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Children with Heavy Prenatal Alcohol Exposure Experience Reduced Control of Isotonic Force

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Abstract

Background—Heavy prenatal alcohol exposure can result in diverse and extensive damage to the central nervous system, including the cerebellum, basal ganglia, and cerebral cortex. Given that these brain regions are involved in the generation and maintenance of motor force, we predicted that prenatal alcohol exposure would adversely affect this parameter of motor control. We previously reported that children with gestational alcohol exposure experience significant deficits in regulating isometric (i.e., constant) force. The purpose of the present study was to determine if these children exhibit similar deficits when producing isotonic (i.e., graded) force.

Methods—Children with heavy prenatal alcohol exposure and typically developing children completed a series of isotonic force contractions by exerting force on a load cell to match a criterion target force displayed on a computer monitor. Two levels of target force (5% or 20% of maximum voluntary force) were investigated in combination with varying levels of visual feedback.

Results—Compared to controls, children with heavy prenatal alcohol exposure generated isotonic force signals that were less accurate, more variable, and less complex in the time domain compared to control children. Specifically, interactions were found between group and visual feedback for response accuracy and signal complexity, suggesting that these children have greater difficulty altering their motor output when visual feedback is low.

Conclusions—These data suggest that prenatal alcohol exposure produces deficits in regulating isotonic force, which presumably result from alcohol-related damage to developing brain regions involved in motor control. These children will most likely experience difficulty performing basic motor skills and daily functional skills that require coordination of finely graded force. Therapeutic strategies designed to increase feedback and, consequently, facilitate visual-motor integration could improve isotonic force production in these children.

Keywords

prenatal alcohol exposure; fetal alcohol spectrum disorders (FASD); motor; force production; isotonic force

Introduction

Prenatal exposure to alcohol results in a wide range of physical, cognitive, and behavioral abnormalities. The most severe and well-known outcome of prenatal alcohol exposure is fetal alcohol syndrome (FAS), which is characterized by pre- and/or postnatal growth deficits, a distinct pattern of facial dysmorphology, and central nervous system (CNS) dysfunction (Jones et al., 1973). However, developmental exposure to alcohol results in a continuum of effects, including damage to the developing brain and neurobehavioral deficits, even in individuals without the facial features required for a diagnosis of FAS. As a result, the nondiagnostic umbrella term fetal alcohol spectrum disorders (FASD) has been established to encompass the wide range of problems that may result from alcohol consumption during pregnancy (Bertrand et al., 2004). Of the potential effects of gestational alcohol exposure, changes in structure of the developing brain and the resulting neurobehavioral function are among the most devastating. Early autopsy reports, animal model studies, and human neuroimaging studies have shown that alcohol can cause gross abnormalities in brain structure as well as localized damage to specific brain regions (e.g., Clarren, 1986; Coles and Li, 2011; Jones and Smith, 1975; Jones et al., 1973a; Lebel et al., 2011; O'Leary-Moore et al., 2011) that result in a range of neuropsychological sequelae, including motor impairment (for a review, see Mattson et al., 2011).

Research has established that many regions of the brain associated with motor function are particularly vulnerable to alcohol-related injury. Magnetic resonance imaging (MRI) studies have documented significant volume and size reductions in the basal ganglia and cerebellum (Archibald et al., 2001; Autti-Ramo et al., 2002; Mattson et al., 1992; Mattson et al., 1996), as well as disproportionate white matter hypoplasia of the anterior vermis of the cerebellum (Sowell et al., 1996). Such findings are of clinical relevance as the basal ganglia and cerebellum are prominent brain structures involved in motor planning and execution in addition to feedback control of motor responses (Plessen et al., 2009; Prodoehl et al., 2009; Prodoehl et al., 2008). Moreover, frontal and parietal cortical areas, such as the primary motor, premotor, supplementary motor, and inferior parietal cortices are particularly vulnerable to alcohol teratogenesis. Prenatal alcohol exposure has been found to alter the distribution of corticospinal neurons in the primary motor, premotor, supplementary motor, and cingulate cortices (Miller, 1987), and structural and functional abnormalities of these regions have also been observed in neuroimaging studies of children with FASD (Coles and Li, 2011; Lebel et al., 2011). Together, these regions play a significant role in the planning, preparation, initiation, and control of voluntary movement (Fogassi and Luppino, 2005; Roland et al., 1980; Vaillancourt et al., 2003). However, the causes of motor impairment observed in FASD are not limited to CNS abnormalities. Developmental alcohol exposure is also associated with abnormal peripheral neural development, including reduced number and size of motor neurons (Bradley et al., 1999; Heaton and Bradley, 1995), abnormal peripheral nerve myelination (Phillips et al., 1991; Strömberg and Pinazo-Durán, 2002), slowed peripheral conductivity (Avaria Mde et al., 2004), atypical neuromuscular innervations (David and Subramaniam, 2005), and poor muscle development (David and Subramaniam, 2005).

Given the degree of damage to both the central and peripheral nervous systems, many children prenatally exposed to alcohol experience a number of motor deficits in both gross and fine motor skills. Motor impairments in FASD include deficits in postural stability (Roebuck et al., 1998), gait (Marcus, 1987), reaction time (Simmons et al., 2002), motor timing variability (Simmons et al., 2009), goal-directed arm movements (Domellof et al., 2010), sensorimotor performance (Jirikowic et al., 2008), bimanual coordination (Roebuck-Spencer et al., 2004), grip strength (Conry, 1990), hand/eye coordination (Adnams et al., 2001), fine-motor speed and coordination (Chiodo et al., 2009; Mattson et al., 1998), and

oculomotor control (Green et al., 2009). However, one aspect of motor control that has not been independently studied in these children is the regulation of motor force. Force regulation is an important feature involved in complex movement, and further investigation of this parameter may highlight an underlying mechanism of poor motor control in children with FASD. Fine graded force is controlled by widespread cortical and subcortical networks, including the primary motor and somatosensory cortices, dorsal and ventral premotor areas, inferior parietal regions, cerebellum, and globus pallidus (Keisker et al., 2009)—all of which, as previously discussed, can be damaged by prenatal alcohol exposure. Force regulation is critical for the successful completion of daily functional tasks. For example, actions such as throwing a ball, holding a pen, or squeezing a bicycle brake lever all require coordination of forces of the hand and fingers (Prodoehl et al., 2009).

We previously evaluated regulation of isometric (i.e., constant) force in children with heavy prenatal alcohol exposure and found that alcohol-exposed children produced force signals that were less accurate, more variable, and simpler in organizational structure in the time domain, compared to typically developing children (Simmons et al., 2012). The purpose of the present study was to determine if the type of deficits previously reported for isometric force regulation also occur when children with prenatal alcohol exposure produce isotonic force. It cannot be assumed that isometric force deficits generalize to isotonic force because the two types of force differ in several respects. At the muscular level, isotonic force involves a graded force application during which the lengths of the agonist-antagonist muscles are constantly and inversely changing; on the other hand, isometric force is a constant force application during which opposing muscles are held at a constant length. Furthermore, at the level of the central nervous system, isotonic force evokes greater functional MRI activation in motor cortical regions than isometric force (Thickbroom et al., 1999), suggesting that neural activity associated with the two types of forces is fundamentally different.

The present study utilized three dependent variables to evaluate isotonic force responses of children with and without histories of heavy prenatal alcohol exposure: accuracy in producing the target force, variability in the force signal, and force signal complexity. Prior research has shown that alcohol-exposed children have difficulty producing accurate and consistent motor responses when aiming for spatial and temporal targets (Wass et al., 2002). Considering this evidence as well as our results for isometric force regulation, we predicted that children with prenatal alcohol exposure would produce greater error in their force signal and display significantly greater force variability compared to control children. Additionally, we expected that typically developing children would use visual feedback to alter their force response but alcohol-exposed children would be less efficient at integrating visual information with motor output. As a result, alcohol-exposed children will minimally modify their force signal across time and produce a response that is relatively simple and repetitive (i.e., less complex) in structure. In contrast, control children will make visual feedback-based adjustments to the force response, resulting in a signal with significantly greater complexity.

Materials and Methods

Participants

Two groups of children between the ages of 7 and 17 years were included in this study: children with heavy prenatal alcohol exposure (ALC group) and typically developing children with no prenatal exposure to alcohol (CON group). All participants were enrolled at the Center for Behavioral Teratology (CBT) at San Diego State University and recruited through professional or self-referrals and advertising at various agencies and child-related venues within the community. Criteria required for inclusion in the study included English

as primary language and Full Scale IQ (FSIQ) greater than 60. Children were excluded from the study if they had suffered significant head injury with loss of consciousness for longer than 30 minutes, significant physical or psychiatric disability that would preclude participation, or other known causes of mental deficiency. All children were evaluated with a comprehensive neuropsychological examination, including intelligence testing, administered by a trained psychometrist. To the extent possible, groups were matched on age, gender, and handedness (see Table 1).

Heavy Prenatal Alcohol Exposure Group—The ALC group consisted of 24 children with confirmed histories of heavy prenatal alcohol exposure. Although the frequency and pattern of alcohol exposure were not always obtainable, maternal alcohol consumption was assessed through retrospective multi-source collateral reports, such as review of medical, social service, and adoption agency records as well as maternal self-reports, when available. Heavy exposure was outlined as four or more drinks per single occasion at least once per week or 14 drinks per week on average during pregnancy. Children with incomplete family histories of prenatal alcohol exposure were not eligible to participate. Children in the ALC group were evaluated by a pediatric dysmorphologist (Kenneth Lyons Jones, M.D.), and eight children met diagnostic criteria for FAS, including pre- and/or postnatal growth deficiency (e.g., height or weight at or below the 10th percentile), craniofacial dysmorphology (e.g., short epicanthal folds, long philtrum, and short palpebral fissures), and evidence of CNS dysfunction. The remaining 16 children, who did not meet all diagnostic criteria but had confirmed histories of gestational exposure to alcohol, were classified as having heavy prenatal exposure to alcohol.

Control Group—The non-exposed CON group consisted of 22 typically developing children also enrolled at the CBT. Participants were screened via phone interview and parent questionnaire. Children were excluded from the CON group if greater than minimal prenatal alcohol exposure (less than or equal to one drink per week on average and never more than two drinks on any one occasion during pregnancy) was known or suspected or if information was unavailable. The CON group was also assessed using the same neuropsychological evaluation as for ALC children.

Apparatus

The force apparatus consisted of a 15-mm diameter circular response key mounted 0.2 mm above a 1.27 cm force transducer (ELFS-B3, range 2-20lbs, sensitivity 7.8mV/lb, voltage range 10 volts; Entran Devices, Fairfield, NJ). The circular response key rested directly above the load cell, and a response involved developing force against an immovable load cell. Force applied to the circular response key was registered by the transducer, amplified, and sampled at a rate of 100 samples per second (16-bit analog-to-digital board; National Instruments, Austin, TX) using customized software based on LabView programming (National Instruments, Austin, TX). Two computer wrist pads were placed in front of the response key, and the participant rested the base of his or her hand on the pads during testing. A flat-screen computer monitor (51 cm diagonal measure, 1280×1024; Dell, Round Rock, TX) was placed 0.5 ft in front of the participant and displayed the target force and participant's force response (see Figure 1).

Procedures

Prior to testing, informed consent was obtained from the legal guardian and assent from the child in compliance with procedures approved by the San Diego State University Institutional Review Board. Throughout testing, the participant maintained a standard position relative to the apparatus. The child sat upright in a height adjustable chair positioned approximately 30 cm in front of the computer monitor with the dominant

shoulder and arm aligned with the response key. The dominant hand rested in a pronated position on the wrist pads with the distal pad of the index finger placed on the response key; the thumb and other fingers were flexed and did not contact the response key. The participant applied force in the sagittal plane about the metacarpophalangeal joint while the proximal and distal interphalangeal joints were locked in extension. The non-dominant hand was placed in the child's lap throughout testing. The general protocol of the experiments was based on experimental procedures previously described by Deutsch and Newell (2001).

Maximal Force Determination—In order to normalize force across participants, each child's maximum voluntary force (MVF) was determined by having the participant use his or her extended index finger to apply maximum force to the response key. Orientation of the hand and fingers relative to the response key was identical for testing of isotonic force and determination of MVF. Four MVF trials were recorded, each lasting four seconds. Only values from the last three trials were used to determine the average MVF estimate for each participant. This estimate was used in the experiment to produce a criterion target force curve, the peak amplitude of which was equivalent to 5 or 20 percent of the participant's average MVF.

Isotonic Force Responses—Following assessment of MVF, the participant completed a series of isotonic force contractions. Trials began with the appearance of a red bell-shaped curve, representing the criterion target force. The curve was centered vertically and horizontally on the monitor and remained in view for the duration of the trial. For each trial, participants were instructed to apply force to the response key, which caused a series of yellow dots to unfold from left-to-right across the monitor over time for the duration of the trial. The dots deviated vertically with changes in force, as the participant increased or decreased force on the response key. Verbal instructions indicated that the goal of the task was to superimpose the yellow dots on the red curve by adjusting the amount of force applied to the response key (see Figure 1).

The yellow dots provided visual feedback of the participant's force output and were manipulated to appear at high (every 20 ms; 50 Hz), moderate (every 320 ms; 3.1 Hz), or low frequencies (every 740 ms; 1.4 Hz). Participants were also given knowledge of their results at the end of each trial. A dialogue box displayed the average deviation of their force response from the target force (root-mean-square error; RMSE), and children were informed that a lower RMSE score indicated a more accurate performance. Children were also periodically provided with general verbal encouragement that provided qualitative information about their response.

Participants responded at force levels of 5% and 20% of MVF. At each force level, participants performed six trials at each of the three visual feedback conditions (low, moderate, and high). The order of force level and feedback condition was counterbalanced across participants. Each trial lasted 20 seconds, and participants were given 10 seconds of rest between each trial. The first trial in each set of six trials served as a practice trial and was not included in the analyses. A trial was considered a mistrial if hand position was not maintained throughout the trial, the participant bounced his or her finger on the response key, or the participant was not able to apply force as instructed. Mistrials were recorded and repeated at the end of each trial set.

Measures of Force Regulation

Three outcome measures were used to assess regulation of isotonic force.

Response Error—Response error was estimated using RMSE, which was calculated by subtracting the target force value from the participant's estimated force value across a series of discrete time intervals throughout each trial. The resulting values were successively squared and averaged, and the square root was calculated. This produced a single absolute accuracy score that represents the average response error relative to the criterion target force.

Response Variability—The signal-to-noise ratio (SN ratio) indexed variability of the force response. The SN ratio was calculated by dividing the average force output (i.e., the signal) by the standard deviation (i.e., the noise) of the force output for each trial. Smaller SN ratios indicate greater response variability, while larger SN values signify less response variability.

Signal Complexity—The organization of the force signal produced within each trial was assessed using sample entropy (SampEn; Richman and Moorman, 2000). SampEn characterizes the sequential structure of a signal by quantifying the probability that a response pattern occurring in one epoch of the time series will repeat in subsequent epochs. A signal with a repeating (i.e., predictable) pattern between successive time epochs will have low complexity and a simple structure, with a SampEn value close to 0. On the other hand, a signal with a non-repeating (i.e., unpredictable) pattern will be irregular and relatively complex in organization, with a SampEn value closer to 2. Greater force signal complexity would be expected with improved perceptual-motor performance (Deutsch and Newell, 2001; Deutsch and Newell, 2004). The length of the epoch over which the signal is evaluated was designated as m , and the tolerance that successive points will match is signified as r . In the present experiment, $m = 3$, $r = 0.2$, and the time series was normalized with the mean set to zero and the standard deviation at 1.0.

Data & Statistical Analyses

Demographic Information—Participant demographic data, including gender, age, race, ethnicity, handedness, FSIQ, and socioeconomic status (SES), as measured by the Hollingshead Four Factor Index of Social Status, were analyzed using independent t-tests.

Measures of Force Regulation—The first seven seconds of each trial were discarded to exclude initial adjustments in reaching the target force level, and the remaining 13 seconds of data were used to calculate performance characteristics and quantify force signal structure. Raw scores within each condition for each group were examined for outlier scores, and values exceeding 2.5 standard deviations about the mean were excluded from statistical analyses. Number of mistrials and average MVF were analyzed using independent t-tests.

The five trials generated for each response condition were averaged. Isotonic force outcome variables were analyzed using a 2 (Group) $\times$ 2 (Force) $\times$ 3 (Feedback) repeated measures analysis of covariance (ANCOVA). Group (ALC and CON) was a between-subjects factor, and Force (5% and 20% of MVF) and Feedback (high, moderate, and low) were within-subject factors. Mauchly and Levene's tests were used to examine the assumptions of sphericity and homogeneity of variance, respectively. The Greenhouse-Geisser conservative estimate of degrees of freedom was used in cases of violations of sphericity; likewise, the Games-Howell multiple comparison procedure was used if variances were not homogeneous. Age was included as a covariate for all analyses. Significant main effects and interactions were followed up with univariate ANOVA. Significance levels were set at $p < .05$.

Results

Demographic Information

The ALC and CON groups did not differ on gender, age, SES, race, or handedness ($p > .05$). The CON group had more Hispanic participants than the ALC group ($p < .05$). Analysis of FSIQ revealed differences between groups. The ALC group had significantly lower FSIQ than the CON group ($p < .001$). A summary of demographic information for both groups is listed in Table 1.

Maximum Voluntary Force

The average MVF for the CON and ALC groups was 31.18 newtons (N) (SD = 9.57) and 30.61 N (SD = 13.12), respectively. Groups did not significantly differ on average MVF values [$t(44) = -0.168, p > .05$].

Exemplar Isotonic Force Production Responses

Figure 2 shows the representative isotonic force-time curves for two age-matched children: (A) a 10.9 year-old typically developing child in the CON group and (B) a 10.8 year-old child in the ALC group with a confirmed history of heavy prenatal alcohol exposure but without a diagnosis of FAS. Graphs show isotonic force signals when replicating a target force of 20% MVF at conditions of low, moderate, and high feedback. The solid black bell-shaped line represents the target isotonic force. Qualitatively, these graphs illustrate that as visual feedback decreased, the difference between the target force and generated force response increased for both children. However, regardless of visual feedback, the alcohol-exposed child was considerably less accurate and more variable in responding than the control participant.

Measures of Force Regulation

Mistrials—On average, the CON group made 0.32 number of mistrials (SD = 0.78), and ALC group made 1.04 (SD = 1.46). The difference in number of mistrials between groups did not reach statistical significance [$t(43) = 1.859, p = .07$]. One child in the ALC group produced outlier values for number of mistrials; as a result, his data were not included in the mistrial analysis.

Response Error—Analysis of performance RMSE revealed a significant main effect of Group [$F(1,43) = 4.99, p = .031, \eta^2 = .10$] and a Group $\times$ Feedback interaction [$F(2,86) = 6.28, p = .003, \eta^2 = .13$] (see Figure 3). The ALC group produced significantly greater response error than the CON group, regardless of force level (Figure 3A). Age was a significant covariate in this analysis [$F(1,43) = 6.55, p = .014, \eta^2 = .13$]. Age and RMSE were inversely associated ($\beta = -.073$), with younger children producing greater response error than older children. No significant main effects were found for Force or Feedback, and no other significant interactions were revealed (p 's $> .05$).

Given the significant Group $\times$ Feedback interaction, follow-up analyses examined group performance across different levels of visual feedback. The ALC group performed with comparable accuracy as the CON group at high [$F(1,43) = .983, p = .327$] and moderate [$F(1,43) = 2.97, p = .09$] levels of visual feedback. However, at low feedback, the ALC group produced significantly greater RMSE values than the CON group [$F(1,43) = 8.10, p = .007$] (Figure 3B).

Response Variability—The SN data revealed a significant main effect of Group [$F(1,43) = 5.28, p = .027, \eta^2 = .11$] as well as a significant Group $\times$ Force interaction [$F(1,43) = 11.0$,

$p = .002$, $\eta^2 = .20$] (see Figure 4). Regardless of visual feedback, the ALC group produced smaller SN ratios than the CON group (Figure 4B). Age was not a significant covariate in this analysis [$F(1,43) = .054$, $p = .818$, $\eta^2 = .11$]. No significant main effects were found for Force or Feedback.

Further investigation of the Group $\times$ Force interaction by examining group SN ratios at each force level revealed a significant difference between the ALC and CON groups at 5% MVF [$F(1,43) = 7.87$, $p = .008$] but not at 20% MVF [$F(1,43) = .971$, $p = .330$] (Figure 4A). The SN ratio of the CON group was higher at 5% MVF compared to 20% MVF, whereas the SN ratio of the ALC group was similar at either 5% or 20% MVF.

Signal Complexity—Analysis of the SampEn data revealed a significant main effect of Group [$F(1,43) = 9.078$, $p = .004$, $\eta^2 = .174$] and a Group $\times$ Feedback interaction [$F(2,86) = 3.33$, $p = .040$, $\eta^2 = .072$] (see Figure 5). The ALC group produced lower SampEn values than the CON group, regardless of force level (Figure 5A). Age was a significant covariate in this analysis [$F(1,43) = 8.14$, $p = .007$, $\eta^2 = .16$], and a significant Age $\times$ Feedback interaction was revealed [$F(2,86) = 9.25$, $p < .001$, $\eta^2 = .16$]. SampEn values increased with age ($\beta = .006$), and younger children produced force signals with less signal complexity than older children. The Age $\times$ Feedback interaction indicates that as age increased the effect of visual feedback on SampEn increased. Specifically, as children aged there was a significantly greater effect of high feedback on SampEn than moderate [$F(1,43) = 13.9$, $p = .001$] or low [$F(1,43) = 5.19$, $p = .013$] feedback. No significant main effects were found for Force or Feedback, and no other significant interactions were found (p 's $> .05$).

The Group $\times$ Feedback interaction was further investigated by examining group performance across each level of visual feedback. The ALC group had significantly lower SampEn values than the CON group at high [$F(1,43) = 10.9$, $p = .002$], moderate [$F(1,43) = 5.94$, $p = .019$], and low [$F(1,43) = 5.40$, $p = .025$] feedback. Additionally, interaction contrasts revealed that the magnitude of group differences was significantly larger at high feedback compared to moderate feedback [$F(1,43) = 5.19$, $p = .028$] but not low feedback [$F(1,43) = 3.82$, $p = .057$], although this effect just failed to reach significance (Figure 5B).

Discussion

The present study is the first to investigate isotonic force regulation in children with heavy prenatal alcohol exposure. Given that research has implicated a specific role of the basal ganglia in dynamic isotonic force control (Spraker et al., 2007; Vaillancourt et al., 2004) and that alcohol's teratogenic effects are particularly damaging to the basal ganglia and other neural systems involved in the generation and control of force (e.g., Coles and Li, 2011; Lebel et al., 2011; Mattson et al., 1996), it was predicted that children with prenatal exposure to alcohol would display impaired abilities to regulate isotonic force. The findings of the current study support our hypotheses that this clinical group demonstrates greater response error and variability and reduced signal complexity when producing isotonic force. Specifically, alcohol-exposed children have greater difficulty when force load and visual feedback are low.

The results for response accuracy revealed that children prenatally exposed to alcohol regulated isotonic force with reduced accuracy compared to typically developing children, regardless of force level. However, the data revealed a different pattern of responding when visual feedback was manipulated. Although both ALC and CON groups performed with equal accuracy when given high to moderate levels of visual feedback, children in the ALC group were significantly less accurate in their force signal when feedback was low. This decline in performance accuracy suggests that force regulation in alcohol-exposed children

is highly dependent on visual feedback. As further illustrated in Figure 3B, when RMSE is plotted as a function of feedback, the CON group maintains a relatively constant level of accuracy regardless of feedback, but the accuracy of the ALC group decreases linearly as the rate of feedback decreases. While typically developing children are relatively unaffected by feedback, children with prenatal alcohol exposure are reliant on sensory information in regulating force, a finding that extends previous research of postural balance in alcohol-exposed children (Roebuck et al., 1998) to force regulation.

With regard to response variability, manipulating target force level produced different outcomes in the two groups. At 5% MVF, the ALC group was significantly more variable in responding than the CON group. However, at 20% MVF groups were no longer different; the response variability of the CON group increased to be no different than that of the ALC group. This increase in response variability produced by the CON group is consistent with previous studies suggesting that motor-output variability increases with greater force output (Enoka et al., 1999; Slifkin and Newell, 1999). Performance variability is traditionally interpreted as noise inherent in the sensorimotor system (Schmidt et al., 1979); consequently, as increased force and neuromuscular activation occurs there is a corresponding increase in neuronal activity (Dai et al., 2001; Thickbroom et al., 1998), leading to greater sensorimotor system noise (Jones et al., 2002; Slifkin and Newell, 1999). However, our data indicate that the relationship between response variability and force output does not extend to alcohol-exposed children. For the ALC group, response variability was comparable across target force levels, suggesting that a greater degree of sensorimotor noise may exist within children prenatally exposed to alcohol and equally in situations requiring high or low force output. Furthermore, the ALC group experienced significantly greater force variability regardless of visual feedback, again suggesting that prenatal alcohol exposure is associated with excessive noise in the sensorimotor system. Thus, group differences on response variability depend on force load while accuracy depends on visual feedback.

Finally, SampEn analyses indicated that, across all levels of force and visual feedback, the ALC group generated force responses that were significantly less complex and more repetitive than those produced by the CON group. This regularity of force signal organization may reflect limited use of visual feedback information by alcohol-exposed children to modify their force response, which leads to the generation of a force signal composed of a series of similar oscillations. An example of this type of response is illustrated in Figure 2B. In contrast, typically developing children better integrate the available feedback information with their motor output, facilitating more accurate matching of the target force and resulting in the production of a relatively complex and irregular signal characterized by feedback-based corrections over time (Figure 2A). The interaction between group and feedback further confirms that alcohol-exposed children are less able than typically developing children to integrate visual information with motor output even when feedback was available.

The proposed difference in the way children with and without prenatal alcohol exposure utilize visual feedback is not without empirical foundation. Neuropsychological research has documented impaired visual-spatial perception and visual-motor integration in children with heavy prenatal alcohol exposure (Chiodo et al., 2009; Conry, 1990; Jirikowic et al., 2008; Korkman et al., 1998; Mattson et al., 1998; Uecker and Nadel, 1996). Functional neuroimaging studies reveal that sensorimotor circuits in the basal ganglia respond to feedback information and regulate force duration, force amplitude, and rate of change of the force signal over time (Spraker et al., 2007; Vaillancourt et al., 2004) and are actively involved in sub-movements that correct errors during ongoing dynamic force control (Grafton and Tunik, 2011). The cerebellum, parietal lobe, and frontal motor cortices are also

integral to visual-motor processing (Vaillancourt et al., 2006). Activity in the dorsal premotor cortex, inferior parietal lobule, supplementary motor area, and cingulate motor area is correlated with visual-motor learning, and the bilateral posterior superior parietal lobule and right ventral premotor cortex have been found to be associated with modulation of movements based on feedback control (Grafton et al., 2008). The structure and functional capacity of many of these neural structures can be compromised by prenatal alcohol exposure (Coles and Li, 2011; Lebel et al., 2011).

Another finding of note was the effect of age on isotonic force regulation. Age was a significant covariate for the outcome measures of response error and signal complexity. Across both groups, older children produced force signals that were increasingly accurate and complex compared to younger children. Despite improved performance with age, alcohol-exposed children still exhibited a developmental delay behind typically developing children of the same age. Although this study is only cross-sectional, the age-force trajectory suggests that alcohol-exposed children exhibit a persistent deficit in this parameter of motor control. Future assessment of these children may elucidate whether these deficits are, indeed, long lasting.

Thirty-seven of the children who participated in the current study were also involved in our previous study examining isometric force regulation (Simmons et al., 2011), and findings from our investigations of the two types of force reveal a common profile of deficits within the same cohort alcohol-exposed children. For both types of force, this clinical group generally manifests greater response error and variability in force production as a function of force load and visual feedback. Additionally, alcohol-exposed children produce relatively simplistic and organized isometric and isotonic force signals compared to the more complex and irregular signals characteristic of typically developing children. One notable difference between the two studies is that regulating isotonic force produces SN ratios that are considerably lower (i.e., increased response variability) for all force and feedback conditions and across both groups. The reason for this difference is unclear, but may reflect the relatively greater difficulty of regulating isotonic force. This notion is consistent with previous research suggesting that response variability increases with task difficulty (Deutsch and Newell, 2001; Deutsch and Newell, 2004). Consequently, it would be expected that SN ratios would decrease for both the alcohol-exposed and control group under isotonic force conditions. The SN results for both groups of children when regulating both types of force are consistent with this expectation and indicate that the observed changes in SN ratios are related to the type of force being regulated and not prenatal alcohol exposure, per se. Moreover, many children, regardless of group, made unsolicited anecdotal comments indicating that attempting to match the bell-shaped criterion force curve used in the isotonic experiment was more difficult than replicating the straight target force line used to investigate isometric force.

The findings of the present study are of clinical importance for children with FASD as dysfunctional isotonic force regulation can lead to impairment in performance of daily functional tasks, such as throwing a ball, squeezing a bicycle brake lever, writing with a pen or pencil, and lifting a cup to drink. Deficits in the performance of such daily skills compared to other typically developing peers can carry significant social, emotional, and psychological consequences that may result in reduction in children's self confidence and esteem. These deficits may inhibit social interaction, as alcohol-exposed children may not be able to accomplish certain tasks in school or participate in the same extracurricular activities, such as sports. Furthermore, understanding the mechanisms of dysfunctional force regulation can serve to inform intervention programs aimed to improve motor function in individuals with FASD. Future investigations might focus on developing therapeutic strategies designed to increase feedback and, consequently, facilitate visual-motor

integration that could potentially improve isotonic force production as well as other fine motor control skills in these children and result in meaningful improvements in their daily functioning.

A potential limitation of the present research may be the effects of confounding IQ with motor control, as children with intellectual disability often experience difficulty learning and generalizing skills (including motor ability) (e.g., Elliot and Bunn, 2004). Detailed instructions, clarification, and encouragement were provided by the trained psychometrist, and participants were provided with practice trials. If a child did not appear to comprehend the task, testing was discontinued, and the participant was not included in analyses. Future studies might include an IQ-matched comparison group to determine if prenatal alcohol exposure is associated with impairments in isotonic force regulation after controlling for IQ differences. Furthermore, although children were provided standardized instructions and were closely monitored to ensure procedures were followed as directed, we did not record whether different strategies were used to perform the task. While this may be a potential limitation, we favor the view that in our experiment utilizing different solutions mimics what happens on a daily basis when performing functional skills. Consequently, our investigation has a degree of ecological validity which suggests that group differences observed in the laboratory setting parallel deficits in force regulation that occur when completing motor skills in real world contexts. Thus, despite these limitations, the current study is the first to demonstrate isotonic force regulation deficits in children exposed to heavy levels of prenatal alcohol exposure, elucidating a potential underlying mechanism for poor motor control in this population. Alcohol-exposed participants produced isotonic force signals that were less accurate, more variable, and less complex than those of typically developing children. The observed motor control deficits in producing and maintaining a variable target force are likely due to the vulnerability of brain structures and the peripheral nervous system associated with motor control and force production to prenatal alcohol insult.

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Figure 1.

The force apparatus consisted of a circular response key (A) mounted directly above a load cell force transducer. A monitor displayed the criterion force curve (B), seen as a red bell-shaped line, and visual feedback of the participant's force response (C), seen as yellow dots. Throughout each trial, the participant tried to superimpose his/her force signal over the criterion force curve, increasing and then decreasing force to match the target. Visual feedback was provided manipulated to appear at high, moderate, and low frequencies. In this figure, visual feedback is presented at high frequency.

Figure 2.

Representative isotonic force-time signals for a 10 year-old typically developing child in the CON group (A) and an age-matched child with heavy prenatal alcohol exposure in the ALC group (B). These graphs show force responses when replicating a target force of 20% MVF at conditions of low (left), moderate (middle), and high (right) visual feedback. The bell-shaped line in each graph represents the target force value (20% MVF).

Figure 3. Root-mean-square error (RMSE) for the ALC and CON groups as a function of force level (A) and visual feedback (B). The ALC group produced increased response error regardless of force level and when feedback was low, relative to the CON group. Significant differences are indicated by the asterisk ($p < .05$).

Figure 4. Signal-to-noise (SN) ratios for the ALC and CON groups as a function of force level (A) and visual feedback (B). Compared to the CON group, response variability was greater in the ALC group when force level is low and regardless of visual feedback. Significant differences are indicated by asterisks ($p < .05$).

Figure 5. Sample entropy (SampEn) values for the ALC and CON groups as a function of force level (A) and visual feedback (B). Across all levels of visual feedback and regardless of force level, the ALC group produced isotonic force signals that were significantly less complex and more repetitive in structure, compared to the CON group. For visual feedback (B), the group difference at high feedback was significantly greater than group differences at moderate but not low feedback. Significant differences are indicated by asterisks ($p < .05$).

Table 1

Demographic information for children with heavy prenatal alcohol exposure (ALC) and non-exposed controls (CON).

Variable	ALC	CON
N	24	22
Sex [M:F]	15:9	16:6
Age in years [M (SD)]	11.6 (2.6)	12.6 (3.0)
Range ¹	7.75–17.083	7.417–17.333
FSIQ ² [M (SD)] **	89.1 (13.2)	110.3 (11.4)
SES ³ [M (SD)]	48.5 (10.6)	50.7 (7.1)
Handedness [N (%) Right]	22 (91.7)	19 (86.3)
Race [N (%) White]	15 (62.5)	16 (72.7)
Ethnicity [N (%) Hispanic] *	2 (8.3)	6 (27.3)
FAS Diagnosis [N (%)]	8 (33.3)	0 (0)
ADHD Diagnosis [N (%)]	15 (62.5)	0 (0)

¹ Age distribution was similar between groups.

² Intelligence scores were obtained using the Wechsler Intelligence Scale for Children-III (WISC-III) or Wechsler Intelligence Scale for Children-IV (WISC-IV) depending on the time of the child's enrollment at the Center for Behavioral Teratology. All children, except for three in the CON group, were administered the WISC-IV.

³ Socioeconomic status (SES) was estimated using the Hollingshead Four Factor Index of Social Status (Hollingshead, 1975).

* Significant difference, $p < .05$

** Significant difference, $p < .001$