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The utility of an RDoC motor domain to understand psychomotor symptoms in depression

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Abstract

Despite the clinical impact of motor symptoms such as agitation or retardation on the course of depression, these symptoms are poorly understood. Novel developments in the field of instrumentation and mobile devices allow for dimensional and continuous recording of motor behavior in various settings, particularly outside the laboratory. Likewise, the use of novel assessments enables to combine multimodal neuroimaging with behavioral measures in order to investigate the neural correlates of motor dysfunction in depression. The research domain criteria (RDoC) framework will soon include a motor domain that will provide a framework for studying motor dysfunction in mood disorders. In addition, new studies within this framework will allow investigators to study motor symptoms across different stages of depression as well as other psychiatric diagnoses. Finally, the introduction of the RDoC motor domain will help test how motor symptoms integrate with the original five RDoC domains (negative valence, positive valence, cognitive, social processes, and arousal/regulation).

Psychomotor retardation and agitation (i.e. psychomotor disturbances) are core features of depression (one of nine primary phenomenology in Diagnostic and Statistical Manual 5) (APA, 2013) and reflect deficits in fine motor function as well as gross motor behavior (Sobin and Sackeim, 1997). Clinicians' ratings of retardation or agitation are as frequent as 60–70% in acute depressive episodes, as indicated by the STAR*D trial (Novick *et al.*, 2005). These disturbances are particularly frequent in episodes of severe depression (Parker, 2000) and have been linked to poor outcome in treatment trials of depression (Ulbricht *et al.*, 2016, 2018; Sakurai *et al.*, 2017). Furthermore, clinician-rated psychomotor disturbances are suggested to distinguish the melancholic subtype of unipolar depression (Sobin and Sackeim, 1997; Parker, 2000) and also distinguish major depressive disorder from bipolar disorder, with stronger effects for retardation than agitation (Leonpacher *et al.*, 2015). A longitudinal investigation of subjects with bipolar disorder reported that clinician-rated agitation was the best discriminator between mood episodes, performing better than retardation, and most importantly, much better than mood symptoms of common clinical rating scales for depression and mania (Cheniaux *et al.*, 2018). Other motor abnormalities such as neurological soft signs are associated with psychosis in multiple disorders, including depression (Owoeye *et al.*, 2013; Sagheer *et al.*, 2018). In sum, psychomotor disturbances are of clinical value in determining poor outcome or treatment response.

Despite this importance, research on motor issues in depression is quite scarce. Some have argued that shifting the focus of psychopathology from (observable) signs to (self-reported) symptoms has led to an under-appreciation of overt behavior, a trend particularly fateful for motor disturbances (Kendler, 2016). However, in the last decade some groups have investigated the role of motor abnormalities in psychiatric disorders using new instrumental measures of motor behavior, allowing for objective and dimensional assessment (van Harten *et al.*, 2017). Today, with mobile technology being widely available, it is possible to collect large scale health instrumental assessments of motor behaviors. This approach to motor phenomena conceptualizes motor disturbance dimensionally, enables the integration with other types of motor assessment (e.g. lab-based tests, experiments with brain stimulation, ecological momentary assessment, and smartphone applications) and consequently, holds significant relevance for the NIMH Research Domain Criteria (RDoC).

These novel measures allow further insight into the neural mechanisms guiding multiple motor disturbances (Walther, 2015; Walther and Mittal, 2017). Classical studies on motor disturbances in psychiatric disorders have usually applied observer-based rating scales covering one particular sign or a group of symptoms (e.g. tardive dyskinesia) in the context of one disorder, therefore, these measures fall short in describing the complete set of motor alterations

possible. As a result, motor domains of unknown pathobiology such as agitation and retardation have been commonly lumped together, even though they may be mediated by different mechanisms, as they tend to do in neurological disorders (DeLong and Wichmann, 2009). Further, as self-reports of psychomotor disturbance are subject to patient insight and bias, and observer-based rating scales are reliant on the most readily observable or impactful disturbances, it is also unclear if these behaviors change across the course of depression. This lack of rigorous measures for motor disturbances in depression is particularly surprising for a core feature of the disease, as motor markers have been highly predictive and intimately tied to disease and course in other disorders such a psychosis, autism, and dementia (Scarmeas *et al*., 2004; Jansiewicz *et al*., 2006; Mittal and Walker, 2007; Asgari and Shafran, 2010; Peralta and Cuesta, 2017).

Another limitation of prior work on motor disturbance in depression is the lack of a framework describing motor disturbances in depression, let alone a neurobiological model explaining these behaviors. The RDoC initiative proposes a framework consisting of five domains of constructs thought to be associated with psychopathology – negative valence, positive valence, cognitive systems, social processes, and arousal/regulatory systems – that can each be studied using multiple units of analysis (e.g. genes, molecules, cells, circuits, behavior, physiology, and self-report). For some of the constructs there is evidence of transdiagnostic principles guiding neural activation (McTeague *et al*., 2017) or physiological reactions (Lang *et al*., 2016) during tasks. However, an important domain that has been missing from the RDoC project is the motor domain, although NIMH is in the final stages of considering adding motor constructs to the RDoC framework (Bernard and Mittal, 2015; Garvey and Cuthbert, 2017; Mittal *et al*., 2017; Mittal and Wakschlag, 2017). Studying the role of motor functioning (along with the other RDoC domains) has tremendous promise for yielding a more holistic understanding of depression. First, within the framework, distinct motor disturbances can be assessed dimensionally and inform on prevalence and course of motor disturbances in depression. Second, mapping these motor disturbances on brain circuits will prepare the field to develop specific treatment, e.g. using brain stimulation techniques. Finally, given the heterogeneity of depression (and the broader internalizing disorders in general), examining the specific role of motor symptoms can parse this heterogeneity, potentially identify more homogeneous subtypes, and yield novel and focal treatment targets that can be assessed with reliable and easily administered observational methods.

However, there are also significant challenges the motor symptoms domain will need to overcome. While other RDoC domains such as cognition had a tradition of testing multiple constructs with a battery of tests in the same individuals, the motor field has previously relied on investigations of single signs (e.g. tardive dyskinesia). Therefore, an RDoC motor domain will have the particular challenge of combining several motor subprocesses and integrating various very specific motor signs with unique definitions and referencing frameworks. On the other hand, instrumentation for the valid dimensional assessment of motor behavior is becoming increasingly available (van Harten *et al*., 2017). An excellent example is the assessment of extrapyramidal signs in untreated psychosis, for which instrumental measures such as force variability or velocity scaling have much higher sensitivity and specificity than clinical rating scales (Cortese *et al*., 2005; van Harten *et al*., 2017). The same improved sensitivity was reported in comparisons of instrumental measures *v*. rating scales in depression; 40% of depressed patients had motor disturbances according to clinicians' ratings, but 60% according to instrumentation (Caligiuri and Ellwanger, 2000). Likewise, computerized fine motor tasks reported motor dysfunction in both medicated and unmedicated depressed subjects, as well as changes in fine motor slowing after antidepressant pharmacotherapy (Sabbe *et al*., 1996*a*; 1996*b*; Pier *et al*., 2004; Schrijvers *et al*., 2009).

Another strength lending to an RDoC motor domain rests in the well-defined brain circuitry underlying normative motor behavior. This can serve as an anchoring point for the circuit-centric nature of the RDoC framework. Furthermore, as the field starts to understand motor-brain mechanisms, this may help to shed light on psychiatric illnesses where these motor behaviors occur. Notably, certain instrumental assessments map on to well-defined motor circuitry, which can be related to behavior or psychopathology (Mittal *et al*., 2017): (1) the cortico-basal ganglia circuit from primary motor cortex (M1) via caudate, putamen, pallidum, and subthalamic nucleus to the thalamic motor nuclei and back to M1, which controls excitation and inhibition of movements (Aron and Poldrack, 2006; Obeso *et al*., 2014). The function of this circuit can be tested using actigraphy or force variability, which map on components of this circuit (Bracht *et al*., 2013; Mittal *et al*., 2013). (2) The cerebello-thalamo-motor circuit, which combines M1, thalamus, and the cerebellar cortex. This loop is suggested to coordinate sensorimotor dynamics (Bostan *et al*., 2010; Bernard *et al*., 2016). Therefore, postural sway is an applicable instrumental measure capturing the function of this circuit (Bernard *et al*., 2014). And finally, (3) the cortico-cortical motor circuit includes premotor and motor cortex, medial prefrontal cortex as well as posterior parietal cortex. This loop is thought to regulate movement organization and speed (Picard and Strick, 1996; Chouinard and Paus, 2006). Quantitative video analysis of complex behaviors such as hand gesture may monitor the function of this circuit (Dutschke *et al*., 2018). Notably, aberrant functional connectivity in exactly these abovementioned motor circuits was demonstrated in psychosis patients with evident motor abnormalities and subjects at risk for psychosis with distinct motor behavior profiles (Walther *et al*., 2017; Dean *et al*., 2018). Given the well-defined functional neuroanatomy of the motor system, it should be possible to identify the neural mechanisms of altered motor behavior in depression.

How could motor disturbances in depression be conceptualized within the proposed RDoC motor domain? Motor disturbances could be tested as a dimension of depression; for example, psychomotor retardation could be quantified by the total amount of movement, allowing for changes within the course of depressive episodes. Indeed, using actigraphy, studies have linked individual differences in total movement with current mood states in depression (Razavi *et al*., 2011; Bewernick *et al*., 2017; van Diermen *et al*., 2018). Motor retardation in terms of fine motor slowing can be assessed by analysis of key strike delay on smart phones, which have been shown to longitudinally predict mood ratings (Stange *et al*., 2018). Likewise, fine motor slowing was evidenced in drawing and writing tasks may separate subgroups of depression (Sabbe *et al*., 1999; Caligiuri and Ellwanger, 2000; Pier *et al*., 2004). Furthermore, continuous recordings of gross motor activity and smart phone typing behavior can easily be assessed outside of the laboratory, adding ecological validity to their measurement.

Reliable assessment of agitation seems to be much more difficult, but could be accomplished by focusing on continuous actigraphy data or frequency of typing errors on mobile devices

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(Walther *et al.*, 2014). In the laboratory, measures such as force variability could be useful to assess agitation (Mittal *et al.*, 2013; Willems *et al.*, 2016).

To further understand psychomotor disturbances in depression from an RDoC perspective, these instrumental dimensional measures could be measured longitudinally to determine whether these motor behaviors are stable or variable during the course of illness, i.e. tapping into state or trait characteristics of the disorder. Finally, to complement the lab-based and ecologically valid measures, new self-report instruments are needed assessing the subjective experience of agitation or retardation (beyond single items from scales such as the Hamilton Depression Rating Scale). Novel questionnaires assessing the subjective experience and everyday consequences of psychomotor retardation and agitation would be useful.

How would retardation or agitation in depression map on the cerebral motor circuits? Following the proposed function of the motor circuits, psychomotor retardation should be associated with structural and functional alterations in both the cortico-basal ganglia circuit and the cortico-cortical motor circuit. Preliminary evidence seems to support this view, demonstrating increased resting state perfusion in the motor cortex of patients with psychomotor retardation (Yin *et al.*, 2018). In addition, studies using actigraphy to assess gross motor activity reported an association of these dimensional measures with resting state perfusion and white matter properties in premotor cortices, external globus pallidus, and white matter motor tracts, all components of the cortico-basal-ganglia or cortico-cortical circuits (Bracht *et al.*, 2012; Walther *et al.*, 2012*a*, 2012*b*; Cantisani *et al.*, 2016). While these findings generally support the impact of the cerebral motor system in depression, the exact mechanism underlying psychomotor retardation still needs to be identified. In contrast, the neural correlates of agitation in depression have not been reported before. Lack of inhibitory control or functional imbalance in basal ganglia loops shifted toward motor excitation could be potential mechanisms, but that remains to be tested.

How could RDoC research on motor functioning in depression relate to treatment and research on other disorders? The proposed motor domain would allow for in depth dimensional assessment of motor behavior in depression. As these measures have been used with other disorders, these data can be combined with data on motor disturbance in other neuropsychiatric disorders such as schizophrenia, bipolar disorder, autism, or dementia in order to study the transdiagnostic nature of motor behavior (Bernard and Mittal, 2015; Mittal *et al.*, 2017). This would also help integrate motor behavior into the depressive syndrome cluster. The proposed RDoC motor domain has the potential to inform tests clarifying whether motor behavior has unique predictive value in the course and treatment response of depression. Current post-hoc analyses suggest that motor disturbances would indicate poor treatment response (Ulbricht *et al.*, 2016, 2018; Sakurai *et al.*, 2017). Again, instrumental measures are very likely to outperform self-rated motor disturbances and predictions could become even more precise (Caligiuri and Ellwanger, 2000). Relatedly, in motor phenomena such as catatonia or Parkinsonism, researchers are increasingly focusing on the syndrome in various conditions, e.g. delirium, schizophrenia, depression, and bipolar disorder (Stuivenga and Morrens, 2014; Wilson *et al.*, 2015). Along this line, the field could test whether psychomotor retardation and agitation in depression were a minor form of catatonia, a sign related to Parkinsonism, or phenomena distinct from catatonia and Parkinsonism. Furthermore, also brain imaging studies exploring motor disturbances in depression within this framework would be readily comparable with similar studies in other disorders. Given that similar mechanisms were involved across a spectrum of psychiatric disorders, specific treatments for motor inhibition or motor excitation could be tested and offered independent of the underlying psychiatric disorder. For example, studies could use noninvasive brain stimulation to target aberrant neural activity within cortical motor areas (Walther *et al.*, 2017) in order to ameliorate motor disturbance in depression. In sum, studying motor functioning in depression with an RDoC lens holds a great deal of promise for enhancing understanding (and ultimately treatment) for this important feature of depression.

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