlap across diagnoses with respect to a particular motor behavior. Critically, in many cases motor systems dysfunction is present in the absence of medication (Caligiuri & Lohr, 1994; Fenton *et al.* 1994), indicating that these deficits are not merely a side effect of pharmacological treatments. Furthermore, evidence also indicates that motor systems dysfunction is present prior to disease onset (e.g. Mittal *et al.* 2010). Together this suggests that it may be a trait feature of psychopathology, although it is likely that there are state effects with respect to the severity of this dysfunction associated with disease course, symptom severity, and medications.

Motor dysfunction across disorders

Although beyond the scope of this Editorial, it is known that multiple neural systems underlie and contribute to motor behaviors, including cerebello-thalamo-cortical and striatal-cortical networks, pre-frontal and pre-motor response selection contributions, and common across these respective systems, the final common pathway wherein a motor signal is sent from the primary motor cortex to initiate a movement. To illustrate the range of motor dysfunction seen across diagnoses, we provide a brief overview with respect to several categories of psychiatric disorder. Motor dysfunction as discussed here includes neuromotor and psychomotor deficits. The former refers to hyper- and dyskinetic movements, dysfunctional sensorimotor integration, neurological soft signs, and deficits in gait and posture. The latter refers to hypokinesia, psychomotor slowing, and catatonia. In addition, deficits in motor learning are included in this proposed cluster, and both neuromotor and psychomotor dysfunction can contribute to these deficits. Although motor learning paradigms may be confounded with cognitive function given higher order cognitive influences (e.g. Anguera *et al.* 2010), learning deficits above and beyond those due to cognitive decline

may also be present given that cognitive factors only account for a portion of the variance in motor learning (Anguera *et al.* 2010). Motor learning paradigms allow investigators to tap into important motor cortical circuits, which may be impacted across diagnoses. Within a given disorder, motor dysfunction of both types may be present, and understanding the associated neural circuitry could allow us to better understand psychopathology, further supporting the case for a motor category within the RDoC framework.

Developmental disorders

A wide range of motor deficits have been reported in ASD including catatonia (e.g. Ghaziuddin *et al.* 2005), although these seem to primarily relate to sensorimotor integration as it relates to motor planning (reviewed in Gowen & Hamilton 2013). Recent work also suggests that there are deficits in both the feed-forward and feedback control mechanisms (neuromotor deficits) associated with cerebellar motor control in ASD (Mosconi *et al.* 2015). In all cases, however, these motor deficits may be driving some of the symptoms seen in these individuals, particularly those with respect to social and language functions. In ADHD the deficits differ, but include neuromotor deficits such as postural control and gait, similar (although lesser in magnitude) to those seen in children with cerebellar lesions (Buderath *et al.* 2009). In addition fine motor control and coordination deficits have also been demonstrated in boys with ADHD (Piek *et al.* 1999). Finally, motor learning deficits have been reported in both populations (Mostofsky *et al.* 2000; Barnes *et al.* 2010; Izawa *et al.* 2012). Thus, across developmental disorders, motor deficits are present. In particular, in ASD, these seem to be a hallmark of the disease itself, as opposed to a side-effect of medications, although this is likely also the case in ADHD. Across these disorders, the motor dysfunction may be indicative of deficits in the underlying circuitry (e.g. fronto-striatal; cerebello-thalamo-cortical) that are seen in other psychiatric disorders.

Psychosis and psychosis risk

A variety of neuromotor and psychomotor signs and symptoms have been reported in patients with schizophrenia, as well as in individuals at risk for developing psychosis (Bernard & Mittal, 2014). Motor dysfunction in psychosis populations varies greatly and includes relatively diffuse neurological soft signs (Mittal *et al.* 2014), dyspraxia (Schiffman *et al.* in press), postural control deficits (Marvel *et al.* 2004; Bernard *et al.* 2014), both hypo- and hyperkinesias (Pappa & Dazzan, 2009; Mittal *et al.* 2010), catatonia and

psychomotor slowing (Walther & Strik, 2012), and motor learning deficits (Marvel *et al.* 2007). What is particularly interesting is that in psychosis risk populations where confounds such as drug abuse and medications are less prevalent, movement abnormalities have been useful in predicting symptom course and disease progression (Mittal *et al.* 2010; Dean *et al.* 2015) indicating that these are trait deficits, and they may serve as an easily quantifiable biomarker of disease course. However, striatally based dyskinesias and cerebellar-mediated postural control also seem to be distinctly associated with positive and negative symptom course, respectively (Mittal *et al.* 2010; Dean *et al.* 2015). Thus, not only is motor dysfunction present in psychosis, but it also seems to be linked to the core symptomatology, and this may be insightful for other diagnostic groups that share symptoms and motor deficits.

Mood disorders

Psychomotor symptoms, particularly slowing, are striking in mood disorders (e.g. Cornell *et al.* 1984). In patients with major depression, movements are slowed, and this impacts speech, eye movements, facial affect, posture, and the movement of the limbs more generally (Buyukdura *et al.* 2011), and catatonia has been reported in up to 20% of patients (Starkstein *et al.* 1996). Both psychomotor and neuromotor deficits may be contributing to motor learning differences seen in patients with depression (Naismith *et al.* 2010). Although bipolar disorder shares some features with depression in that blunted affect and similar mood symptoms are present during periods of depression, these cycle with periods of mania. The motor deficits seen in this particular population also differ to some degree. In bipolar disorder, neuromotor dysfunction including postural sway deficits have been reported (Bolbecker *et al.* 2011), and neurological soft signs are also present (Goswami *et al.* 2006). Thus, at the surface at least in terms of motor dysfunction, bipolar disorder seems to have more in common with psychosis than it does with major depression. However, this remains an empirical question. Investigating these motor deficits across disorders, however, will allow for the direct investigation of this suggestion, and may also shed light on to key underlying neural dysfunction seen across disorders with similar motor deficits.

Aging and Alzheimer's disease

Even in healthy aging, individuals experience a decline in normal motor function (reviewed in Seidler *et al.* 2010). This includes general slowing of movements, declines in postural control, changes in force

production and stability, and motor learning deficits (Seidler *et al.* 2010). However, in age-related pathologies such as Alzheimer's disease and mild cognitive impairment, motor systems dysfunction has also been reported. This includes neuromotor deficits in balance and gait, but also extends to dual-task motor paradigms (Pettersson *et al.* 2005). Furthermore, in both Parkinson's disease (with and without dementia) and Lewy body dementia, the biological underpinnings are well-known, and may aid in linking neural circuits and biology to motor signs and symptoms seen across psychopathology. Not only would the inclusion of a motor dimension allow for the investigation of similarities in symptoms and etiology across disorders, but this also dovetails with the recent suggestion from Casey and colleagues for the inclusion of a neurodevelopmental component to the RDoC framework (Casey *et al.* 2014).

Benefits of a motor dimension

Because different neural systems (e.g. cerebellar, basal ganglia, frontal action selection, corticospinal tract) subserve different aspects of motor control, they also may be differentially associated with symptoms and dysfunctional aspects of motor control across diagnoses. For example, dopaminergic dysfunction impacting the basal ganglia results in a variety of movement abnormalities. One can truly grasp the range of impact that this system has on movement when one considers that patients with Parkinson's disease often experience difficulty in initiating internally generated movements, but with medications can also experience dyskinesias (Obeso *et al.* 2000). A similar range of dysfunction, from psychomotor slowing to dyskinetic movements can be seen when we investigate mood disorders as well as psychosis, and ADHD, pointing to a potential dopaminergic basal ganglia contribution. Indeed, the basal ganglia have been implicated in psychomotor slowing in depression (Buyukdura *et al.* 2011), as well as in dyskinesias seen in psychosis risk populations (Mittal *et al.* 2010). Paralleling this motor basal ganglia dysfunction, cerebellar motor circuits are also implicated across disorders including ASD and psychosis, taking the form of motor learning deficits, timing dysfunction, and poor postural control. Finally, a recent investigation in major depression has found that there are white-matter abnormalities in the corticospinal tract of patients relative to controls (Sacchet *et al.* 2014), implicating the final common pathway in psychopathology as well. In all cases, overt motor dysfunction points to several well-studied neural subsystems, and also may be related to differing symptom profiles. Finally, by looking at associations between different motor signs and symptoms, and their relationships to one another, as well as to cognition, we may gain

further insight into the neural systems, and subsystems contributing uniquely, and in concert, across diagnoses and symptom profiles.

We suggest that the inclusion of a motor systems dimension to the RDoC initiative is useful for three primary reasons. First, motor dysfunction is primarily an overt behavior. Motor signs and symptoms are easily quantifiable using observer methods and movement coding (e.g. Mittal *et al.* 2010), but can also be tested using a variety of validated instrumental measures. Second, differing motor subsystems are relatively well-mapped, and are relatively distinct. Interestingly though, when we consider both the basal ganglia and cerebellum, there are also non-motor regions within these larger structures. Thus, motor behaviors may point to a more general dysfunction that impacts non-motor domains, including cognition, emotion, motivation, personality, and symptomatology. By investigating this more overt domain, it may provide important insight into other critical domains as well. Third, consistent with the goal of the RDoC initiative, motor systems can indeed be studied from all levels of analysis. Investigations of differing cytoarchitectonics in the cortex and cerebellum may prove insightful, as may investigations of dopaminergic systems that govern movement, but many other functions as well. As noted, behavior can be quantified, and a variety of well-established paradigms have also been designed for use in the functional neuroimaging environment, as well as with animal models and pharmacological challenge paradigms. Finally, self-report and reports from family members regarding motor skills, developmental milestones (e.g. walking, fine motor control) and general motor function can also be reliably collected.

Finally, as noted above with respect to psychosis-risk, cerebellar- and basal ganglia-mediated motor deficits seem to be distinctly associated with symptom progression across symptom types (Mittal *et al.* 2010; Dean *et al.* 2015), indicating that they are a trait feature of the disease, but are confounded by disease state. This example illustrates the potential utility of investigating different motor circuits and patterns of behavioral dysfunction across disorders, as these different motor systems may also extend across diagnostic boundaries, implicating specific neural circuits in the pathophysiology of multiple psychiatric diagnoses. A better understanding of the motor systems associated with deficits across disorders may allow for the development of new targets for treatment and remediation.

Conclusions

While the RDoC initiative stands to greatly improve and expand our understanding of psychopathology,

the inclusion of a motor systems domain would provide a more well-rounded picture of the behavioral deficits seen in normative populations and those with a variety of psychiatric diagnoses. Motor systems fit well with the pillars of study proposed as part of RDoC allowing for study across levels of analysis, and the easily quantifiable deficits associated with motor systems dysfunction may make for important biomarkers associated with disease. Together, the inclusion of motor systems as part of the RDoC framework stands to greatly improve our understanding of motor function across a range of abilities, as well as the role of motor systems in psychopathology across the lifespan.

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Declaration of Interest

None.

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