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# The Importance of Measurement Precision and Behavioral Homologies in Evaluating the Behavioral Consequences of Fetal Ethanol Exposure : Commentary on Williams et al. ("Sensory-Motor Deficits in Children with Fetal Alcohol Spectrum Disorder Assessed Using a Robotic Virtual Reality Platform")

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The influence of technological advancements on the scope, limits and precision of quantitative measurement is a ubiquitous and driving feature behind scientific progress. The study conducted by Williams et al. (in press) employed a novel and recently developed robotic exoskeleton technology to quantify the accuracy and kinematics of visually-guided reaching movements in children (ages 5-18) diagnosed with a fetal alcohol spectrum disorders (FASDs) and a comparison group of typically developing children. The children were instructed to move their hand from a central location to one of eight possible target locations indicated by a visual stimulus controlled by the apparatus. The robotic exoskeleton and virtual stimulus presentation system allowed the authors to quantify 12 parameters of visually-guided reaching with excellent temporal (~1ms) and spatial resolution (~4 microns)[1] during performance of this task. The specific movement parameters selected for quantification were based on prior work (described in Coderre et al., 2010) and were combined to obtain five characteristics of performance: postural control, reaction time, initial movement, corrected movement, and total (global) movement metrics. Children with FASDs were impaired relative to typically developing children on most (9 out of 12) measures, with effects observed for some features of all five characteristics of performance. Notably, some dimensions, including postural control, initial movement and corrected movements were affected more dramatically and many individual variables associated with these dimensions yielded large effect sizes ($d > 0.8$), including measures of initial direction error, the proportion of overall movement attributable initial movement, a measure of overall movement length, postural speed, and a measure of error correction or movement constancy (number of differences in peak speed). Non-significant differences were observed only for the number of movement onsets, overall movement time and maximum hand speed. Broadly, these observations indicate that fetal ethanol exposure results in robust deficits in several constituent processes involved in visually-guided reaching and that the use of sensitive, automated technologies for quantification of visually-guided movements may be useful in characterizing the types of motor deficits observed in this population.

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[1]The spatial and temporal resolution values were retrieved from product information for the KINARM system provided at www.bkintechnologies.com (accessed August 31, 2013).

In addition to evaluating the utility of the robotic exoskeleton technology for assessment of fetal-ethanol-related motor deficits, the authors expressed the goal of pursuing more precise, quantitative metrics for assessing motor behaviors in children with FASDs as a major motivating factor. Deficits in sensory, cognitive and motor processes have long been identified as consequences of ethanol exposure during nervous system development (Kodituwakku, 2007, Mattson et al., 2013, Nguyen et al., 2013, Riley et al., 2011, Roebuck-Spencer et al., 2004, Simmons et al., 2010), however, prior demonstrations of motor deficits have largely utilized coarse quantitative or qualitative measures to assess motor skills and performance. Precision is commonly considered in a strictly quantitative sense, however, the inclusion of multiple constituent behavioral processes in the scoring system rather than exclusively global assessment of performance (e.g., overall movement latencies and accuracy) is an important feature of the approach utilized by Williams et al. The capacity to obtain more precise behavior measurements and assessment of constituent processes provides several benefits for behavioral analysis, and though not unique to effects of ethanol exposure, several benefits are particularly timely and relevant to the study of fetal ethanol effects. For one, more precise measurements may support detection of deficits that would go undetected by more coarse quantitative or purely qualitative measurement instruments. Similarly, the capacity to identify specific constituent processes that contribute to an overall pattern or sequence of behavior can support more precise characterizations of behavior and enhance the discriminative capacity of the measurement system. That is, by quantifying distinct constituent processes involved in movement direction, speed, constancy, and postural control the likelihood of identifying a subset of behavioral processes that discriminate ethanol-exposed and non-exposed participants is enhanced. FASDs encompass a wide range of sensory, behavior and cognitive deficits that vary in scope and severity depending upon the diagnosis. Greater precision in both respects outlined above may also enhance the capacity of a measurement instrument to distinguish sub-diagnoses under the more general umbrella of FASDs. Although the current study only evaluated a group of children diagnosed with FASDs, an obvious next step would be to evaluate the capacity of this technology and the resulting data in distinguishing specific FASDs.

The use of more comprehensive and precise measures of behavior may also be useful in identifying a unique behavioral profile associated with FASDs in comparison to other neurodevelopmental disorders. As the authors note, whether children with FASDs can be distinguished from children diagnosed with distinct but related disorders with high comorbidity, such as autism or ADHD, is an important target for future research. Whether FASDs can be distinguished from prenatal exposure to other drugs known to cause deficits in motor behavior, such as cocaine (Miller-Loncar et al., 2005), would also be informative. Of further importance is the potential utility of this approach for the assessment of improvements associated with interventions designed to ameliorate deficits associated with fetal ethanol exposure. One possibility not noted explicitly by the authors is that this technology could be used to provide one such intervention in the form of sensory-motor training, as the robotic system the authors utilized appears well suited to provide precise and dynamic feedback regarding performance. Specific motor training interventions are effective in improving performance in animal models of FASDs (Hannigan et al., 2007, Klintsova et al., 2002). Because distinct motor behavioral processes can be linked to specific neural

circuits, this approach may hold considerable value for gaining insight into the underlying neurobiological circuits processes impaired in FASDs. Quantifying the benefits of training on distinct parameters of movement performance and how these are related to improvement in other domains of performance might also provide novel insights into the common behavioral and neural processes underlying diverse deficits observed in children with FASDs.

With regard to the specific deficits observed by Williams et al., a point for special consideration is the sequential nature of the behavioral processes that were quantified. The initial direction of movement was impaired in FASDs indicating that disruptions are present at the earliest stages of overt reaching behavior. Other aspects of visually-guided reaching, such as sharp changes in movement speed indicative of error correction, suggests that subsequent aspects of the sequencing of motor movements is also profoundly impaired. A general characteristic of forelimb movements guided by exteroceptive stimuli is that the movement sequence is initiated with gross orienting movements that involve movement in the general direction of a goal (Gallistel, 1980). These initial movements are then followed by more precise movements designed to direct the distal aspect of the limb (e.g., the hand) toward a goal object that can then be touched or grasped for retrieval. The sequential nature of the reaching behaviors examined by Williams et al. are reminiscent of the reaching behaviors observed in other species and the topography, sequence, and kinematics of skilled reaching movements in the rat (Whishaw and Pellis, 1990, Whishaw et al., 2008). Historically, skilled forelimb movements were thought to be exclusive to primates (Iwaniuk and Whishaw, 2000), however, the analysis of skilled forelimb movements in the rat have been particularly useful in better understanding the neural bases of movement processes. When rats are trained to perform skilled forelimb movements, such as those involved in reaching for a single food pellet, a characteristic structure and sequence of behaviors emerges. Part of the characteristic response topography is the progression from initial coarse aiming movements that proceed from the shoulder, to more precise aiming movements associated with the forearm, to more precise distal behaviors (of the paw and digit) directed toward a target objects (Whishaw and Pellis, 1990). These behaviors are typically assessed by expert raters viewing high-speed video footage, rather than automated systems, however, the precision provided by sensitivity to different movement topographies in the scoring system endows this approach with excellent capacity to isolate deficits in specific behavioral processes. Using a single pellet reaching task, (Heck et al., 2008) demonstrated that rats exposed to ethanol prenatally are impaired in the acquisition of skilled reaching behavior, however, their analysis was limited to quantification of acquisition time. The quantification of specific aspects of movement sequences using a system like that of Whishaw and colleagues could yield important clues about the underlying systems involved in ethanol-related deficits in motor behavior, including initial movement orientation and error correction during reaching such as those identified by Williams et al. in children. Prior research has demonstrated that the size of cortical motor maps measured using intracortical microstimulation is reduced in rats exposed to ethanol prenatally (Xie et al., 2010). Maintenance of cortical motor maps requires ongoing protein synthesis (Kleim et al., 2003), indicating that these maps are highly plastic and modifiable even in adulthood. Such

processes may be impaired by fetal ethanol exposure and could be a possible explanation of impaired motor control and performance in children with FASDs reported by Williams et al.

Translational efforts designed to better understand the mechanisms of fetal ethanol related deficits in behavior and to develop and evaluate treatment approaches will benefit from the use of commesurate and behaviorally homologous tasks and analysis systems in rats and humans. The approach used by Williams et al. appears to be well suited as part of a larger program to examine the effects of fetal ethanol exposure on motor behavior. The enhanced precision afforded by computerized, virtual tasks might prove important for strengthening translational approaches and identifying potential mechanistic bases of FASD-related deficits. Attempts to utilize similar behavioral paradigms in humans and non-human animals, such as eye-blink conditioning (Jacobson et al., 2011) and spatial navigation tasks (Hamilton et al., 2003) have met with some success. Given the large effect sizes associated with deficits in sensory-guided reaching behaviors following fetal ethanol exposure, a comparative approach could provide an important avenue for examining the neural bases of ethanol- related behavioral impairments and facilitate the translation of work from the laboratory to the clinic.

One limitation of the technology utilized by Williams et al. is that children under 5 years of age cannot be examined, thus, measurement of goal-directed reaching behavior in younger children would require other approaches. Motor deficits in fetal ethanol exposed children can be detected in infancy (Autti-Ramo and Granstrom, 1991), and the application of more precise measurements of motor behavior, whether they be task-related or spontaneous (Wallace and Whishaw, 2003), during very early postnatal development could also be beneficial for early detection of FASDs. Whether ethanol-related alterations in motor behavior observed early in infancy are predictive of specific deficits observed later in this visually-guided reaching task would be interesting to address in future work.

In summary, the use of novel technologies that provide more precise quantification of motor behavior may hold a special importance for the future of research on the behavioral and neural consequences of fetal ethanol exposure. A major challenge to the field is to determine how the relevant constituent sensory, cognitive and motor functions are altered in FASDs, and the emergence of new technologies such the one employed by Williams et al. will likely play an important role in these efforts. An open question is whether the application of this technology can yield behavioral outcomes that distinguish FASDs from other disorders and different sub-diagnoses under the general umbrella category of FASDs. This is particularly important given that conspicuous signs of ethanol exposure in lesser-exposed children may go undetected by more crude assessments of behavior. Of course, the ultimate utility of this technology in the service of understanding fetal ethanol related deficits remains to be seen and will largely depend upon the replication and adoption of these or similar methods by the larger community of FASD researchers. The promise offered by the type of innovations described by Williams et al. should provide ample motivation for the investigation of motor deficits in FASD children using this or similar technologies, and for attempts to establish homologous behavioral and analytical approaches in comparative translational research efforts on the effects of fetal ethanol exposure.

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