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An Investigation of Intra-Individual Variability in children with Fetal Alcohol Spectrum Disorder (FASD).

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Abstract

Intra-individual variability (IIV) is defined as systematic within person variation in performance either across testing occasions (e.g., test/re-test performance on the same task) or within an occasion (e.g., variations in performance on multiple trials of a single task). Higher levels of IIV)) have been noted as a characteristic of neurodevelopmental disorders such as Attention Deficit/ Hyperactivity Disorder (Geurts et al., 2008), but IIV is yet to be investigated in Fetal Alcohol Spectrum Disorder (FASD). FASD is a term used to describe several conditions resulting from prenatal exposure to alcohol. As part of a comprehensive neuropsychological battery, four study groups (1. fetal alcohol syndrome ⁄ partial fetal alcohol syndrome; 2. static encephalopathy ⁄ alcohol exposed; 3. neurobehavioral disorder ⁄ alcohol exposed as diagnosed using the University of Washington FASD 4-Digit Code; and 4. healthy age-matched children with no prenatal alcohol exposure) were administered measures of motor response and inhibitory control, attention, and adaptive behavior. Results indicated increased levels of IIV in those with FASD compared to controls. IIV was found to uniquely contribute to predicting adaptive behavior above and beyond attention, while attention partially mediated the relationship between IIV and adaptive behavior. This is the first study to our knowledge to show the presence of increased IIV in children with FASD. It additionally provides evidence that IIV measures some inherent variability in performance independent of poor attention in children with FASD.

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Keywords

Fetal Alcohol Spectrum Disorder; Prenatal alcohol; Intra-Individual Variability; Variability; Attention; Adaptive Behavior

Introduction

Fetal Alcohol Spectrum Disorder (FASD) is a broad nonclinical term used to describe several conditions resulting from prenatal exposure to alcohol. FASD has been documented to occur worldwide and according to Roozen et al. (2016), the prevalence of FASD per 1,000 live births in the United States is estimated to be 0.7 for FAS, 2.2 for pFAS, 9.1 for Alcohol-related Neurodevelopmental Disorder (ARND), and 2.6 for Alcohol-related Birth Defects (ARBD). Other diagnostic criteria and terminology have been developed for children with prenatal exposure to alcohol, for example, in Canada ‘FASD’ can now be used as a diagnostic term with specifiers (Cook et al., 2016), rather than a non-clinical umbrella term. This lack of universal criteria and terminology means that children can be given different diagnoses depending on the criteria used. It should be noted that this paper uses terms that are consistent with the University of Washington FASD 4-Digit Code, a case-defined, validated system that characterizes a pattern of growth deficiency, facial dysmorphology, central nervous system (CNS) functional and structural abnormalities, and prenatal alcohol exposure (Astley, 2013). This system derives four diagnoses under the umbrella of FASD: Fetal Alcohol Syndrome (FAS), partial FAS (pFAS), Static Encephalopathy / Alcohol Exposed (SE/AE), and Neurobehavioral Disorder/Alcohol Exposed (ND/AE). There has been an increasing amount of research into the cause, and symptoms of children with FASD, however research is still in the early stages of understanding the widespread effects of prenatal exposure to alcohol (see Kable, et al., 2016; Mukherjee, 2015; and Guerri, Bazinet & Riley, 2009 for a review). In order to expand our understanding of the behavioral outcomes of children with FASD, in this paper we investigate intra-individual variability (IIV) and its relationship with attention, and adaptive behavior in children with FASD.

The individual symptoms seen in those with FASD differ depending on circumstances such as the amount of alcohol consumed by the mother, nutrition, maternal age, the stage of gestation, etc. (Sulik, 2005; May et al. 2013a) therefore, not all symptoms will be present and those that are can be in varying degrees of severity (see Astley, 2013).

Individuals diagnosed with FASD frequently exhibit considerable within group variability in the presentation of symptoms and are clinically noted to exhibit higher levels of variation in performance of academic and daily activities, when compared to typically developing children. For example, variability seen in social communication has been rationalized as being due to children with FASD having deficits in attention and executive function leading to hyperactivity and a lack of awareness of the displeasure of their peers (Kjellmer & Olswang, 2012; for a review see Mattson, Crocker & Nguyen, 2011). Variability has also been seen in motor response times where Simmons and colleagues (2010) found that as the planning demands of a motor task increased, so did the within-group variability and length of response times of the FAS group compared to a control group and prenatal alcohol exposed (PAE) group. There was no difference between the FASD groups and control group when the response planning required was minimal, suggesting that variability in performance between members in the group increased with cognitive demand.

Although considerable information about variability *between* individuals with FASD has been noted, as far as we are aware, to date there have been no studies investigating task performance response variability *within* individuals with FASD, that is, what has been termed intra-individual variability (IIV). IIV is defined as systematic within person variation in performance either across testing occasions (e.g., test/re-test performance on the same task) or at a single occasion (e.g., variations in performance on multiple trials of a single task). Compared to between-person variability, the measurement of IIV adds information related to consistency or stability of performance over time (where high IIV implies low consistency). This type of variability, though not formally measured in children with FASD, has been noted as a common feature of the disorder. A case study by Timler and Olswang (2001) investigated an 8-year old boy diagnosed with FAS to determine discrepancies between parent and teacher determination of the best educational program for him and noted “behavior was inconsistent from day to day” (Timler & Olswang, 2001; p.51) and was not due to intentional disobedience. Similar statements can be found from support forums where parents and guardians of children with FASD report this inexplicable intra-individual variability in their children ranging from social interactions to academic performance. Many forums and information booklets describe these inconsistencies in performance as the child having ‘on’ days and ‘off’ days. Malbin (2004) stated that inconsistencies in memory or performance are a primary behavior in children with FASD and is reflective of the functioning of underlying brain structures. Kjellmer and Olswang (2012) further note that children with FASD exhibit higher levels of variability in social communication. They elaborate that these inconsistencies in communication make interactions with these children unpredictable, especially when they perform similarly to their typically developing peers on some days and not on others. In addition, Olson, Feldman, Streissguth, Sampson & Bookstein (1998), as well as Streissguth and colleagues (1986; 1994; 1995) have documented greater within participant variability in reaction times (i.e., reaction time standard deviation: RTSD) on sustained attention tasks in children with prenatal alcohol exposure, a finding replicated in studies of animals prenatally exposed to alcohol (Hausknecht et. al., 2005).

Intra-individual variability

IIV is defined as a within-person variation in performance either across testing occasions (such as the variability measured for a single person on a single task across multiple occasions spanning short-term (trials) to long-term (days, weeks, etc.)) or at a single occasion (variability for a single person at a single occasion across multiple trials; see MacDonald & Stawski, 2014). Whereas some level of variability is typical, due to practice or fatigue effects, when the variability seen is not a random occurrence but becomes trait-like, and characteristic of that individual’s performance, then it is of clinical interest. It should be noted that a distinction is made between systematic and permanent changes over time, often referred to as intra-individual change (see Nesselroade, 1991), and reversible changes over short periods of time. For the purpose of this paper we will use IIV to mean the latter definition.

IIV appears to be a sensitive predictor of neural dysfunction. An overall increase in IIV has been documented to occur in clinical groups with cognitive difficulties including aging populations (Dykiert, Der, Starr, & Deary, 2012), those with traumatic brain injury (Stuss, Murphy, Binns, & Alexander, 2003; Hill, Rohling, Boettcher, & Meyers, 2013), dementia (MacDonald, Nyberg, & Backman, 2006) as well as in children with attention deficit/ hyperactivity disorder (ADHD), and other neurodevelopmental disorders (Geurts et al., 2008). The study of IIV in aging and traumatic brain injury populations is of interest as it may shed light onto the possible changes in neural structures that can account for this variability in performance. Similarly, it is also of interest when studying young children with neurodevelopmental disorders to understand variations in abilities in these children compared to typically developing peers.

IIV is not a consistent aspect of the neural system, but appears to have a developmental trajectory. In their review of IIV, MacDonald and colleagues (2006) discussed the U-shaped function of IIV over the life-span – in general, IIV is higher in early childhood, begins to decrease into adolescence and adulthood as the neural system becomes more efficient during the natural pruning and myelination processes, and then begins to increase again in later adulthood which is associated with lower efficiency and cognitive decline. Given this connection between a decrease in IIV with synaptic pruning, as this process is compromised in children with prenatal alcohol exposure (Lebel et al., 2012; Treit et al., 2013), it is possible that IIV seen in FASD may be higher than in typically developing children. Lebel et al. (2012) found that in children with FASD, cortical loss over time was positively related to the amount of alcohol exposure prenatally. Specifically, they found that those with FASD did not have increases in cortical volume *before* synaptic pruning began; these increases are seen in typically developing controls. They suggest that these trajectories indicate a lack of plasticity so that when pruning occurs during later years, those with FASD may actually be losing important neural connections thereby decreasing cognitive efficiency (Lebel et al., 2012).

While there are a number of structural central nervous system symptoms associated with FASD (see Wilhelm & Guizzetti, 2015 and Moore et al., 2014 for a review), Treit et al. (2013) investigated abnormalities in the white matter tracts of children with FASD using Diffusion Tensor Imaging (DTI). Two measures used in DTI are fractional anisotropy (FA), which measures the direction of proton diffusion, and mean diffusivity (MD), which measures the magnitude of diffusion. As children typically mature, so too do their white matter connections in the brain allowing for more efficient conduction and a decrease in variability, therefore in DTI maturation is associated with an increase in FA and a decrease in MD. Treit et al. (2013) noted that during development, the FASD group showed some expected changes in white matter (increased FA and decreased MD) but not to the degree of the controls, especially in frontal regions of the brain, suggesting poor myelination as a possible explanation. As IIV is often conceptualized as a metric for efficiency in the neural connections, these findings can be extrapolated to suggest an increase in variability in the FASD group, along with lower efficiency. Indeed, Tamnes, Fjell, Westlye, Ostby, and

Walhovd (2011) reported a decrease in IIV from childhood into adolescence, rationalized as secondary to improved white matter connectivity and maturity. Research has also found evidence supporting differences in more central regions while using DTI to investigate the integrity of white matter connections in the brain of typically developing children (Tamnes et al., 2011) and those with FASD (see Treit et al., 2013). A recent review by Wilhelm and Guizzetti (2015) consolidates research detailing the negative effect of prenatal exposure to alcohol on glial cells that play an essential role in CNS structural development including myelination and plasticity, which may account for the widespread effect of the teratogen on brain development.

IIV and attention

As measures of IIV are typically calculated on tasks that require some level of sustained attention over repeated trials (e.g., continuous performance tasks, go/no-go tasks, etc.), it is important to understand the relationship between IIV and aspects of attention. Kelly et al. (2008) investigated two competing networks with regards to IIV and attention in healthy participants; the ‘task-positive’ network that becomes active during a task and is related to attention, and the ‘task-negative’ network that is deactivated during a task but active at rest (also known as the default mode network; DMN). They found that as the negative correlation between the two networks increased, the variability in performance decreased, meaning performance stabilized as more attention was given to the task. However, when both these networks were activated, and therefore competing with each other, the variability of performance increased especially as the task became more complex. This suggests that as attention becomes more compromised, so (too) does the response to the stimuli. This provides a possible mechanism whereby disorders affecting attention networks may also be associated with increased variability in performance.

Although similar research to Kelly et al. (2008) has not been done with an FASD population, there have been resting state studies investigating the DMN in this population. Specifically, Santhanam et al. (2011) investigated the DMN of adults with prenatal alcohol exposure compared to controls and found, using resting-state fMRI, that the level of deactivation in the DMN was lower for the alcohol-exposed group than for controls. The DMN has higher activity during rest so change is measured in levels of deactivation. Based on the Kelly et al. (2008) findings, less deactivation implies increased competition with the task-positive network. Santhanam et al. (2011) similarly suggested that the lower levels of deactivation seen in the clinical groups implies that there is some competition (attentional modulation) between the DMN and cognitive activity, resulting in dysfunctional or poorer performance by the clinical groups. Castellanos, Kelly, and Milham (2009) describe a similar relation between the DMN and IIV in children with ADHD.

There has also been some research on IIV in children with ADHD, a common comorbid diagnosis with FASD, and a population where within-person *variability* in performance is considered by some researchers to be a *stable* between-person characteristic of the disorder (see Castellanos & Tannock, 2002). Additionally, Gmehlin et al. (2014) investigated attention and inhibition in a population of non-medicated adults with ADHD using IIV and errors of commission and omission on a go/no-go task. They argued that their findings of increased IIV and errors of omission suggest deficits in sustained attention, that disruptions to sustained attention that do not ultimately result in errors of omission instead lead to longer response times, and secondarily increased IIV.

Research by Geurts and colleagues (2008) argues that variability in performance is not specific to ADHD as their findings support increased IIV in children with high functioning autism (HFA), with comorbid Autism spectrum disorder (ASD) and ADHD, as opposed to those with ADHD alone or typically developing children. They supported their findings with the argument that previous studies did not control for comorbidity in their participants; this conclusion is also echoed by studies investigating similar responses in children with HFA, ADHD, and Tourette's syndrome (Verte, Geurts, Roeyers, Oosterlaan, & Sergeant, 2006).

IIV and adaptive behavior

Burton, Strauss, Hunter, and Hultsch (2009) investigated the relationship between IIV and everyday problem solving in older adults. They pointed out that everyday problem solving is an ecologically valid way of measuring an individual's abilities (as opposed to IQ), and determined that those with more inconsistent reaction times (that is, higher IIV) had poorer everyday problem solving abilities thereby suggesting that the IIV measure has some 'functional' relevance. Additionally, studies have pointed to the link between the frontal lobes and adaptive behavior (Schoenbaum, Roesch, & Stalnaker, 2009), as well as the frontal lobes and IIV (Bellgrove, Hester, & Garavan, 2004; MacDonald et al., 2006; Simmonds et al., 2007), thus suggesting a relationship between IIV and adaptive behavior. However, it should be noted that although Burton and colleagues (2009) highlighted that everyday problem solving is a more ecologically valid way of measuring ability than IQ, a relationship between the two constructs does exist. This is not surprising given the overlap in these constructs, and definitions of IQ such as "intelligence is the aggregate or global capacity of the individual to act purposefully, to think rationally and to *deal effectively with his environment*" (Wechsler, 1944, p. 3). Indeed, IQ is typically found to be predictive of adaptive behavior in children with developmental disorders especially in lower functioning groups (Bolte & Poustka, 2002; Duncan & Bishop, 2013; Liss et al., 2001).

Children with FASD have also been documented to exhibit deficits in adaptive behavior when compared to controls on communication, daily living skills, and socialization domains (Crocker, Vaurio, Riley & Mattson, 2009; Jirikowic, Kartin, & Olson, 2008; Rasmussen, Andrew, Zwaigenbaun, & Tough, 2008) and these deficits are significantly more impaired than in children with ADHD. Crocker and colleagues (2009) highlighted that even though there are shared symptoms between children with ADHD and those with FASD, the latter are more impaired on daily living skills, and while children with ADHD tend to improve with age, such a relation is not seen in those with FASD suggesting an "arrest" in development in these skills versus a "delay" (Crocker et al., 2009, p.22).

Aim and hypothesis

The current study aimed to investigate IIV in children with FASD compared to typically developing controls with no prenatal exposure to alcohol. Based on the existing literature, children with FASD are anticipated to have higher levels of IIV when compared to controls.

The relationship between IIV and attention has been outlined in previous studies (e.g., Kelly et al., 2008) as well as the relationship between attention and adaptive behavior (e.g., Clark, Prior, & Kinsella, 2002), and IIV and adaptive behavior (for example Burton, Strauss, Hunter, & Hultsch, 2009). These relationships also lead to the question of how, and if, the assessment of IIV provides any information that is distinct from the assessment of attention, for example in relation to behavioral outcomes such as accounting for adaptive behavior. In other words, is IIV a unique or sensitive measure in an FASD population, as has been proposed in older populations (see Hultsch et al., 2008)? As such, this study also aims to investigate the relationship between IIV, attention, and adaptive behavior: specifically, it is hypothesized that IIV would account for additional variability in adaptive behavior independent of attention. Finally, we hypothesize that attention will mediate the relationship between IIV and adaptive behavior.

Methods

Subjects

The protocol was approved by the University of Washington Human Subjects Review Board. The subjects involved in this study were participants in the FASD MRI/MRS/fMRI study conducted by Astley and colleagues in 2007 (Astley et al., 2009 a, b, c, d). Three FASD groups were chosen from 1,200 patients who were previously diagnosed by an interdisciplinary team in the WA State FAS Diagnostic & Prevention Network (FAS DPN) or clinics using the FASD 4-Digit Code (Astley, 2013; Astley, 2004).

The first group, FAS or Partial FAS (FAS/pFAS; n=20), were children with severe cognitive/behavioral dysfunction and/or CNS structural/neurological abnormalities, and the FAS facial phenotype. These groups were combined because the primary clinical difference between FAS and pFAS is the presence of growth deficiency in the former. The second group, Static Encephalopathy/Alcohol Exposed (SE/AE; n=24), included children with severe cognitive/behavioral dysfunction and/or CNS structural/neurological abnormalities, but without the FAS facial phenotype (the main distinguishing feature from group 1). The FASD 4-Digit Code defines severe cognitive/behavioral dysfunction as 3 or more domains of function (e.g., cognition, memory, language, etc.) that are 2 or more standard deviations below the mean, based on standardized psychometric tools administered by clinicians. The 4-Digit Code ranks severe dysfunction as CNS Rank 3. CNS structural/neurological abnormalities may include microcephaly, structural abnormalities detected on MRI, and/or a seizure disorder. These structural/neurological abnormalities are assigned a CNS Rank 4. The third clinical group, Neurobehavioral Disorder/Alcohol Exposed (ND/AE; n=21) included children with prenatal alcohol exposure and moderate cognitive/behavioral dysfunction. This group did not present with CNS structural/neurological abnormalities or the FAS facial phenotype. Moderate dysfunction is defined by the FASD 4-Digit Code as cognitive/behavioral function or development that is impaired, but insufficient to receive a CNS Rank 3 classification. Moderate dysfunction is classified as CNS Rank 2. The fourth group, Healthy Controls/No Alcohol Exposure (Controls; n=16), included children with no prenatal alcohol exposure, who were healthy and did not present with academic concerns. They were chosen from a large cohort of children who, at birth, were enrolled in a University of Washington study of typical development conducted via the Department of Speech and Hearing Sciences. This registry of children has been maintained over the years to serve as a source of healthy controls for studies throughout the University.

The children in all four groups were balanced on age (within 6 months), gender, and race. See Table 1 for demographic information and Astley et al. (2009a & c) for additional neuropsychological profile data not used in the current study.

IIV measurement

While there are multiple ways of measuring IIV, including simple measures of intra-subject variability such as the intra-individual coefficient of variation (ICV) and the raw-score intra-individual standard deviation (raw-score ISD), in the current study IIV was calculated using a residual ISD method (Hultsch et al., 2008; Geurts et al., 2008; Bielak, Hultsch, Strauss, MacDonald, & Hunter, 2010). In their discussion of methods of calculating IIV using measurements of response times (RT) to simple motor tasks, Hultsch and colleagues (2008) state that this ISD method provides information about either the amount of IIV (analyses investigating short-term variability in behavior), or the form of IIV (analyses aimed at investigating systematic changes over time): the present study seeks to examine the *amount* of IIV. For the 'amount' calculations, Hultsch and colleagues (2008) described the residual ISD method (among others) as a preferred method. The residual ISD method (see Methods: Statistical Procedures) for calculating IIV on reaction time involves saving residual scores for the RT of each individual trial (unpredictable variation) following a regression partialing out confounding variables (e.g., mean RT, systematic time-based effects related to practice or learning) thus leaving only unsystematic trial-to-trial variation. The within-person, across-trial standard deviation of these residual values is known as the residual ISD (see Hultsch et al., 2008; Geurts et al., 2008).

Hultsch et al. (2008) highlighted advantages to using the residual ISD method over the raw-score ISD for the calculation of IIV. One benefit of the residual ISD is that it accounts for the correlation typically observed between intra-individual mean and raw-score ISD. For example, unlike the raw-score ISD method, which may be impacted by between-group variation in performance (e.g., group differences in mean RT), the residual ISD method adjusts for between-group differences in mean RT with linear regression, eliminating this as a potential source of bias. Secondly, residual ISD also allows IIV scores to be adjusted for differences due to systematic within-person variation (variation due to a known mechanism), such as from the effects of fatigue or practice; this is the rationale for including trial sequence as a predictor in the regression model. In summary, residual ISD can be thought of as a "purer" and therefore more construct valid measure of IIV than raw-score ISD. While raw-score ISD reflects both unsystematic and systematic trial-to-trial variation in RT, residual ISD reflects only that within-person variation in RT that is not systematically related to linear change across trials or to group differences in mean RT. Raw score ISD does not adequately capture the phenomenon of interest (seemingly random fluctuations in RT across trials) because it does not isolate unsystematic variance from that which is systematic (i.e. related to differences across trials or between groups).

IIV tasks

All participants completed two tasks (Letters Game & Arrows Game) aimed at assessing unique components of inhibitory control during a task requiring sustained attention. These tasks included a control continuous performance condition (typically simple detection of a stimulus) and an inhibitory condition (requiring participants to attend to salient but irrelevant stimuli). Specifically, in the Letters Game (a go/no-go paradigm), in the control condition single capital letters appeared on a computer screen and participants were required to hit the space bar for ‘X’ trials. In the inhibitory condition participants again hit the space bar for all letters but ‘X’, that is, they were asked to inhibit the response when ‘X’ is on screen (Figure 1A). In the Arrows Game (a game requiring overcoming prepotent motor response), an arrow would appear on screen requiring participants to either push the arrow key pointing in the same direction (control condition) or the opposite direction (inhibitory condition) of the arrow (Figure 1B).

Attention task

All participants completed the Integrated Visual and Auditory (IVA: Tinius, 2003) continuous performance test (CPT). The IVA CPT is a standardized go/no-go type computerized test that simultaneously assesses both visual and auditory aspects of attention providing measures of vigilance, focus, and speed. During the task, participants either see or hear the numbers ‘1’ and ‘2’. They are then expected to respond by clicking a button or mouse when a ‘1’ is seen or heard and to inhibit that response when a ‘2’ is seen or heard. This measure thus produces a separate score for visual and auditory attention that are combined into a “full scale attention quotient.” For the purpose of this study, the full scale attention quotient was used in analyses (See Table 1; additional IVA scores published in Astley et al. (2009c)).

Adaptive behavior measure

The Vineland Adaptive Behavior Scales: Interview Format (VABS: Sparrow, Balla, & Cicchetti, 1984) was completed for each participant by their respective parent or guardian. Adaptive behavior represents the typical performance of an individual, that is, it is meant to assess what an individual actually does, behaviorally, on a daily basis. The VABS is a standardized age-based parent questionnaire containing statements that are rated as ‘usually’, ‘sometimes’, or ‘never’ based on the target individual’s abilities. The statements fall into three major domains (‘Communication’, ‘Daily living skills’, and ‘Socialization’) which combine into an overall ‘Adaptive Behavior Composite’ that was used in the present analyses (See Table 1; additional VABS scores published in Astley et al. (2009c)). The VABS is a common measure used to assess an individual’s deficits in adaptive functioning in order to assist in diagnosis (such as intellectual disability or autism spectrum disorder), to understand the impact of a diagnosis, or to advise intervention planning since it is deemed to be directly applicable to the skills an individual will use in daily living (Cicchetti, Carter, & Gray, 2013).

Statistical procedures

Preparation.—The data for each task (Letters Game and Arrows Game) were analyzed separately for ease of operation. It was firstly prepared by removing participants where there was missing data due to equipment failure or incomplete tasks. As a result, 1 participant from the SE/AE group was removed from the Arrows Game and no participants were removed from the Letters Game analysis. As is standard for the calculation of IIV, implausible outliers in the response times were removed, such as extremely fast responses (less than 150ms; generally indicative of anticipatory errors). Extremely slow responses were thought to be due to distraction from task and were also removed for calculation of IIV. These upper boundaries for slow responses were computed separately for each task: the games differ in presumed complexity and therefore it is thought that the mean response time for each task would reflect this. The upper boundary for each task was equated to the mean RT for the task plus three times its standard deviation. The removal of these outliers in the RTs allow for a more conservative estimation of IIV. In total, for the Letters Game approximately 4% of trials were removed while 2% were removed for the Arrows Game.

Intra-individual variability (IIV).—IIV was indexed by computing intra-individual standard deviations (ISDs) (see Bielak, Hultsch, Strauss, MacDonald, & Hunter, 2010). The ISD represents the variability of each individual’s RT across the individual task trials. Separate ISDs were computed for each condition (control and inhibition) within each task. Because the mean and standard deviation of raw RTs are correlated within persons, the ISD method involves saving the residuals from a regression to partial out effects of possible confounding variables (including trial, condition, and group) to parse the unique variance of each individual. This residual was then converted to a standardized T score (M=50, SD≈10) to allow for comparison across tasks. The final IIV measure is the SD across trials of these T scores - this is the ISD per individual, per condition, per task.

Results

Mean response times

Mixed analysis of variance (ANOVA) was done to compare the main effects of group (between-subjects variable) and condition (within-subjects variable), as well as to determine if an interaction exists between group and condition. For both the Letters and Arrows Game, an investigation of the mean RT between groups for each condition indicated a main effect for condition where, as expected, the mean RT of the inhibition condition was significantly slower than the control condition, $F(1, 77)=49.44$, $p<0.001$, partial $\eta^2=0.39$ and $F(1, 76)=28.23$, $p<0.001$, partial $\eta^2=0.27$ respectively.

A main effect for group was also present $F(3, 77)=3.36$, $p<0.05$, partial $\eta^2=0.12$ and $F(3, 76)=5.03$, $p<0.01$, partial $\eta^2=0.17$ for the Letters and Arrows Game respectively. There was no significant interaction effect. Significant group differences were further explored via the Duncan post hoc test that essentially identifies which group means differ (see Table 2 for mean values and Duncan post hoc groupings).

IIV

IIV estimates per task per condition were compared using a mixed ANOVA to examine main effects of group and condition, and their interaction. Investigation of the IIV for the Letters Game revealed main effects for both Group; $F(3, 77) = 4.33$, $p<0.01$, partial $\eta^2= 0.14$, and Condition; $F(1, 77) = 52.51$, $p<0.001$, partial $\eta^2= 0.41$. No significant interaction effect was found. The variability in the Inhibition condition was higher than that of the Control condition across all groups (see Table 2).

Investigation of the IIV for the Arrows Game revealed a main effect for Group; $F(3,76) = 2.90$, $p<0.05$, partial $\eta^2= 0.10$. There was no significant main effect for Condition nor was there an interaction effect (see Table 2).

Attention and adaptive behavior

A one-way ANOVA revealed significant differences between group performance on attention and adaptive behavior measures: $F(3, 76)=13.39$, $p<0.001$, $\eta^2 =0.35$ and $F(3, 75)=21.12$, $p<0.001$, $\eta^2 =0.46$ respectively.

IIV, attention, and adaptive behavior

Hierarchical regression was utilized to analyze the relationship between these variables, specifically whether IIV accounts for more variation in adaptive behavior above and beyond attention. The total attention quotient was entered into the first block, followed by IIV the Letters Game. This specific IIV score was chosen due to the simplicity of the Letters Game task, thus resulting in a pure baseline measure of IIV.

A hierarchical regression for the full sample was completed. The results indicated an overall significant regression $F(2, 77)=12.66$, $p<0.001$, where attention and IIV together accounted for 25.2% of the variance in adaptive behavior. Attention significantly accounted for 16.8% of the variance in adaptive behavior while IIV significantly accounted for an additional 8.4% of variance in adaptive behavior (see Table 3). Alternatively, IIV was entered into the hierarchical regression first and significantly accounted for 15.0% of the variance in adaptive behavior while attention significantly accounted for 10.3% of variance above and beyond IIV. This suggests that there is shared variance between IIV and attention (approximately 6%), as well as unique contributions, with regards to predicting adaptive behavior.

An additional hierarchical regression analysis was done where IQ was controlled by entering it into the equation first, followed by attention, then IIV. The results indicated a significant regression model $F(3, 77)=25.61$, $p<0.001$, where overall 50.9% of the variance in adaptive behavior was accounted for by IQ, attention, and IIV. Interestingly, after IQ was entered, attention and IIV no longer accounted for any unique significant variation in adaptive behavior. Specifically, IQ accounted for 49.1% of variance in adaptive behavior (see Table 3).

Mediation analysis

A simple mediation analysis was done using ordinary least squares path analysis. Results indicated that IIV indirectly affects levels of adaptive behavior through its effect on levels of attention. As noted in Figure 2 and Table 4, IIV had a negative effect on attention levels (a = −2.949), while attention levels had a positive effect on adaptive behavior (b = 0.282). A bias-corrected bootstrap confidence interval for the indirect effect of IIV on adaptive behavior through its effect on attention (ab = −0.832), based on 10,000 bootstrap samples, did not include zero (−2.021 to −0.096) thus indicating a significant indirect effect. There was also evidence that IIV influenced adaptive behavior independent of its effect through impacting attention (c' = −2.882).

Discussion

The present study investigated the mean RT and IIV of three distinct groups of children with FASD (FAS/pFAS, SE/AE, and ND/AE) and one control group comprised of typically developing children with no prenatal alcohol exposure, using two different tasks. Mean RT and IIV were calculated for each task, group, and condition. The results indicated that overall, the control group was both faster and had lower IIV than the FASD groups.

As expected, the mean RT for the inhibition condition of each task was found to be significantly higher, meaning that the participants responded slower when alternating between an activation and inhibition task. This finding is consistent with this condition as it is more challenging, even if only slightly, than the control condition. The differences in mean RT between groups, across trials and tasks, are reflective of the control group being significantly faster than the FASD groups. Additionally, similar to the report of Simmons et al. (2010), overall RT of both clinical and control groups increased as the difficulty of the task increased, secondary to the greater cognitive processing required for response planning. For this study, not only was the mean RT of both tasks higher on average in the inhibition condition for each group, but it was higher overall for the Arrows Game which required the participant to decide between two differing motor responses (consistent with differences seen in simple versus choice reaction times; Simmons et al., 2010). Simmons et al. (2010) suggest that for children with FASD, the additional increase in RT in motor tasks that require a response selection (such as in the Arrows Game) may be due to alcohol related changes affecting the central nervous system (related to planning time) and peripheral nervous system (related to motor response time).

It has been well established that children tend to be more variable in cognitive performance when compared to adolescents and adults (MacDonald et al., 2006). The present findings on IIV suggest that children on the fetal alcohol spectrum tend to be even more variable than age matched controls on a go/no-go paradigm requiring a motor response. The higher IIV in clinical groups compared to controls possibly adds to the understanding of how prenatal exposure to alcohol can affect the developmental trajectory of the brain. The IIV findings indicated group effects for both tasks where the control group was typically less variable. Whereas Simmons et al. (2010) reported that as cognitive demands of a task increase so does the response variability within an FASD group, our findings take this a step further by indicating that as cognitive demand increases so too does variability *within* an individual with FASD IIV. Our findings are consistent with Geurts et al., (2008) study where they noted that both the mean RT and IIV of their clinical populations where higher than controls.

Visual inspection of the IIV data also revealed that within the clinical groups, the SE/AE group had on average the highest level of IIV compared to the FAS/pFAS and ND/AE group.

To our knowledge, this is the first study to investigate IIV in individuals with FASD, but it is by no means the only neurodevelopmental disorder with this feature: similar findings are reported in children with ADHD, ASD, and Tourette's syndrome (Geurts et al., 2008; Verte et al., 2006). This leads to the question of whether the IIV noted in these populations is any different; that is, is the IIV seen in children with FASD any different from that of children with ADHD, or even those with co-morbid diagnoses, and can we distinguish these groups based on their levels of variability? This is an area that clearly requires further investigation.

A common conclusion in the literature is that IIV is reflective of the integrity of brain structures and may be additionally due to competition between the DMN and the task-oriented network in other populations (Castellanos et al., 2009; Kelly et al., 2008). Although there has been investigation of the DMN in those with FASD (e.g., Santhanam et al., 2011) there has yet to be a direct comparison with levels of IIV in this population. Additionally, the negative impact of alcohol on the developing brain includes impairments in neuronal migration (e.g., Wilhelm & Guizzetti, 2015; Guerri, Bazinet & Riley, 2009), and synaptic pruning (e.g., Lebel et al., 2012; Treit et al., 2013), to name a few. Impairment in these neurodevelopmental processes may additionally contribute to the expression of IIV in this population.

In order to investigate the clinical utility of IIV compared to attention, analyses were done to determine whether IIV accounted for variability in adaptive behavior above and beyond that due to poor attention. With regards to IIV, attention, and adaptive behavior, initial regression results across all groups indicated that attention and IIV together accounted for 25.2% of the variance in adaptive behavior. Attention and IIV shared approximately 6% of this variance, while they also contributed uniquely. Specifically, IIV accounted for an additional 8.4% of the variance in adaptive behavior after the variance accounted for by attention and the shared variance between attention and IIV (totaling 16.8%) was removed, suggesting that IIV does in fact measure something different than basic attention deficits and is not simply a result of poor attention. While attention and IIV have been suggested to be related (Kelly et al., 2008; Gmehlin et al., 2014) the present findings also highlight a unique contribution from each to real life functioning as assessed by an adaptive behavior measure. This finding is similar to that reported by Burton and colleagues (2009) with an aging population where higher IIV was determined to be a useful predictor of activities of daily living. If IIV of reaction time is related to disruptions of underlying neural processes (e.g., Kelly et al., 2008) then it can similarly lead to inconsistency in activities of everyday living (e.g., Timler & Olswang, 2001) reflected as lower levels of adaptive behavior.

On the other hand, previous studies have highlighted the predictive power of IQ regarding adaptive behavior (see Bolte & Poustka, 2002; Duncan & Bishop, 2013; Liss et al., 2001). In the present study, when the impact of IQ on adaptive behavior was controlled (regressed out), neither attention nor IIV accounted for additional variance in adaptive behavior. Therefore, while IIV and attention have unique contributions when predicting adaptive behavior, it appears that IQ remains the best predictor. This may not be surprising given the overlap between these latter two constructs. The focus of adaptive behavior tests is on the measurement of behaviors, including the ability to cope with environmental changes, to learn new everyday skills and to demonstrate independence, which to some extent likely overlaps with their ability to "deal effectively with the environment" as assessed by IQ. Regressing IQ onto adaptive behavior first would indeed remove the 'shared' aspects of adaptive behavior and intellectual ability, perhaps the variability that is most related to IIV and attention. Indeed, Dennis et al. (2009) state that statistically covarying or controlling for a demographic trait that is relevant to and characteristic of a group is misleading and often provides anomalous and counterintuitive findings. In addition, the lack of meaningful relationship between IIV and adaptive behavior when IQ is controlled does not suggest that there is no utility to understanding the role of IIV as it relates to processes such as attention. In fact, IIV has been noted to anticipate the onset and trajectory of changes in cognitive performance in an aging population (Bielak et al., 2010) and may be useful in predicting the same in a younger population. Additionally, it may be worthwhile to investigate whether the role of IIV in predicting adaptive behavior is different in an aging FASD population.

A simple mediation analysis was done to further explore the relationship between IIV and attention when predicting adaptive behavior. Both a direct and indirect relationship was found where IIV directly accounted for variance in adaptive behavior while it also indirectly accounted for variance in adaptive behavior through its influence on attention. While attention did not fully mediate the relationship between IIV and adaptive behavior, it did play a partial role in the relationship (Figure 2). For this analysis, the assumption was that IIV precedes both attention and adaptive behavior in time, that is, IIV influences attention. While some discuss IIV as a result of impaired attention (e.g., Kelly et al., 2008), evidence of IIV being associated with developmental disorders such as ADHD (e.g., Castellanos & Tannock, 2002; Gmehlin et al., 2014), as well as aging (MacDonald et al., 2006) suggests that it may be due to the lack of development or breakdown of processes more basic than levels of attention and may be a cause rather than an outcome of poor attention.

Limitations and future directions

Along with the possible directions outlined throughout the discussion, it would be of worth to investigate the trajectory of IIV in children with FASD over time. It has been previously mentioned that IIV in a typically developing population presents in the form of a U-shaped curve over the lifespan (see MacDonald et al., 2006 for a review). The question remains to be answered as to whether a similar decrease in IIV is seen in children with FASD when they approach adolescence and adulthood, and additionally whether the difference in variability compared to typically developing individuals will hold, as we believe it likely will.

Assessing longitudinally the outcome of a targeted intervention in clinical groups with varying levels of IIV would add more information with regards to the benefits of measuring IIV early on, especially for an age group where IQ testing is unavailable or unfeasible (e.g., younger than 6 years of age, or impaired language). As children become older their requirements/demands for daily living increase which is where we tend to see a departure of clinical groups and typically developing children (Crocker et al., 2009). If there is additional differentiation in this adaptive behavior between groups with varying levels of IIV it may prove useful in determining the level of care required. Finally, other studies investigating IIV have looked at neural and cognitive correlates (e.g., Bellgrove, Hester, & Garavan, 2004), and this is a proposed future direction for this clinical population.

Another important issue to consider is the fact that children with FASD tend to have higher levels of environmental instability such as an increased number of placements in foster care (Streissguth, et al., 2004), and this likely has an effect on brain development. As a result, this environmental instability, in addition to teratogenic effects of alcohol, may contribute to the varying levels of IIV seen in clinical populations. Conversely, due to an unclear cause and effect relationship, high levels of IIV in these children may present an additional challenge when providing care resulting in frequent changes to their living environment. While the current study did not investigate specific contributors to IIV, this may be a relevant future direction.

A limitation to the current study is that IIV was measured from the motor response time of a basic task that is reflective of a test of continuous performance attention that indeed was similar to the way the measure of attention was administered. As a result, future investigations of IIV in this population may benefit from using a response time measure that is not as closely tied to measures of attention. Secondly, after cognitive testing, the control group was found to have cognitive abilities that are in the above average range which may not represent the population of typically developing children however, this may also be a result of excluding participants from the control group if there was any uncertainty of alcohol being consumed prenatally. Thirdly, due to the low sample size of each group, regression analyses were done for all participants and the study lacked sufficient power for looking at whether the impact of IIV in each group was similar. Additionally, a cause and effect relationship cannot be guaranteed based on the simple mediation analyses done. These analyses included specific variables that do not rule out the possible impact of other unmeasured variables. Finally, the correlation found between the variables measured is dependent on the reliability of those measures, that is, how accurately they measure the true score.

Conclusion

Our results are the first to demonstrate an increased level of IIV in children with FASD as compared to typically developing children, and add further information on the effect of prenatal exposure to alcohol. We additionally establish that IIV does contribute uniquely above and beyond attention when predicting the variance in daily adaptive behaviors, and attention acts as a partial mediator between IIV and adaptive behavior.

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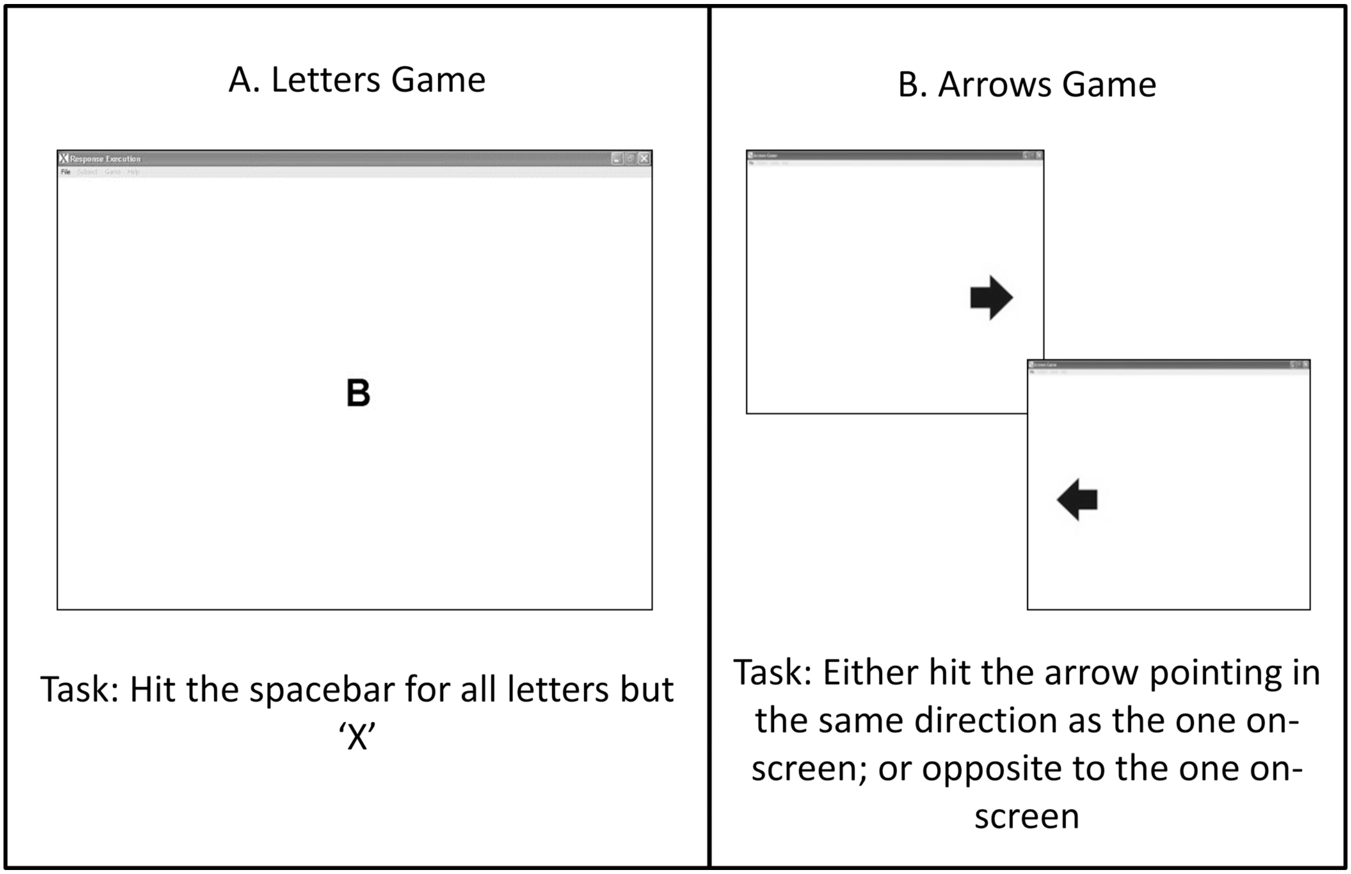

Figure 1.

A screenshot of the Letters Game and Arrows Game tasks

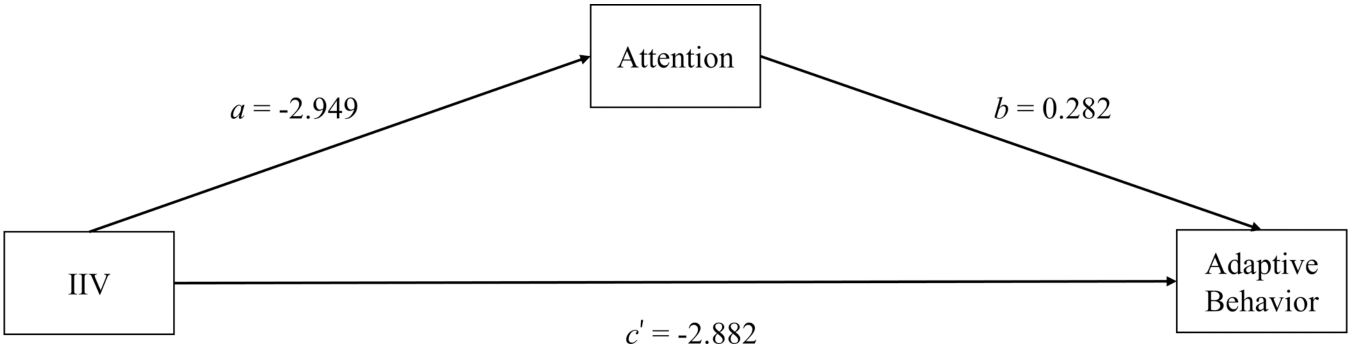

Figure 2.
Simple mediation model of the direct and indirect effects of IIV on adaptive behavior.

Table 1.

Demographic profiles and performance on measures of IQ, Attention and Adaptive Behavior

Characteristics	Group			
	FAS/pFAS ***n*=20**	**SE/AE** ***n*=24**	**ND/AE** ***n*=21**	**CON** ***n*=16**
Gender:				
Female: n (%)	10 (50)	8 (33.3)	10 (47.6)	8 (50.0)
Age in years:				
Mean (SD)	12.7 (2.4)	12.2 (2.0)	12.4 (2.3)	12.4 (2.7)
Race: n (%)				
Caucasian	12 (60.0)	11 (45.8)	12 (57.1)	13 (81.3)
African American	6 (30.0)	4 (16.7)	6 (28.6)	2 (12.6)
Native American	2 (10.0)	7 (29.2)	2 (9.5)	0 (0)
Other	0 (0.0)	2 (8.3)	1 (4.8)	1 (6.3)
FSIQ[1*]:				
Mean (SD)	77.5 (14.4)	79.3 (10.5)	99.2 (11.3)	123.9 (6.5)
Attention[2*]:				
Mean (SD)	59.8 (20.1)	70.9 (22.9)	81.9 (24.7)	103.6 (15.5)
Adaptive Behavior[3*]:				
Mean (SD)	59.0 (17.5)	55.0 (14.2)	65.4 (21.1)	95.3 (12.3)

[*] Standard Score (M= 100, SD= 15)

[1] Wechsler Intelligence Scale for Children, Third Edition (WISC III)

[2] Full Scale Attention Quotient, IVA

[3] Adaptive Behavior Composite, VABS

Table 2.

Means for Response Times (RT), and IIV.

		Letters game			Arrows game		
Group	**Condition**	**N**	**RT (ms)**	**IIV**	**N**	**RT (ms)**	**IIV**
FAS/pFAS (1)	Control	20	385.275	6.263	20	537.366	7.963
	Inhibition		437.828	10.163		651.772	8.453
SE/AE (2)	Control	24	434.738	7.624	23	516.719	9.263
	Inhibition		480.838	11.806		628.128	9.618
ND/AE (3)	Control	21	393.475	6.399	21	456.592	5.764
	Inhibition		447.009	10.337		543.288	6.485
CON (4)	Control	16	367.744	4.560	16	383.491	5.400
	Inhibition		404.654	7.052		439.032	5.483
Duncan Post Hoc Tests			134, 123	123, 4		123, 34	12, 134

Table 3.

Hierarchical regression analyses for Adaptive Behavior.

Variable	β	R^2 change	F change
Model 1			
Attention	0.332	0.168 **	15.389
IIV	−0.300	0.084 *	8.430
Model 2			
IIV	−0.300	0.150 **	13.392
Attention	0.332	0.103 *	10.294
Model 3			
IQ	0.622	0.491 **	73.349
Attention	0.051	0.003	0.426
IIV	−0.135	0.015	2.314

* Correlation significant at the 0.01 level (2-tailed)

** Correlation significant at the 0.001 level (2-tailed)

Table 4.

Model Outcomes for Test of Mediation: Does Attention Mediate the Relationship between IIV and Adaptive Behavior.

		Consequent						
		Attention				Adaptive Behavior		
Antecedent		**Coefficient**	**SE**	***p***		**Coefficient**	**SE**	***P***
IIV	*a*	−2.949	1.249	<0.05	*c'*	−2.882	0.993	<0.01
Attention		—	—	—	*b*	0.282	0.088	<0.01
		$R^2 = 0.068$				$R^2 = 0.252$		
		$F(1, 76) = 5.573$, $p<0.05$				$F(2, 75) = 12.662$, $p<0.001$		