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Cross-Cutting Advancements Usher in a New Era for Motor Research in Psychosis

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As gesture serves as an interaction point between motor, language, and sensory-integration processes, an intersection also implicated in psychosis, schizophrenia researchers have recently turned toward this area as well.[1] The findings of Walther et al[2] move our understanding of this nascent field significantly ahead, with results indicating that deficits in gesture performance and perception are closely tied with clinical and functional outcome in individuals with schizophrenia over a 6-month period. More broadly, this article suggests that a test of hand gesture may provide a viable method for predicting clinical course and potentially highlighting a novel vulnerability subtype in schizophrenia patients. Given the importance of these findings, and the relative ease of such assessments, the questions remain—why are we not seeing more studies like this, and where are the translational applications? Further, in addition to aberrant gesture, schizophrenia has been linked with a range of motor signs including delays in developmental milestones, clumsiness, poor coordination, abnormalities in gait, posture and neuromusculature, diffuse neurological soft signs, catatonia, psychomotor slowing, and both medication-induced and spontaneous hyper/hypo dyskinesias spanning muscle groups throughout the body. Despite the broad array of affected behaviors and characteristics, and the long history of movement and motor research in this area,[3] the question remains, why is this such a neglected area in our field?

There are several factors that have been impeding more widespread use of motor variables in cutting-edge research. First, rigid intradisciplinary boundaries between neurology and psychiatry have historically kept abnormalities in movement and socio-emotional behavior distinct. In a related issue, until recently, key relevant target structures such as the basal ganglia and cerebellum have been viewed primarily as a motor centers and related movement behaviors have not been linked into the sophisticated comprehensive models or etiological theories that are often necessary generate enthusiasm about a domain or target. Second, the advent of first-generation antipsychotic medications, which produce characteristic movement disorders in some patients, contributed to further confusion about etiology of movement signs. More broadly, both generations of neuroleptics have also continued to serve as a tricky barrier for definitive research in this area.[4] Third, empirical studies have relied almost entirely on drug-induced motor abnormality assessments,[5] or scales designed to follow diffuse markers (eg, neurological soft signs).[6] While these instruments can be reliable at a particular site, they require highly specialized training, miss more subtle movements, and can press investigators to impose subjective categories on continuous phenotypes. Fourth, although it has been clear for some time that there are motor abnormalities present in psychosis, the translational relevance of these markers is uncertain. Finally, motor behaviors have been left out of initiatives such as the Research Domain Criteria (RDoC).[7]

Despite these limitations, several trends have taken motor abnormalities to the cusp of what promises to be a renaissance in this area. First, a proliferation of cognitive-neuroscience studies utilizing multimodal imaging methodologies and sophisticated animal models have led to several exciting new directions. Specifically, both the basal ganglia and cerebellum are now viewed as integral parts of larger circuits (cortical-striatal-pallido-thalamic and cerebellar-thalamic-cortical-cerebellar loops), and seen as critical modulators for motor behaviors as well as a range of higher-order cognitive and affective functions.[8,9] Indeed, if schizophrenia is a disorder characterized by domains of symptoms as well as cognitive and emotive deficits spanning a host of disparate mechanisms and structures, then perhaps these circuits, responsible for dynamic communication with frontal areas, may be a good target for explaining this heterogeneity.[10] Although theories have pointed to this idea in the past,[11,12] sophisticated cross-disciplinary empirical work is now filling in the missing pieces. One of the most exciting developments in this area focuses on new evidence suggesting direct 2-way communication between the basal ganglia and the cerebellum, independent of the cortex.[13]

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This sets the stage for a new integrated theory of subcortical dysfunction in psychosis. In this context, related motor behaviors remain among the most promising proximal behavioral markers.

Several factors have also helped to rectify motor-related confusion surrounding neuroleptic medications. As a class, the second generation antipsychotics have a lower propensity to cause extrapyramidal symptoms,[14] and widespread adoption of the atypicals may have set the stage for clinicians and researchers to become more aware of a range of aberrant motor behaviors. In the past, when prescribing a patient first generation antipsychotics, clinical attention to initial extrapyramidal symptoms, and then later in treatment to tardive dyskinesia specifically, may have diverted focus from these features. Second, evidence has been gathering over the past two decades to suggest that spontaneous motor abnormalities can occur as a function of pathophysiology in a sizeable subsample of individuals with schizophrenia.[15,16] This has been demonstrated in studies of unaffected relatives,[17] prodromal youth,[18,19] as well as medication naïve groups (for a review see Pappa and Dazzan[20]). Although it is still difficult to study motor behaviors in patients treated with any medications that affect subcortical dopamine (DA) activity, a more widespread understanding that these behaviors reflect pathogenic processes, research approaches with low dosage inclusion criteria and medication-free or medication-naïve patients, as well as designs focusing on individuals who represent a lower vulnerability loading on the psychosis continuum (ie, populations with elevated schizotypy, schizotypal personality disorder, and nonclinical psychosis exhibit motor abnormalities but are often unmedicated),[21–26] will continue to open new avenues.

One of the most substantial advances in this area relates to novel instrumental approaches to assessing motor dysfunction. In contrast to early iterations of instrumental approaches, which paved the way but were limited by the use of different apparatus and thresholds/conventions across sites (investigators often designed and built these devices themselves), these new approaches lend well to standardization. Among the many promising approaches are computerized handwriting analysis,[27,28] balance assessments,[29] motion sensors, and actigraphy.[30] Researchers also continue work with industry to develop validated smartphone applications.[31] In terms of translational applications, it is noteworthy that these approaches can be implemented and scored quickly primary-care settings without specialized training. There are several advantages from a research perspective as well. Quantification with these measures does not require subjective decisions about the presence or absence of abnormalities. In a related point, these methods provide continuous data allowing for more powerful research designs. Most noteworthy is that they are capable of detecting subthreshold movement abnormalities that are not detectible to the eye. For example, estimates from traditional observer-based inventories of spontaneous motor abnormalities suggest rates of 9% for dyskinesia and 17% for Parkinsonian signs in medication naïve adults with schizophrenia[20] whereas studies utilizing the more sensitive instrumental measures report rates up to 20% and 28%, respectively.[32] Further, motor assessments have continued to benefit from the integration with experimental modalities such as transcranial direct current stimulation (tDCS).[33] Finally, paring these assessments with multimodal neuroimaging methods has provided evidence to suggest that some motor behaviors previously thought of as diffuse are actually specific; eg, there is evidence that neurological domains that were previously categorized as "soft" have been linked to specific regions such as the cerebellum, or specific cerebellar-thalamic tracts.[34] This trend is likely to continue, as recent years have seen adaptation for use of the noted instrumental assessments inside the scanner.[35]

Although abnormal motor behaviors have been detected long before the onset of the first positive symptoms in psychosis,[36–38] until now the potential for translational applications has been somewhat unclear. However, as motor behaviors are integrally tied to many of the same processes that, in part, drive the onset and maintenance of psychosis (eg, aberrant DA activity in basal ganglia circuits), there are several areas of rich potential here. Some work suggests promise for incorporating motor markers into individualized medicine. For example, there is evidence that neuromotor signs predict treatment response to neuroleptics.[39,40] Further, the area of prodromal research has provided another promising translational application. During the adolescent prodromal period, when DA abnormalities escalate,[41] and potentially interact with extant early vulnerabilities (eg, signs of general motor system impairment pinpointed in archival and childhood home-video designs),[38] emerging specific motor signs such as hyperkinetic movements may serve as a highly sensitive prognostic indicator of basal ganglia dysfunction.[42] In support of this theory, prospective investigations in youth with prodromal syndromes have observed that the presence of specific motor abnormalities significantly increases the odds of developing psychosis in a brief 2-year period.[10,43] In a new exciting direction, some work also suggests that cerebellar-specific motor behavior (i.e., balance) may also have unique predictive value for negative symptoms as well.[29,44] This series of findings has significant practical use for the refinement of risk calculators[45] as well as efforts to understand unique potential subtypes.

Finally, it is important to note that while motor dysfunction was not incorporated into the initial RDoC Matrix, this will not likely be the case for long. Consistent with this notion, it is important to note that several motor signs appear to occur across a range of psychopathology (eg, attention deficit hyper-activity disorder, autism spectrum disorder, depression, bipolar disorder,

Alzheimer's).[46–50] We are just now beginning to investigate diagnostic boundaries of these core behaviors, but it is clear that because specific movement domains are closely tied to underlying brain circuits, motor markers lend well to cross-diagnostic approaches. Within the context of RDoC, this type of progress will inevitably encourage motor researchers to consider new units of analysis and groups of other research experts to incorporate motor variables into their proposals. Taken together with this emerging cross-pollination and the other recent advancements, it is clear that we are in store for new era for motor research in psychosis.

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