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Motor signatures in autism spectrum disorder: the importance of variability

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Parma V, de Marchena AB. Motor signatures in autism spectrum disorder: the importance of variability. *J Neurophysiol* 115: 1081–1084, 2016. First published August 12, 2015; doi:10.1152/jn.00647.2015.—In a recent study, Wang et al. (*J Neurophysiol* 113: 1989–2001, 2015) used a precision grip force control task to unveil the contribution of feedforward and feedback mechanisms to sensorimotor dysfunction in autism spectrum disorder (ASD). Impairment of both motor control mechanisms was observed, along with significant variability in the motor response. In this Neuro Forum article we discuss these findings within the conceptual framework of the grasping circuit and within the broader context of clinical and research applications based on motor behavior.

autism spectrum disorder; basal ganglia; cerebellum; motor signature; motor variability

RESEARCH ON AUTISM SPECTRUM DISORDER (ASD) has traditionally focused on the core problems of social and communication skills weaknesses. However, sensorimotor abnormalities are almost omnipresent in ASD (De Jong et al. 2011), even in individuals without global delays or intellectual disability, and occur extremely early during development (i.e., as early as infancy). Furthermore, anomalous motor behavior robustly correlates with measures of social and communicative function, suggesting a relationship between sociocommunicative deficits and impaired motor development, in at least some individuals. Altogether, these features make the study of the sensorimotor system an ideal candidate for the discovery of new intermediate phenotypes, facilitating earlier detection of ASD, and identifying the neural basis contributing to the disorder. In this article we comment on a recent study by Wang et al. (2015), which found abnormalities associated with precision grip in children and adolescents with ASD. We frame these findings in the broader context of the ASD motor literature, discuss possible neural mechanisms accounting for motor differences, and discuss potential clinical and research applications arising from the study of motor behavior in ASD.

Motor Features in ASD: the Centrality of Variability

Some aspects of the motor phenotype in ASD are clear and easily observed clinically (e.g., low muscle tone). In these cases the intrinsic variability of motor phenomena does not prevent its identification. However, more and more often the literature suggests that there is a range of subtle motor features that are highly influenced by within- and between-trial variability and that are, for this reason, hard to detect "by the naked eye." Such behaviors are to be operationalized into quantifiable tasks that are *1*) sufficiently easy so that they can be completed by individuals with a range of ages and levels of functioning, *2*) not susceptible to ceiling effects, and *3*) able to capture the intrinsic variability of the musculoskeletal system involved in action execution.

In a recent study, Wang et al. (2015) succeeded in identifying such a basic yet informative task in the form of a precision grip force control (PGFC) task. Children with and without ASD (ages 5–15 yr old) used their thumb and index finger to push together two blocks (technically, computer-controlled load cells) as they watched two feedback bars on a computer monitor. As participants squeezed the cells, the bars aligned; the goal of the task was to align them perfectly. Thus participants needed to attend to feedback from both visual (i.e., the bars on the computer screen) and proprioceptive modalities (i.e., strength of precision grip) to execute the task. Participants completed the task in a two by three design, which varied by time of maintenance of the precision grip (2 s vs. 8 s) and opposing resistance (15% vs. 45% vs. 85% of maximum voluntary contraction; i.e., the hardest participants could squeeze the load cells). Findings from this simple PGFC task provide insights into at least two phenomena: *1*) the differential contribution of feedforward mechanisms involved in the production of initial open-loop force based on an inverse model constructed implicitly, and *2*) reactive or feedback mechanisms involved in the controlling of a sustained action. In other words, Wang et al. shed light on the mechanisms contributing to the reduced control of initial motor output in ASD, which so far have been very controversial (Gowen and Hamilton 2013).

Overall, the findings of Wang et al. (2015) are in line with independent evidence indicating reduced integrity of sensorimotor behavior in ASD (e.g., weaker baseline grip strength). In a task-dependent manner, participants with ASD showed more variability in PGFC movements, both as they initially matched the feedback bars and as they sustained their grip over time. Typically developing participants tended to apply the right amount of initial force to smoothly align the visual feedback bars; in contrast, participants with ASD applied excessive initial force, resulting in overshooting the alignment. Because of the initial force overshooting, participants with ASD needed to make a second release movement to complete the trial successfully, producing an overall disjointed movement. Interestingly, this initial overapplication of force followed by a compensatory release was associated with age in both groups, with older participants requiring fewer adjustments. The association with age was more pronounced in the ASD group, suggesting abnormal sensorimotor learning across develop-

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ment. Children with ASD also showed more variable movements as they sustained their grip over the duration of both 2- and 8-s trials.

The movement variability observed by Wang et al. (2015) is consistent with a series of kinematics and dynamics studies of people with ASD, involving tasks from simple pointing to gait (Brincker and Torres 2013). Across motor tasks and throughout development, movement variability is consistently higher in ASD samples. In general, we must be cautious when interpreting performance variability. Indeed, variability in common measures (e.g., response time) may reflect domain-general weaknesses in motivation or attention and is not specific to motor performance. Despite these challenges of interpretation, several lines of research suggest that movement variability in ASD is at least partially independent of volition. For example, children's arm movements were analyzed as they returned their arms to a resting state after pointing (Torres et al. 2013). This retraction movement is as close to a non-goal-directed movement as possible, and yet clear group differences in movement variability were observed, suggesting that movement variability in ASD goes beyond general differences in task performance.

Variability Within the Motor Hierarchy

Variability across groups can emerge due to dysfunctions at different levels of the motor hierarchy. For instance, differences across groups can be determined by differential strategies in the extraction of sensory information from the environment. The processing of individual sensory features appears to be preserved in ASD, whereas tasks requiring sensory judgments often reveal abnormalities, at the levels of both interpretation and integration (for a review, see Gowen and Hamilton 2013). Optimal motor behavior requires a continuous interaction between afferent and efferent processes as inputs from all senses are continuously updated to guide ongoing and subsequent motor plans. If individuals with ASD have difficulty interpreting these sensory streams, then their motor planning will be affected. As suggested by Brincker and Torres (2013), poor integration of sensory input with motor output should result in increased variability of motor execution, even within a simple, repetitive motor task. This prediction is supported by Wang et al.'s findings of increased compensatory movements in ASD.

Climbing the motor hierarchy even further, we find that sensorimotor transformations (i.e., internal models) of participants with and without ASD are different. It is not surprising that the participants with ASD in Wang et al. (2015) show reduced ability to transform visual information (i.e., the feedback bars) into a motor plan (i.e., smooth precision grip), because this is a finding consistent across tasks (Marko et al. 2015).

The increased variability and noise present during the processing of sensory stimuli and conveyed to the motor outputs can also be explained in terms of motor learning theories. By comparing a sensory-based experience of a motor act with a desired movement, the brain can identify a very detailed gradient of error referring to a specific part of the motor command, especially when one considers that most movements are performed in noisy dynamic environments. Therefore, and to be meaningful, the internal model formation algorithm must be robust at least to some degree of trial-to-trial variability. If it is expected that such kinematic and dynamic variability is larger during childhood, the ASD population, independently of developmental stage, exceeds this variation.

The Role of Cerebellum and Basal Ganglia

Variability in behavioral performance can reflect alterations at the level of neural underpinnings. Wang et al. (2015) focus the explanation of their findings on cerebellar activity. The cerebellum is a neural structure receiving projections from all sensory cortices and is able to both process the timing and predict the sensory consequences of action. It represents one of the main structures of the brain in which sensory information and previously experienced complex patterns can be compared. When cerebellar mechanisms malfunction, disturbances of sensory data acquisition in all sensory modalities emerge and reverberate as impoverished motor accuracy and coordination. The highly variable performance of children with ASD at the PGFC task can be linked to putative cerebellar dysfunction. This seems to be supported by the fact that children with ASD show deficits of predictive grip force control similar to those of patients with cerebellar disorders, whereas reactive control mechanisms appear relatively unimpaired. In other words, the fact that participants with ASD initially applied excessive force to the load cells in the study by Wang et al. (2015) is in line with the performance of patients with cerebellar pathologies and may represent a compensatory strategy to ensure a stable grasp in situations where the motor system works suboptimally. Strategies to fight the inaccuracies of the internal models are then necessary, especially in light of the fact that the timescale functioning of the cortical motor areas (e.g., primary motor cortex and supplementary motor area) depends on slow changes in sensory feedback.

Limiting the motor variability in ASD only to abnormal cerebellar functioning may be an oversimplification. Indeed, other neural structures, such as the basal ganglia, have been taken into account when explaining motor differences in ASD, including those relevant for PGFC. The anterior nuclei of the basal ganglia (i.e., caudate, anterior putamen, and external portion of the globus pallidus) control planning aspects of the action, whereas the posterior nuclei (i.e., posterior putamen, internal portion of the globus pallidus, and the subthalamic nucleus) contribute to the regulation of specific aspects of the force pulse production, including peak grip force control (Prodoehl et al. 2009). The initial overshooting of grip force and its increased variability in participants with ASD in Wang et al. (2015) parallels the increased variability in grip force output found in Parkinson's disease, Huntington's disease, dystonia, and Tourette syndrome patients (Prodoehl et al. 2009). If on the one hand, there is no strong evidence for anatomic abnormality of the basal ganglia in ASD (Hardan et al. 2003), then on the other hand, Parkinson's disease has taught us that even limited cell loss (such as that occurring in the substantia nigra) can lead to extensive downstream changes, resulting in motor strategies compatible with an overshooting of initial force and subsequent readjustment.

Additionally, the disynaptic pathway linking cerebellum and the basal ganglia suggests a direct interplay between these two

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regions (Bostan et al. 2010). The role of this integrated system is to develop computational strategies to counteract the cerebellum-dependent noisy sensory information in input, which makes the motor output less accurate and slower. In light of the fact that the role of this integrated system goes well beyond the production of actions and it is extended to perceptual, conceptual, lexical, and behavioral outcomes alike (Manto et al. 2012), it will be interesting to empirically investigate how the coordinated involvement of cerebellum and basal ganglia contribute to the variability of social deficits in ASD.

Social-Motor Behavior and Possible Applications of the Motor Phenotype

The work of Wang et al. (2015) underscores the fact that perception is the grounding foundation of motor function, which in turn is a basic constituent of many social behaviors that are problematic in ASD (e.g., imitation, nonverbal communication). Indeed, a lack of synchronization of sensorimotor information will make an individual's movements more variable, which in turn will impair his/her ability to extract meaningful patterns from sensory feedback itself, resulting in a cascade of impoverished motor learning with downstream effects on social-motor phenomena (e.g., imitation). Correlation between increased variability in grip force tasks and clinical impairment has been shown in other pathologies (e.g., Huntington's disease). The link between motor and social behavior suggests that identifying characteristic patterns of motor behavior in ASD may help support novel clinical and research applications. For example, currently the most reliable early markers of ASD are sociocommunicative; however, sophisticated motor behavior, as well as the neural networks subserving such behavior, emerges long before intentional communication, suggesting that analyses of motor behavior may be particularly promising for very early identification of ASD. The identification of motor signatures across basic, spontaneously produced motor acts (such as gripping) could lead to the recognition of precursors to these signatures extremely early in development, potentially in utero (Zoia et al. 2013), with potential to elucidate the neurobiological basis of the disorder and thereby improve diagnostic definition and subsequent treatment.

The identification of such motor signatures can be aided by understanding the individual contribution of cerebellar and frontostriatal systems to the motor variability found in ASD. Indeed, studies assessing how individuals with neurodevelopmental disorders with selective frontostriatal (e.g., ADHD) or cerebellar dysfunctions perform on specific motor tasks are necessary. Comorbidity of these disorders with ASD will provide further insight on the specificity of the patterns of contribution of the two systems. Furthermore, to prevent overgeneralization of motor variability outcomes, studies including the quantitative measurement of the motor performance in ecological environments and in less-selected samples of patients (i.e., high functioning children, teenagers, and adults) are needed.

Ultimately, motor signatures could be incorporated into our understanding of the extreme phenotypic heterogeneity observed in ASD. Heterogeneity exists at many levels in ASD, including cognitive functioning, ASD symptom severity, and comorbid psychiatric and genetic syndromes. The identification of different motor signatures can be seen as an additional tool to help parse this heterogeneity. For example, it might be the case that characteristic motor patterns are associated with a specific subtype of ASD, which may have unique underlying genetics, respond differently to treatments, and have other relevant clinical features in common that have gone overlooked.

We believe that studies such as that of Wang et al. (2015) can help identify motor signatures associated with ASD, should they exist. Although the identification of motor signatures is still in its infancy, some studies have paved the way for an ecological investigation of motor behavior in all its complexity. Motor signatures would emerge more readily when the same participants complete a large number of motor behaviors, and features extracted from across these tasks can be analyzed within the same models. One promising approach is that represented by the analysis of data-driven patterns, including the multivariate and stochastic analyses of features such as motor, brain imaging, and social behavior (Ingalhalikar et al. 2012).

In conclusion, understanding motor behavior in ASD via tasks as simple and informative as that conducted by Wang et al. (2015) contributes to the elucidation of the neurobiological bases of the disorder and paves they way to discovering new early clinical/translational applications based on motor function.

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DISCLOSURES

The authors declare that their opinion was provided in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

V.P. and A.B.d.M. drafted manuscript; V.P. and A.B.d.M. edited and revised manuscript; V.P. and A.B.d.M. approved final version of manuscript.

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