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The Use of Open- and Closed-Loop Control During Goal-Directed Force Responses by Children with Heavy Prenatal Alcohol Exposure

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Abstract

Background—Many daily functional activities involve goal-directed responses based on open-loop and closed-loop motor control, yet little is known about how children with heavy prenatal alcohol-exposure organize and regulate these two types of control systems when completing a goal-directed force response.

Methods—Children with ($n = 19$) or without ($n = 23$) heavy prenatal alcohol exposure were required to match a target force (25% and 50% of maximum voluntary force) in a specified target time (200 ms, 800 ms, and 2000 ms). Target force and produced force were visually displayed on a computer monitor. The analog force-time record was parsed into two segments: the period beginning from force initiation to the first reversal in force was designated the open-loop phase, and the remainder of the response was the closed-loop phase.

Results—Compared to controls, alcohol-exposed children produced a significantly shorter duration of open-loop control, a higher open-loop phase rate of force development, a shorter time to reach maximum force during the closed-loop phase and greater absolute target force error. Increasing target force magnitude did not differentially alter the performance of the clinical group.

Conclusions—The results indicate that alcohol-exposed children experience deficits in completing goal-directed force responses that likely stem from an alcohol related insult to the CNS. Therapeutic exercises should be designed to re-calibrate internal timing systems and improve visuomotor integration.

Keywords

Prenatal alcohol exposure; open-loop and closed-loop control

INTRODUCTION

Many daily functional activities involve movement to a target, such as inserting a key into a lock (Hughes et al., 2012), or non-movement force responses, such as grasping a pencil with optimum force to prevent slippage during the act of writing (Danion and Sarlegna, 2007). Movement based and non-movement based goal-directed actions of relatively short duration involve an open-loop phase comprised of pre-programmed motor commands that are executed without corrections. For responses of longer duration, the open-loop phase is followed by a closed-loop phase that includes moment-to-moment, visually guided, on-line corrections that shape the latter part of the response (Mosconi et al., 2015).

The present study examined how children with heavy prenatal alcohol-exposure organize open-loop and closed-loop phases of a force matching task and whether selected response characteristics (e.g., time to reach maximum force, etc.) within each phase differ from response characteristics produced by typically developing children. There are at least two reasons to investigate these two phases in this clinical group. First, the teratogenic effects of prenatal alcohol exposure on multiple regions of the brain involved with motor control may result in behavioral deficits in response characteristics during goal-directed behaviors, which could significantly impact everyday functional movements. Identifying these deficits increases our current understanding of motor performance for this clinical group and assists clinicians in designing appropriate therapeutic motor exercises. Second, performing goal-directed daily functional activities, including playing games (Fliers et al., 2008; Kopp et al., 2010), at levels below those achieved by typically developing children can result in stigmatization, verbal ridicule, and bullying (Twyman et al., 2010). Prolonged feelings of rejection or non-conformity can permanently reduce self-image and self-esteem (Cairney et al., 2005; Poulsen et al., 2004). Therefore, motor therapies designed to improve motor control might also ameliorate these negative social and psychological outcomes.

Some of the children in the present study were classified as having fetal alcohol syndrome (FAS), which is characterized by central nervous system (CNS) dysfunction, pre- and/or postnatal growth deficits at or below the 10th percentile, and a distinct pattern of craniofacial anomalies (e.g., smooth philtrum, thin upper lip, and small palpebral fissures) (Jones and Smith, 1973). We also assessed children with histories of heavy prenatal alcohol-exposure, who experience alcohol related insult to the CNS (Norman, 2009), but who do not manifest the facial dysmorphology associated with FAS. Research has shown that both dysmorphic and non-dysmorphic children demonstrate CNS anomalies including reduced overall brain volume (Lebel et al., 2011; Norman et al., 2009), reduced volume and size in the cerebellum and basal ganglia, and atypical development of the corpus callosum and motor cortex (Archibald et al., 2001; Mattson et al., 1996; Sowell et al., 1996).

In this study, children were required to attain a target (i.e., a goal) force by applying force to a response key/load cell unit. Two levels of target force were used (25% and 50% of maximum voluntary force (MVF)) in combination with three different target times (200 ms, 800 ms and 2000 ms). We predicted that for this goal-directed force-matching task both groups would use open-loop control during the initial phase of the response, but the response characteristics generated within the open-loop phase would be different for each group of

children. We also predicted that when the response included a closed-loop phase involving on-line corrections to the force signal, in *utero* alcohol related deficits in visuomotor integration (Sowell et al., 2008) and reduced volumes of the parietal and occipital structures associated with visual processing (Meinties et al., 2014) would adversely affect the response characteristics occurring within this phase. Finally, we predicted that group differences in the response characteristics generated during the open-loop and closed-loop phases would be accentuated with increased target force.

MATERIALS AND METHODS

Participants

Children with histories of heavy prenatal alcohol exposure were recruited from the Center of Behavioral Teratology (CBT) at San Diego State University. Inclusionary criteria were: Full Scale IQ (FSIQ) > 60, confirmed history of heavy maternal alcohol abuse during pregnancy, and English as the primary language. Heavy maternal alcohol consumption—defined as at least 4 drinks per occasion at least once per week or at least 14 drinks per week on average throughout pregnancy—was confirmed using social service, legal and medical records, and responses to questionnaires completed by the legal guardian or biological mother, if possible. Children were also examined by a dysmorphologist using criteria defined by the Dysmorphology Core of the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD). According to the CIFASD guidelines (Mattson et al., 2010), FAS is defined by the presence of 2 of 3 key facial features typical of FAS (short palpebral fissures, smooth philtrum, thin vermilion) and either microcephaly or growth deficiency at or below the 10th percentile for either height or weight, or both. Dysmorphological examination identified 4 children as meeting the criteria for a classification of FAS and 15 children with heavy prenatal exposure but without the dysmorphic sequelae associated with FAS. A preliminary statistical comparison between dysmorphic and non-dysmorphic children on all dependent variables used in the present experiment, and as defined in the Data Analysis section, revealed no differences and children were combined into a single alcohol-exposed group (ALC group).

Twenty-three control children without prenatal alcohol exposure (CON group) were recruited through referral to the CBT, electronic and non-electronic public notices, and through community events such as health fairs. Inclusionary criteria were: FSIQ > 60, no more than minimal exposure to alcohol (defined as no more than 1 drink per week on average and never more than 2 drinks on any one occasion), and English as a primary language. The ALC and CON groups were matched as closely as possible on age, gender, socioeconomic status and handedness. All children were evaluated by a trained psychometrist using a comprehensive neuropsychological test battery that included assessment of FSIQ using the Wechsler Intelligence Scale for Children – Third or Fourth Editions. Demographic information is presented in Table 1. In compliance with Institutional Review Board approved procedures, the legal guardian and child participant signed informed consent and assent forms, respectively prior to any testing.

Apparatus and Methods

The apparatus and visual display of the target and produced force is presented in Figure 1. Participants sat in a height adjustable chair in front of a flat screen computer monitor (51-cm diagonal) positioned on a standard table 0.5 m from the child. Between the participant and the monitor was a circular response key (15 mm diameter) mounted directly above a force transducer (ELFS-B3: 1.27 cm diameter; range 2–20 lbs; sensitivity 7.8 mV/lb; Entran Devices, Fairfield NJ). The underside of the response key contacted the upper surface of the force transducer but did not register any force. Force applied to the response key by the participant was sampled on-line at 100 Hz using a 16-bit analog-to-digital board and customized LabView programming (National Instruments, Austin, Texas, USA).

Each child placed his/her dominant hand (defined as the hand used for writing) in a neutral, pronated position on a computer wrist pad with the distal end of the index finger placed on the response key. The other fingers of the hand did not touch the response key and the non-involved hand was placed in the child's lap or on the table. To initiate testing, the child applied maximum force with an extended index finger to the load cell for 4 seconds. Four maximum force trials were completed with the average of the last 3 trials providing an estimate of MVF. All other force responses produced by the child were normalized with respect to the average MVF value to facilitate between-participant comparisons.

For test trials, the outline of a red rectangular target box was displayed on the monitor throughout the trial. LabView-based customized software was used to standardize the size (4.5 cm wide $\times$ 2.54 cm high) and position (top right quadrant) of the target box on the monitor for all response conditions. With reference to the x-axis, the center of the target box corresponded to a target time of 200 ms, 800 ms and 2000 ms, with the width of the target representing 20% of the target time. With reference to the y-axis, the center of the target box represented a target force of 25% and 50% MVF, with the height of the box being 20% of the target force value. When the participant applied force to the response key, a single yellow line appeared on the monitor and unfolded from left-to-right across the screen; this was the analog record of the force applied to the response key throughout each test trial. Increasing or decreasing force on the load cell caused the yellow line to move vertically up and down, respectively. Children were instructed to gradually apply force to the load cell to 'hit' the target box. The trial was terminated when the child lifted their finger off the response key. The yellow line and target box served as visual feedback. Subsequently, the screen cleared and a new target box reappeared on the monitor in preparation for the next test trial.

There were 6 possible pairings of target time and target force (e.g., 200 ms and 25 % MVF; 200 ms and 50 % MVF). For each combination of target force (25% or 50 % MVF) and target time (200 ms, 800 ms or 2000 ms), children completed 13 trials. The first 5 trials were practice trials and the last 8 trials were test trials used for data analysis. Combinations of target force and target time were counterbalanced across participants. The inter-trial interval was approximately 7 s, during which the experimenter visually inspected the force-time signal on a second computer monitor (unseen by the child) and determined whether a mistrial occurred. A mistrial was defined as the child using more than one finger to apply force to the load cell, double touching the response key, or inadvertently touching the

response key, which prematurely triggered initiation of a trial. Mistrials were repeated within the same trial block. At the conclusion of testing the participant was debriefed and received a small financial incentive for participation.

Data Analysis

Individual force-time curves were processed using a 2nd order reversing low pass Butterworth filter with a cutoff frequency of 20 Hz. Using customized software (LabView), an algorithm applied to each force-time curve identified the first reversal point from increasing (positive) to decreasing (negative) consecutive force values with the reversal lasting a minimum of 140 ms. The criterion of 140 ms was based on published values of the minimum time required for on-line corrections to unexpected perturbations in hand trajectory during goal-directed movements (range 40 ms to 135 ms; Carlton 1981; Prablanc and Martin, 1992; Saunders and Krill, 2005; Wijdenes, Brenner and Smeets, 2011) and changes in force responses to unexpected viscous resistance (149 ms; Grafton and Tunik, 2011). The time between the onset of force application to the reversal point defined the open-loop phase of the response, and the interval between the first reversal point and the produced force returning to zero defined the closed-loop phase. Within the open-loop and closed-loop phases, several key response characteristics of the force-time curve were identified as dependent variables and are illustrated in Figure 2 and defined as follows.

Open-loop phase duration (ms)—The time interval between the onset of force production and the first reversal point in the produced force curve. (Marked A in Figure 2).

Open-loop phase peak force (% MVF)—The produced force value at the first reversal point in the force curve (Marked B in Figure 2).

Open-loop phase rate of force development (N/s)—The amount of force developed during the *open-loop phase* expressed as a function of the duration of the *open-loop phase* (Marked C in Figure 2).

Time to reach maximum force (ms)—Time interval between the onset of force production and time at which maximum force occurred (Marked D in Figure 2).

Target force error (N)—Two target force error measures were used. Algebraic error (CE) about the target force at the target time, which provides a measure of directional biasing in the response (i.e., overshooting and undershooting the target). Absolute error (AE) indexes the unsigned difference between the target force and developed force at the criterion target time (Marked E in Figure 2).

Duration of force response (ms)—The time interval between the onset of developed force and the time at which the developed force returned to a zero value (Marked F in Figure 2).

Statistical Analysis

Participant age, FSIQ, and socioeconomic status (SES) were independently assessed using one-way analysis of variance (ANOVA). For each dependent variable, data were averaged across trials within each response condition and analyzed using a 2 (Group) x 2 (Target Force) x 3 (Target Time) repeated measures ANCOVA. Group (ALC and CON) was a between-subject variable, Target Force (25% and 50% MVF) and Target Time (200 ms, 800 ms and 2000 ms) were within-subject variables and age was treated as a covariate. Significant interactions of two or more variables were further analyzed using univariate ANOVAs, and Bonferroni corrections were used for post-hoc comparisons. Assumptions of sphericity and homogeneity of variance were examined using Mauchly's and Levene's test, respectively. Violations of sphericity prompted use of the Geisser-Greenhouse conservative estimate of degrees of freedom, and violations of homogeneity of variance were addressed by using Games-Howell procedures for post hoc comparisons. Regression slopes were examined for each dependent variable to ensure linearity and homogeneity of regression, and data met these assumptions across groups and conditions for all ANCOVA analyses. FSIQ was not included as a covariate in the analyses given the inappropriateness of covarying a variable on which populations differ and among children with neurodevelopmental disorders (Adams et al., 1985; Dennis et al., 2009) and because controlling for IQ might remove important variance explained given its relationship with motor tasks. Alpha was set to 0.05 for all tests of significance. Data were analyzed using SPSS version 20.0 (SPSS Inc., Chicago).

RESULTS

Exemplar force-time curves for two 14-year old male participants attempting to match a target force of 50% MVF are presented in Figure 3. The top, middle and bottom panels illustrate the produced force at target times of 200 ms, 800 ms and 2000 ms, respectively. The left panels are produced by a child with prenatal alcohol-exposure and the right panels are for a control child. The curves indicate how both groups use open-loop control when the target time is short in duration and closed-loop control as the target time increases.

Demographic Data

Table 1 presents demographic information for the two groups. Contrasts between group age and SES were not significant ($p > .05$), but analysis of FSIQ revealed that the ALC group had a significantly lower average FSIQ score than the CON group ($p < .002$). This latter result is consistent with other studies reporting impaired intellectual functioning associated with prenatal alcohol exposure (Mattson et al., 2011).

Number of Mistrials

The number of mistrials by the ALC and CON groups across all conditions was 15 and 11 respectively, or an average number of mistrials per child of 0.8 and 0.5 in the ALC and CON groups. There were no significant differences in number of mistrials among groups, as verified with Fisher's exact probability.

Force Response Dependent Variables

Group mean values (with standard error) for each dependent variable as a function of target time are presented in Table 2. Analysis of data revealed that target force did not differentially affect force production by either group. Therefore, the data presented in Table 2 is collapsed across target force.

Open-loop phase duration—Analysis of the open-loop phase duration revealed significant main effects of Group, $F(1, 39) = 10.67, p = .0001, \eta^2 = .22$, and Target Time $F(1.15, 44.78) = 3.96, p = .04, \eta^2 = .09$, together with a significant Group x Target Time interaction, $F(1.15, 44.78) = 7.33, p = .007, \eta^2 = .16$. Post hoc analysis of the interaction indicated that alcohol-exposed children produced a significantly shorter open-loop phase than control children at target times of 200 ms, $F(1,39) = 4.09, p = .05, \eta^2 = .09$, 800 ms, $F(1,39) = 4.54, p = .04, \eta^2 = .15$, and 2000 ms, $F(1,39) = 8.59, p = .006, \eta^2 = .18$, with the difference between groups in open-loop phase duration increasing from 35.8 ms to 71.3 ms to 401.0 ms as target time increased from 200 ms to 800 ms to 2000 ms, respectively. Thus, although open-loop phase duration significantly increased for both for the ALC group, $F(2,53) = 35.77, p = .0001, \eta^2 = .57$, and CON group, $F(2,69) = 64.94, p = .0001, \eta^2 = .67$, as the duration of the target time increased from 200 ms to 800 ms to 2000 ms, the magnitude of difference increased as target time increased, creating the interaction. No other main effects or interactions were significant ($p = .05$).

Open-loop phase peak force—A main effect of Target Time indicated that the level of peak force during the open-loop phase significantly decreased (mean values = 42.6 %MVF, 36.9 %MVF, 29.5% MVF) as target time increased from 200 ms to 800 ms to 2000 ms, respectively, $F(1.45, 52.05) = 6.83, p = .006, \eta^2 = .16$. A non-significant Group effect, $F(1, 36) = .51, p = .48, \eta^2 = .01$, for the ALC group (mean = 35.9 %MVF) and CON group (mean = 35.0 %MVF) was indicated. No other main effects or interactions were significant for this dependent variable ($p = .05$).

Open-loop phase rate of force development—Analysis of the open-loop phase rate of force development produced a significant main effect of Group, $F(1, 37) = 4.05, p = .05, \eta^2 = .10$. With data collapsed across target time and target force conditions, the ALC group produced a significantly higher rate of force development (mean = 18.4 N/s) than the CON group (mean = 14.5 N/s). There was no significant difference in rate of open-loop phase force development as a function of Target Force, $F(1, 37) = .44, p = .51, \eta^2 = .01$, or Target Time, $F(1.09, 40.46) = .51, p = .66, \eta^2 = .01$.

Time to reach maximum force—A significant main effect of Target Time, $F(1.62, 61.6) = 81.95, p = .00001, \eta^2 = .68$, indicated that for target times of 200 ms, 800 ms and 2000 ms the time to reach maximum force increased from 307.8 ms, to 818.3 ms, to 1949.5 ms, respectively. Analysis also revealed a significant Group effect, $F(1, 38) = 4.87, p = .03, \eta^2 = .11$. When collapsed across target time ALC children produced a faster time to reach maximum force (1001.2 ms) than the CON children (1049.2 ms). No other main effect or interactions were significant ($p = .05$).

Target force error—Analysis of target force CE revealed no significant main effects or interactions ($p = .05$). When target force error was indexed by AE, a significant main effect of Group, $F(1, 37) = 6.55$, $p = .02$, $\eta^2 = .15$, revealed that the difference between the target force and developed force at the criterion target time was significantly greater for the ALC group (2.5 N) than the CON group (1.8 N). No other main effect or interactions were significant ($p = .05$).

Duration of the force response—A main effect of Target Time, $F(1.55, 57.3) = 190.5$, $p = .00001$, $\eta^2 = .84$, indicated that the duration of the force response significantly increased as a function of target time. For the 200 ms, 800 ms and 2000 ms target times, the mean duration of the response was 319.7 ms, 868.1 ms, and 2028.9 ms, respectively. The mean values for each of these intervals were significantly different ($p < .0001$). No other main effects or interactions were found ($p = .05$).

DISCUSSION

Results revealed that during a goal-directed force matching task children with or without heavy prenatal alcohol-exposure use open-loop control for the initial segment of the produced force. When sufficient time is available to make on-line changes to the force response the open-loop phase is followed by a closed-loop phase of control until the response is completed. However, within each phase the results confirmed that alcohol-exposed children produced different response characteristics than those generated by non-alcohol exposed children. Figure 4 contains two stylized force-matching response curves (the solid line represents the ALC group and the broken line indicates the CON group) together with dialog boxes that provide a summary of the specific differences between the two groups of children within each phase.

The duration of the open-loop phase was significantly shorter for alcohol-exposed children at each target time condition (i.e., 200 ms, 800 ms and 2000 ms), but open-loop peak force was equivalent to that produced by typically developing children. This combination of response characteristics resulted in a significantly greater rate of force development for alcohol-exposed children. These children also attained maximum force in a significantly shorter time than control children. Finally, in addition to producing atypical different timing characteristics during the force responses, alcohol-exposed children also generated greater unsigned target force error (i.e., AE). It should be noted that signed target force error (i.e., CE) did not reveal any group differences (mean CE for the ALC group = 1.8 N and the CON = 1.5 N). This result could indicate that the two groups produced comparable directional response biasing. However, given the significant group difference in AE target force error, the null effect for the CE group comparison might also be the result of cancelling of positive (i.e., overshoot) and negative (i.e., undershoot) scores that can occur with calculations based on CE.

The observed deficits in force production are unrelated to group differences in the duration of the entire force response, as this time interval was identical for both groups of children. Similarly, atypical movement kinematics (e.g., displacement, velocity, etc.) associated with prenatal alcohol-exposure (Domellof et al., 2011) did not influence timing or error deficits

because the force-matching task used in the present study did not involve movement of the index finger or response key.

The atypical force-matching response characteristics noted for the ALC group may reflect CNS damage resulting from prenatal alcohol insult. For example, neuroimaging studies indicate the right inferior parietal-right frontal lobe structures involved in response inhibition (Mars et al., 2007) are sensitive to prenatal alcohol insult (Fryer et al., 2007). Without appropriate inhibition of the timing process, open-loop peak force and maximum force could be attained earlier than would be typically expected. In a similar vein, during the closed-loop phase of a response, the bilateral parietal cortex, left motor and premotor cortex are actively involved with regulating the force response, with initiation of online corrections occurring in the cerebellar and basal ganglia networks (Grafton and Tunik, 2011; Tunik et al., 2009).

Many of these CNS structures also represent neural correlates of implicit and explicit learning (Yang and Ping, 2012). Our force-matching task involves both forms of learning, with sensory information from the finger contacting the load cell (i.e., implicit learning) and visual information generated by tracking the produced force on a monitor (i.e., explicit learning) being used to scale force (Buckingham et al., 2011). Again, alcohol related damage to these CNS structures (Donald et al., 2015; Sowell et al., 2008), could negatively impact implicit and explicit learning that is expressed as atypical target force responses in alcohol exposed children.

The combination of a shorter open-loop phase and greater target force error during the longer target time response condition (i.e., 2000 ms) reveals another difference in the way the ALC and CON groups of children approach the force-matching task. Given that the response duration is the same for both groups, a truncated open-loop phase results in alcohol-exposed children generating a longer closed-loop phase, which provides additional time for on-line corrections to the produced force. However as previously noted, these children also generate greater AE target force error than control children, which suggests that, even with extra time, prenatal alcohol-exposure impairs the ability to appropriately adjust the produced force. This result may be a consequence of deficits in visuomotor integration observed at the behavioral (Uecker and Nadal, 1996) and CNS levels (Sowell et al., 2008; Staines et al., 2002) in alcohol-exposed children. The mechanism of visuomotor integration in alcohol exposed children is not well understood, but if integration of visual input and motor output cannot be established, or is degraded, a child must resort to estimating and executing the motor commands of the required response with minimal alteration, even if the estimation is inaccurate. In the absence of any correction based on visual input, this error is sustained over time leading to significantly greater target force error (Travios, 1999). In contrast, during the closed-loop phase, typically developing children use visual information to guide the force response towards the target force.

Increasing target force did not have the predicted effect of magnifying group differences in the response characteristics. With respect to AE target force error, this result contrasts with reports of a direct relation between the amount of produced force error and magnitude of target force (Simmons et al., 2012). Exerting low-level force over an extended period of time period (i.e., sustained force) increases fatigue and generates greater response error than

when high force levels are developed within a short time period (Yoon et al., 2007). The combined use of short target force durations (a maximum of 2 s) and comparatively higher levels of target force (25% and 50% MVF) in the present study may have attenuated fatigue build-up and left target force error unaffected.

The results of our study have several practical ramifications for children with prenatal alcohol-exposure when performing daily functional tasks. With regard to open-loop control, reducing the duration of this phase during a functional task, even by a few milliseconds, can adversely affect the accuracy of timing changes in force production. To improve open-loop timing in alcohol-exposed children, the endogenous central timing mechanism must be re-calibrated to levels observed for typically developing children. This may be accomplished by having alcohol-exposed children generate pulses of force in synchrony with a rhythm set by an external time-keeping device, such as a metronome. This form of rehabilitation improves timing accuracy, motor control, and attention in children with attention deficit-hyperactivity disorder (Shaffer et al., 2001) and developmental coordination disorder (Casper et al., 2009), and similar improvements could be expected in alcohol-exposed children.

During closed-loop control, clinical emphasis should be placed on improving visuomotor integration skills. For example, a computer game that displays target and developed forces could include augmented feedback information, such as auditory (e.g., buzzing) and visual cues (e.g., directional arrows, flashing icons, etc.), that accentuate when and how the two forces differ. This form of therapy addresses deficits in visuomotor integration and promotes permanent reduction in target force error by facilitating on-line corrections to the produced force (Patton et al., 2013).

A limitation of the present experiment is that our assessment of goal-directed force in children with or without prenatal alcohol exposure is based on a one-time evaluation. Consequently, it is not possible to determine if the reported deficits associated with prenatal alcohol exposure are due to developmental delay or represent progression along a different trajectory than typically developing children. Differentiating these two possibilities should be the focus of future studies.

The method used to identify the time duration of open- and closed-loop phases of the force waveform may also be a study limitation. The minimal amount of time required to make on-line corrections to a goal-directed force signal is not well defined and, consequently, we adopted a value (i.e., 140 ms) based on several reports investigating the temporal structure of open- and closed-loop control. Use of a different criterion time to determine the first reversal in produced force may reveal a different pattern of responding in the two groups.

In summary, during short goal-directed responses, the magnitude of the open-loop peak force was the same for both groups, but alcohol-exposed children produced a shortened duration of this phase and generated a greater rate of force development than typically developing children. When a longer force response was required and closed-loop control was evident, alcohol-exposed children generated peak force earlier than control children and produced greater target force error. Changing the magnitude of the target force did not alter

the force response produced by the alcohol-exposed children. Elucidation of the nature of motor deficits in children with FASD is critical for establishing effective interventions to improve function.

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References

- Archibald SL, Fennema-Notestine C, Gamst A, Riley EP, Mattson SN, Jernigan TL. Brain dysmorphology in individuals with severe prenatal alcohol exposure. *Dev Med Child Neurol*. 2001; 43:148–154. [PubMed: 11263683]
- Adams KM, Brown GG, Grant I. Analysis of covariance as a remedy for demographic mismatch of research subject groups: some sobering simulations. *J Clin Exp Neuropsychol*. 1985; 7:445–462. [PubMed: 4031027]
- Buckingham G, Ranger NS, Goodale MA. The role of detecting and correcting fingertip force errors during object lifting. *J Vis*. 2011; 11:4.10.1167/11.1.4 [PubMed: 21205872]
- Cairney J, Hay JA, Faught BE, Wade TJ, Corna L, Flouris A. Developmental coordination disorder, generalized self-efficacy toward physical activity, and participation in organized and free play activities. *J Pediatr*. 2005; 147:515–520. [PubMed: 16227039]
- Carlton LG. Processing visual feedback information for movement control. *J Exp Psychol Hum Percept Perform*. 1981; 7:1019–1039. [PubMed: 6457106]
- Cosper SM, Lee GO, Peters SB, Bishop E. Interactive metronome training in children with attention deficit and developmental coordination disorders. *Int J Rehabil Res*. 2009; 32:331–336. [PubMed: 19202457]
- Danion F, Sarlegna FR. Can the human brain predict the consequences of arm movement corrections when transporting an object? Hints from grip force adjustments. *J Neurosci*. 2007; 27:12839–12843. [PubMed: 18032655]
- Dennis M, Francis DJ, Cirino PT, Schachar R, Barnes MA, Fletcher JM. Why IQ is not a covariate in cognitive studies of neurodevelopmental disorders. *J Int Neuropsychol Soc*. 2009; 15:331–343. [PubMed: 19402919]
- Domellof E, Fagaard J, Jacquest AY, Ronnqvist L. Goal-directed arm movements in children with fetal alcohol syndrome: a kinematic approach. *Eur J Neurol*. 2011; 18:312–320. [PubMed: 20629717]
- Donald KA, Eastman E, Howells FM, Adnams C, Riley EP, Woods RP, Narr KL, Stein DJ. Neuroimaging effects of prenatal alcohol exposure on the developing human brain: a magnetic resonance imaging review. *Acta Neuropsychiatr*. 2015; 7:1–19.
- Fliers E, Rommeise N, Vermeulen SH, Altink M, Buschgens CJ, Faraone SV, Sargent JA, Frankie B, Buitelaar JK. Motor coordination problems in children and adolescents with ADHD rated by parents and teachers: effects of age and gender. *J Neural Transm*. 2008; 115:211–220. [PubMed: 17994185]
- Fryer SL, Tapert SF, Mattson SN, Paulus MP, Spadoni AD, Riley EP. Prenatal alcohol exposure affects frontal-striatal BOLD response during inhibitory control. *Alcohol Clin Exp Res*. 2007; 31(8):1415–1424. [PubMed: 17559542]
- Grafton ST, Tunik E. Human basal ganglia and the dynamic control of force during on-line corrections. *J Neurosci*. 2011; 31:1600–1605. [PubMed: 21289168]
- Hughes CM, Seegelke C, Spiegel MA, Oehmichen C, Hammes J, Schack T. Corrections in grasp posture in response to modifications of action goals. *PLoS One*. 2012; 7(9):e43015.10.1371/journal.pone.0043015 [PubMed: 22970119]
- Jones JL, Smith DW. Recognition of the fetal alcohol syndrome in early infancy. *Lancet*. 1973; 2:999–1001. [PubMed: 4127281]

- Kopp S, Beckung E, Gillberg C. Developmental coordination disorder and other motor control problems in girls with autism spectrum disorder and/or attention-deficit/hyperactivity disorder. *Res Develop Dis.* 2010; 31:350–361.
- Lebel C, Rousoutte F, Sowell ER. Imaging the impact of prenatal alcohol exposure on the structure of the developing human brain. *Neuropsychol Rev.* 2011; 21:102–118. [PubMed: 21369875]
- Mars RB, Piekema C, Coles MG, Hulstijn W, Toni I. On the programming and reprogramming of actions. *Cereb Cortex.* 2007; 17:2972–2979. [PubMed: 17389629]
- Mattson SN, Crocker N, Nguyen TT. Fetal alcohol spectrum disorders: Neuropsychological and behavioral features. *Neuropsychol Rev.* 2011; 21:81–101. [PubMed: 21503685]
- Mattson SN, Foroud T, Sowell ER, Jones KL, Coles CD, Fagerlund A, Autti-Ramo I, May PA, Adnams CM, Konvalova V, Wetherill L, Arenson AD, Barnett WK, Riley EP. Collaborative initiative of Fetal Alcohol Spectrum Disorders: Methodology of Clinical Projects. *Alcohol.* 2010; 44:635–641. [PubMed: 20036488]
- Mattson SN, Riley EP, Sowell ER, Jernigan TL, Sobel DF, Jones KL. A decrease in the size of the basal ganglia in children with fetal alcohol syndrome. *Alcohol Clin Exp Res.* 1996; 20:1088–1093. [PubMed: 8892532]
- Meinties EM, Narr KL, van der Kouwe, Molteno CD, Pimia T, Gutman B, Woods RP, Thompson PM, Jacobson JL, Jacobson SW. A tensor-based morphology analysis of regional differences in brain volume in relation to prenatal alcohol exposure. *Neuroimage Clin.* 2014; 5:152–160.10.1016/j.nicl.2014.04.001 [PubMed: 25057467]
- Mosconi MW, Mohanty S, Greene RK, Cook EH, Vaillancourt DE, Sweeney JA. Feedforward and feedback motor control abnormalities implicate cerebellar dysfunctions in autism spectrum disorder. *J Neurosci.* 2015; 35:2015–25.10.1523/JNEUROSCI.2731-14.2015 [PubMed: 25653359]
- Norman AL, Crocker N, Mattson SN, Riley EP. Neuroimaging and fetal alcohol spectrum disorders. *Dev Disabil Res Rev.* 2009; 15:209–217. [PubMed: 19731391]
- Patton JL, Wei YJ, Bajaj P, Scheidt RA. Visuomotor learning enhanced by augmenting instantaneous trajectory error feedback during reaching. *PLoS One.* 2013; 8(1):e46466.10.1371/journal.pone0046466 [PubMed: 23382796]
- Poulsen AA, Ziviani JM. Can I play too? Physical activity engagement of children with developmental coordination disorders. *Can J Occup Ther.* 2004; 71:100–107. [PubMed: 15152725]
- Prablanc C, Martin O. Automatic control during hand reaching at undetected two-dimensional target displacements. *J Neurophysiol.* 1992; 67:455–469. [PubMed: 1569469]
- Saunders JA, Krill DC. Humans use continuous visual feedback from the hand to control both the directions and distance of pointing movements. *Exp Brain Res.* 2005; 162:458–473. [PubMed: 15754182]
- Shaffer RJ, Jacokes LE, Cassily JE, Greenspan SJ, Tuchman RF, Stemmer PJ. Effect of interactive metronome training on children with ADHD. *Am J Occup Ther.* 2001; 55:163–166. [PubMed: 11761131]
- Simmons RW, Nguyen TT, Levy SS, Thomas JD, Riley EP. Children with heavy prenatal alcohol exposure exhibit deficits when regulating isometric force. *Alcohol Clin Exp Res.* 2012; 36:302–309. [PubMed: 22014260]
- Sowell ER, Jernigan TL, Mattson SN, Riley EP, Sobel DF, Jones KL. Abnormal development of the cerebellar vermis in children prenatally exposed to alcohol: size reduction in lobules I–V. *Alcohol Clin Exp Res.* 1996; 20:31–34. [PubMed: 8651458]
- Sowell ER, Johnson A, Kan E, Lu LH, Van Horn JD, Toga AW, O'Connor MJ, Bookheimer SY. Mapping white matter integrity and neurobehavioral correlates in children with fetal alcohol spectrum disorders. *J Neurosci.* 2008; 28:1313–1319. [PubMed: 18256251]
- Staines WR, Padilla M, Knight RT. Frontal-parietal event related potential changes associated with practicing a novel visuomotor task. *Brain Res Cogn Brain Res.* 2002; 13:195–202. [PubMed: 11958962]
- Travlos AK. KR-withdrawal and self-paced motor performance. *Percept Mot Skills.* 1999; 89:1111–1126.
- Tunik E, Houk JC, Grafton ST. Basal ganglia contribution to the initiation of corrective submovements. *Neuroimage.* 2009; 47:1757–1766. [PubMed: 19422921]

- Twyman KA, Saylor CF, Saia D, Macias MM, Taylor LA, Spratt L. Bullying and ostracism experiences in children with special health care needs. *J Dev Behav Pediatr*. 2010; 31:1–8. [PubMed: 20081430]
- Uecker A, Nadal L. Spatial locations gone awry: object and spatial memory deficits in children with fetal alcohol syndrome. *Neuropsychologia*. 1996; 34:209–223. [PubMed: 8868278]
- Wijdenes LO, Brenner E, Smeets JB. Fast and fine-tuned corrections when the target of a hand movement is displaced. *Exp Brain Res*. 2011; 214:453–462. [PubMed: 21874536]
- Yang J, Ping L. Brain networks of explicit and implicit learning. *PLoS One*. 2012; 7:e42993.10.1371/journal.pone.0042993 [PubMed: 22952624]
- Yoon T, Schlinder Delap B, Griffith EE, Hunter SK. Mechanisms of fatigue differ after low- and high-force fatiguing contractions on men and women. *Muscle Nerve*. 2007; 36:515–524. [PubMed: 17626289]

Figure 1.

Front view of the apparatus showing the response key, the force target (rectangle in the top right quadrant) and the produced force. The illustration is for a single trial with a target force of 25% MVF and a target time of 2000 ms.

Figure 2.

A schematic chart illustrating the dependent variables used in the experiment. The solid line represents the force-time analog signal and the rectangle is the target (not drawn to scale). A is the open-loop phase duration; B is the open-loop phase peak force; C is the open-loop phase rate of force development; D is the time to reach maximum force; E is target force error; F is the duration of the force response.

Figure 3.

Exemplar force-time curves generated by an alcohol-exposed (ALC) child and age and gender matched non-alcohol exposed (CON) child. Solid lines in each panel represent trials completed by each child within each response condition and the broken line is the average force-time curve for each block of trials. The panels illustrate the produced force at target times of 200 ms (top panel), 800 ms (middle panel) and 2000 ms (bottom panel), with a target force of 50% MVF. The scale of the x-axis and y-axis is standardized to facilitate comparison between panels. Target force is represented by the solid black square (not drawn to scale) and is located on each panel at the target time.

Figure 4.

Schematic representation of the main findings of the study. The ALC and CON groups are the solid line and dotted lines, respectively. The rectangle is the target. Diagram not drawn to scale.

Table 1

Demographic information for the alcohol exposed group (ALC) and non-alcohol exposed control group (CON).

	ALC	CON	
Sex [M:F (M:F%)]	11:8 (58:42)	11:12 (48:52)	
Age (years) [M (SD)]	14.1 (2.3)	12.9 (2.4)	$p > .05$
FSIQ ¹ [M (SD)]	88.5 (17.8)	107.8 (12.6)	$p < .001$
SES ² [M (SD)]	45.3 (11.8)	48.0 (14.2)	$p > .05$
Handedness [L:R(L:R%)]	2:17(10.5:89.5)	2:21 (8.7:91.3)	
Race N (%)			
African American	2 (11.0)	1 (4.3)	
Caucasian	10 (52.6)	17 (73.9)	
Mixed	6 (31.6)	5 (21.7)	
Asian	1 (5.2)	0	

¹ Intelligence scores were derived from either the Wechsler Intelligence Scale for Children-III or Wechsler Intelligence Scale for Children-IV depending on the time the child enrolled at the CBT.

² Socioeconomic status (SES) was estimated using the Hollingshead Four Factor Index of Social Status (Hollingshead 1975, unpublished data)

Table 2

Mean and standard error values for the alcohol-exposed group (ALC) and non-alcohol exposed group (CON) for each dependent variable as a function of Target Time (200 ms, 800 ms, and 2000 ms). Data are collapsed across Target Force conditions (25% and 50% MVF).

	Group	Target Time (ms)		
		200	800	2000
Open-loop phase duration (ms)	ALC	285.9(12.9)*	677.4(29.8)*	954.1(93.0)**
	CON	321.7(11.7)	748.7(27.0)	1346.1(84.7)
Open-loop phase peak force (% MVF)	ALC	42.7(1.7)	37.4(0.8)	27.7(1.2)
	CON	42.4(1.5)	31.4(0.8)	31.3(1.1)
Open-loop phase rate of force development (N/s)	ALC	34.5(3.1)	12.9(1.0)	7.8(0.9)***
	CON	27.2(2.8)	10.4(0.9)	5.8(0.8)
Time to reach maximum force(ms)	ALC	289.2(13.2)	793.8(21.2)	1920.7(33.5)***
	CON	326.4(12.2)	842.8(19.6)	1978.3(31.0)
Target force error (N)	ALC	2.9(0.3)	2.1(0.2)	2.6(0.2)***
	CON	1.9(0.3)	1.6(0.2)	1.9(0.3)
Duration of force response (ms)	ALC	291.5(15.2)	857.8(20.3)	2006.5(30.8)
	CON	347.9(13.0)	878.3(17.3)	2051.8(26.4)

* significantly different from controls, $p < .05$;

** significantly different from controls, $p < .01$;

*** ALC significantly different from CON when collapsed across all target times