

Child Neuropsychology

A Journal on Normal and Abnormal Development in Childhood and Adolescence

ISSN: 0929-7049 (Print) 1744-4136 (Online) Journal homepage: <http://www.tandfonline.com/loi/ncny20>

An investigation of intra-individual variability in children with fetal alcohol spectrum disorder (FASD)

Sheliza Ali, Kimberly A. Kerns, Bryce P. Mulligan, Heather Carmichael Olson & Susan J. Astley

To cite this article: Sheliza Ali, Kimberly A. Kerns, Bryce P. Mulligan, Heather Carmichael Olson & Susan J. Astley (2017): An investigation of intra-individual variability in children with fetal alcohol spectrum disorder (FASD), *Child Neuropsychology*, DOI: [10.1080/09297049.2017.1302579](https://doi.org/10.1080/09297049.2017.1302579)

To link to this article: <http://dx.doi.org/10.1080/09297049.2017.1302579>



Published online: 16 Mar 2017.



Submit your article to this journal [↗](#)



Article views: 42



View related articles [↗](#)




View Crossmark data [↗](#)

ARTICLE



An investigation of intra-individual variability in children with fetal alcohol spectrum disorder (FASD)

Sheliza Ali ^a, Kimberly A. Kerns^a, Bryce P. Mulligan^a, Heather Carmichael Olson^{b,c} and Susan J. Astley^{d,e}

^aDepartment of Psychology, University of Victoria, Canada; ^bDepartment of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA, USA; ^cSeattle Children's Research Institute, Seattle, WA, USA; ^dDepartment of Epidemiology, University of Washington School of Public Health, Seattle, WA, USA; ^eDepartment of Pediatrics, University of Washington School of Medicine, Seattle, WA, USA

ABSTRACT

Intra-individual variability (IIV) is defined as systematic within-person variation in performance either across test sessions (e.g., test/retest performance on the same task) or in one session (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 (ADHD), but IIV is yet to be investigated in fetal alcohol spectrum disorder (FASD). FASD is a term used to describe a range of 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; 4. typically-developing (TD) age-matched children with no prenatal alcohol exposure) were administered measures of motor response and inhibitory control, attention, and adaptive behavior. The results indicate increased levels of IIV in those with FASD compared to the TD controls. It was found that IIV uniquely contributes to predicting adaptive behavior above and beyond attention, while attention partially mediates the relationship between IIV and adaptive behavior. This is the first study to the authors' 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.



ARTICLE HISTORY

Received 20 June 2016
Accepted 27 February 2017

KEYWORDS

Fetal alcohol spectrum disorder; Prenatal alcohol; Intra-individual variability; Variability; Attention; Adaptive behavior

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 as occurring worldwide and according to Roozen et al. (2016), the prevalence of FASD per 1000 live births in the United States (US) is estimated to be 0.7 for fetal alcohol syndrome (FAS), 2.2 for partial fetal alcohol syndrome (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

CONTACT Sheliza Ali  sheliza@uvic.ca  Department of Psychology, University of Victoria, PO Box 1700 STN CSC, Victoria, BC V8W 2Y2, Canada

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 nonclinical 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 dysmorphism, central nervous system (CNS) functional and structural abnormalities, and prenatal alcohol exposure (Astley, 2013). This system derives four diagnoses under the umbrella of FASD: FAS, pFAS, static encephalopathy/alcohol exposed (SE/AE), and neurobehavioral disorder/alcohol exposed (ND/AE). There has been an increasing amount of research conducted on the cause and symptoms of children with FASD—however, the research is still in the early stages of facilitating a clear understanding of the widespread effects of prenatal exposure to alcohol (for reviews, see Guerri, Bazinet, & Riley, 2009; Kable et al., 2016; Mukherjee, 2015). In order to expand the current understanding of the behavioral outcomes of children with FASD, this paper investigates 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, stage of gestation, etc. (May et al., 2013; Sulik, 2005); therefore, not all symptoms are present in every case, and those that are vary in their degree of severity (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 the performance of academic and daily activities when compared to typically-developing (TD) 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; Simmons, Thomas, Levy, and Riley (2010) found that as the planning demands of a motor task increased, so did the within-group variability and length of response times of their FAS group compared with their control and prenatal alcohol exposed (PAE) groups. There was no difference found between the FASD groups and control group when the response planning required was minimal, suggesting that the variability in performance in individuals with FASD increases with cognitive demand.

Although considerable information about the variability *between* individuals with FASD has been noted, as far as the authors’ are aware, to date there have been no studies investigating task performance response variability *within* individuals with FASD—that is, what has been termed IIV, which is defined as systematic within-person variation in performance either across testing sessions (e.g., test/retest performance on the same task) or on a single session (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 the 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 determinations of the best educational program for him, noting that “behavior was inconsistent from day to day” (Timler & Olswang, 2001, p. 51) and that this 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 IIV 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” and “off” days. Malbin (2004) states that inconsistencies in memory or performance are a primary feature of children with FASD and that this 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, elaborating that these inconsistencies in communication make interactions with these children unpredictable—especially when they perform similarly to their TD peers on some days but not on others. A number of studies have documented greater within-participant variability in reaction times—i.e., reaction time *SD* (RTSD)—on sustained attention tasks in children with prenatal alcohol exposure (Olson, Feldman, Streissguth, Sampson, & Bookstein, 1998; Streissguth, Barr, Sampson, and Parrish-Johnson, 1986; Streissguth, Bookstein, Sampson, & Barr, 1995; Streissguth et al., 1994), a finding replicated in studies of animals prenatally exposed to alcohol (Hausknecht et al., 2005).

Intra-individual Variability (IIV)

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 sessions spanning the short term (trials) to the long term (days, weeks, etc.)—or in a single session—variability for a single person at a single occasion across multiple trials (MacDonald & Stawski, 2014). Whereas some level of variability is typical due to practice and fatigue effects, when the variability seen is not a random occurrence but becomes trait-like and characteristic of an 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 (Nesselrode, 1991), and reversible changes over short periods of time. For the purpose of this paper, IIV is used to mean the latter definition.

IIV appears to be a sensitive predictor of neural dysfunction. An overall increase in IIV has been documented as occurring in clinical groups with cognitive difficulties, including aging populations (Dykiert, Der, Starr, & Deary, 2012), those with traumatic brain injury (Hill, Rohling, Boettcher, & Meyers, 2013; Stuss, Murphy, Binns, & Alexander, 2003), individuals with dementia (MacDonald, Nyberg, & Bäckman, 2006), and 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 on 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 the abilities of these children compared to their TD peers.

IIV is not a consistent aspect of the neural system, but rather appears to have a developmental trajectory. In their review of IIV, MacDonald et al. (2006) discuss 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 and 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 the IIV seen in FASD may be higher than in TD children. Lebel et al. (2012) found that in children with FASD, cortical loss over time is 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 TD 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 (for reviews, see Moore, Migliorini, Infante, & Riley, 2014; Wilhelm & Guizzetti, 2015), 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) notes 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 the 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 (2012) report 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 TD children (Tamnes et al., 2012) and those with FASD (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, Uddin, Biswal, Castellanos, and Milham (2008) investigated two competing networks with regard 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 increases, the variability in performance decreases, meaning that performance stabilizes as more attention is given to the task. However, when both these networks are activated and therefore competing with each other, the variability of performance increases, especially as the task becomes 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 research similar to that of Kelly et al. (2008) has not been conducted on 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 a resting-state functional magnetic resonance imaging (fMRI), that the level of deactivation in the DMN was lower for the alcohol-exposed group than for the controls. The DMN is more active during rest, so change is measured in levels of deactivation. Based on the findings of Kelly et al. (2008), less deactivation implies increased competition with the task-positive network. Santhanam et al. (2011) similarly suggest 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 in 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 conducted 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 in sustained attention that do not ultimately result in errors of omission instead lead to longer response times—and secondarily increased IIV.

Research by Geurts et al. (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 TD children. They support their findings with the argument that previous studies have not controlled for comorbidity in their participants; this conclusion is also echoed by studies investigating similar responses in children with HFA, ADHD, and Tourette’s syndrome (Verté, Geurts, Roeyers, Oosterlaan, & Sergeant, 2006).

IIV and Adaptive Behavior

Burton, Strauss, Hultsch, and Hunter (2009) investigated the relationship between IIV and everyday problem-solving in older adults. They point 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) have 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, & Takahashi, 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 et al. (2009) highlight 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 (Bölte & Poustka, 2002; Duncan & Bishop, 2013; Liss et al., 2001).

Children with FASD have also been documented as exhibiting 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, Zwaigenbaum, & Tough, 2008) and these deficits are significantly more impaired than in children with ADHD. Crocker et al. (2009) highlight 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 aims to investigate IIV in children with FASD compared to TD 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 between IIV and adaptive behavior (e.g., Burton et al., 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 (Hultsch, Strauss, Hunter, & MacDonald, 2008)? As such, this study also aims to investigate the relationship between IIV, attention, and adaptive behavior: specifically, it was hypothesized that IIV would account for additional variability in adaptive behavior independent of attention. Finally, it was hypothesized that attention would be found to mediate the relationship between IIV and adaptive behavior.

Method

Participants

The protocol was approved by the University of Washington Human Subjects Review Board. The individuals involved in this study were participants in the FASD MRI/MRS (magnetic resonance spectroscopy)/fMRI study conducted by Astley and colleagues in 2007 (Astley, Aylward, et al., 2009a, 2009b; Astley, Olson, et al., 2009; Astley, Richards, et al., 2009). Three FASD groups were chosen from 1200 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, 2004).

The first group, FAS/pFAS ($n = 20$), is comprised of 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, SE/AE ($n = 24$), is comprised of 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 three or more domains of function (e.g., cognition, memory, language, etc.) that are two or more SDs 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, ND/AE ($n = 21$), is comprised of children with prenatal alcohol exposure and moderate cognitive/behavioral dysfunction. The children in 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, TD controls ($n = 16$), is comprised of 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 conducted across 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. (2009b) and Astley, Olson, et al. (2009) 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

Table 1. Demographic Profiles and Performance on Measures of IQ, Attention and Adaptive Behavior.

Characteristics	Group			
	FAS/pFAS <i>n</i> = 20	SE/AE <i>n</i> = 24	ND/AE <i>n</i> = 21	Control <i>n</i> = 16
Female, <i>n</i> (%)	10 (50.0)	8 (33.3)	10 (47.6)	8 (50.0)
Age (years), <i>M</i> (<i>SD</i>)	12.7 (2.4)	12.2 (2.0)	12.4 (2.3)	12.4 (2.7)
Race, <i>n</i> (%)				
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 (0.0)
Other	0 (0.0)	2 (8.3)	1 (4.8)	1 (6.3)
FSIQ ¹ *, <i>M</i> (<i>SD</i>)	77.5 (14.4)	79.3 (10.5)	99.2 (11.3)	123.9 (6.5)
Attention ² *, <i>M</i> (<i>SD</i>)	59.8 (20.1)	70.9 (22.9)	81.9 (24.7)	103.6 (15.5)
Adaptive Behavior ³ *, <i>M</i> (<i>SD</i>)	59.0 (17.5)	55.0 (14.2)	65.4 (21.1)	95.3 (12.3)

Note. *Standard score: *M* = 100, *SD* = 15; ¹Wechsler Intelligence Scale for Children – Third Edition (WISC-III; Wechsler, 1991); ²Full-Scale Attention Quotient, Integrated Visual and Auditory Continuous Performance Test; ³Adaptive Behavior Composite, Vineland Adaptive Behavior Scales – Interview Format. FAS/pFAS = fetal alcohol syndrome/partial fetal alcohol syndrome; ND/AE = neurobehavioral disorder/alcohol exposed; SE/AE = static encephalopathy/alcohol exposed.

raw-score intra-individual *SD* (raw-score ISD), in the current study the IIV is calculated using a residual ISD method (Bielak, Hultsch, Strauss, MacDonald, & Hunter, 2010; Geurts et al., 2008; Hultsch et al., 2008). In their discussion of methods of calculating IIV using measurements of reaction times (RTs) to simple motor tasks, Hultsch et al. (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 the IIV (analyses aimed at investigating systematic changes over time); the present study seeks to examine the *amount* of IIV. For the “amount” calculations, Hultsch et al. (2008) describe residual ISD (among others) as a preferred method. The residual ISD method (see the Statistical Procedures section below) for calculating IIV on RT 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 *SD* of these residual values is known as the residual ISD (Geurts et al., 2008; Hultsch et al., 2008).

Hultsch et al. (2008) highlight the advantages of 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 the intra-individual mean and the raw-score ISD. For example, unlike the raw-score ISD method, which may be impacted by between-group variations 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 variations in RT, residual ISD reflects only that within-person variation in RT which is not systematically related to linear change across trials or to group

differences in mean RT. The 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 include 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 appear on a computer screen and the participants are required to hit the space bar for the “X” trials. In the inhibitory condition, the participants hit the space bar for all letters except “X”, that is, they are asked to inhibit the response when “X” is on-screen (Figure 1(a)). In the Arrows Game (a game requiring overcoming prepotent motor response), an arrow appears on-screen requiring participants to either push the arrow key pointing in the same direction (control condition) or the opposite direction (inhibitory condition) as the displayed arrow (Figure 1(b)).

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

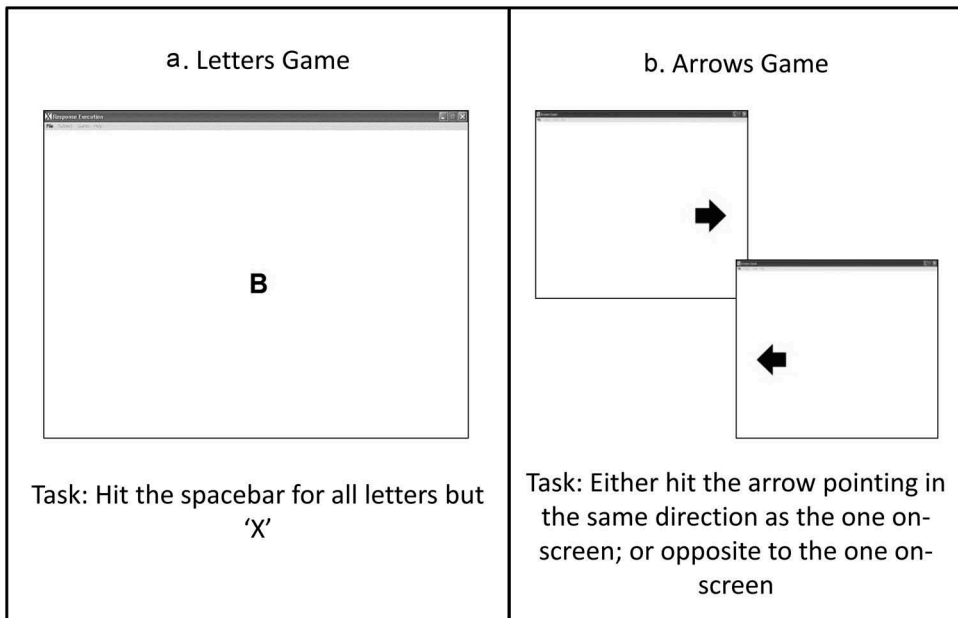


Figure 1. Screenshots of a task for (a) the Letters Game and (b) the Arrows Game.

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 separate scores for visual and auditory attention that are combined into a “full-scale attention quotient”. For the purposes of this study, the full-scale attention quotient is used in the analyses (see Table 1; additional IVA scores are published in Astley, Olson, et al., 2009).

Adaptive Behavior Measure

The Vineland Adaptive Behavior Scales – Interview Format (VABS; Sparrow, Balla, & Cicchetti, 1984) was completed by a parent or guardian of each participant. 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) that combine into the overall Adaptive Behavior Composite that is used in the present analyses (see Table 1; additional VABS scores are published in Astley, Olson, et al., 2009). The VABS is a common measure that is used to assess an individual’s deficits in adaptive functioning in order to assist in diagnosis (such as intellectual disability or ASD), to understand the impact of a diagnosis, or to advise intervention planning, since it is deemed to be directly applicable to the skills that an individual will use in daily living (Cicchetti, Carter, & Gray, 2013).

Statistical Procedures

Preparation.

The data for each task (the Letters Game and the Arrows Game) were analyzed separately for ease of operation. They were firstly prepared by removing participants where there are missing data due to equipment failure or incomplete tasks. As a result, one participant from the SE/AE group was removed from the Arrows Game, while no participants were removed from the Letters Game analyses. As is standard for the calculation of IIV, implausible outliers in the response times were removed, such as extremely fast responses (less than 150 ms, generally indicative of anticipatory errors). Extremely slow responses are thought to be due to distraction from the task and were also removed for the 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 RT for each task will reflect this. The upper boundary for each task was equated to the mean RT for the task plus three times its *SD*. The removal of these outliers in the RTs allows 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 ISDs (see Bielak et al., 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 means and *SDs* 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 ($M = 50$, $SD \approx 10$) to allow for comparison across tasks. The final IIV measure is the *SD* across the trials of these *t*-scores, which is the ISD per individual, per condition, per task.

Results

Mean Reaction Times (RTs)

A mixed analysis of variance (ANOVA) was undertaken 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 Game and the Arrows Game, an investigation of the mean RT between groups for each condition indicated a main effect of condition where, as expected, the mean RT of the inhibition condition, $F(1, 77) = 49.44$, $p < .001$, partial $\eta^2 = .39$, is significantly slower than the control condition, $F(1, 76) = 28.23$, $p < .001$, partial $\eta^2 = .27$.

A main effect for group is also present for the Letters Game, $F(3, 77) = 3.36$, $p < .05$, partial $\eta^2 = .12$, and the Arrows Game, $F(3, 76) = 5.03$, $p < .01$, partial $\eta^2 = .17$. There is 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 the main effects of group and condition and their interaction. Investigation of the IIV for the Letters Game revealed main effects for both group, $F(3, 77) = 4.33$, $p < .01$, partial $\eta^2 = .14$, and condition, $F(1, 77) = 52.51$, $p < .001$, partial $\eta^2 = .41$. 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).

Table 2. Means for Reaction Times (RTs) and IIV.

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

Note. FAS/pFAS = fetal alcohol syndrome/partial fetal alcohol syndrome; ND/AE = neurobehavioral disorder/alcohol exposed; SE/AE = static encephalopathy/alcohol exposed.

Investigation of the IIV for the Arrows Game revealed a main effect for group, $F(3, 76) = 2.90, p < .05$, partial $\eta^2 = .10$. There is no significant main effect for condition, nor is there an interaction effect (see Table 2).

Attention and Adaptive Behavior

A one-way ANOVA revealed significant differences between group performance on attention measures, $F(3, 76) = 13.39, p < .001, \eta^2 = .35$, and adaptive behavior measures, $F(3, 75) = 21.12, p < .001, \eta^2 = .46$.

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 the IIV for 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 indicate an overall significant regression, $F(2, 77) = 12.66, p < .001$, where attention and IIV together account for 25.2% of the variance in adaptive behavior. Attention significantly accounts for 16.8% of the variance in adaptive behavior, while IIV significantly accounts for an additional 8.4% of variance in adaptive behavior (see Table 3). Alternatively, entering IIV into the hierarchical regression first results in it significantly accounting for 15.0% of the variance in adaptive behavior, while attention significantly accounts for 10.3% of the variance above and beyond the IIV. This suggests that there is a shared variance between IIV and attention (approximately 6%), as well as unique contributions, with regard to predicting adaptive behavior.

An additional hierarchical regression analysis was carried out where IQ was controlled by entering it into the equation first, followed by attention, then IIV. The results indicate a significant regression model, $F(3, 77) = 25.61, p < .001$, where overall 50.9% of the variance in adaptive behavior is accounted for by IQ, attention, and IIV. Interestingly, after IQ is entered, attention and IIV no longer account for any unique significant variation in adaptive behavior. Specifically, IQ accounts for 49.1% of the variance in adaptive behavior in this model (see Table 3).

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

Note. *Correlation significant at the .01 level (two-tailed); **Correlation significant at the .001 level (two-tailed).

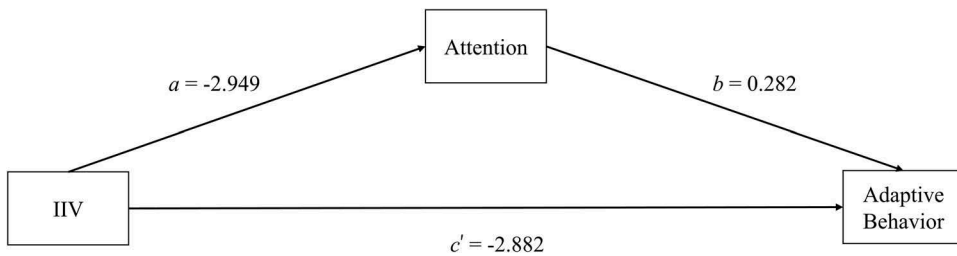


Figure 2. Simple mediation model of the direct and indirect effects of IIV on adaptive behavior.

Table 4. Model Outcomes for Test of Mediation: Does Attention Mediate the Relationship between IIV and Adaptive Behavior?

Antecedent		Consequent						
		Attention			Adaptive Behavior			
		Coefficient	SE	<i>p</i>		Coefficient	SE	<i>p</i>
IIV	<i>a</i>	-2.949	1.249	<.05	<i>c'</i>	-2.882	0.993	<.01
Attention		—	—	—	<i>b</i>	0.282	0.088	<.01
		$R^2 = .068$				$R^2 = .252$		
		$F(1, 76) = 5.573, p < .05$				$F(2, 75) = 12.662, p < .001$		

Mediation Analysis

A simple mediation analysis was carried out using ordinary least-squares path analysis. The results indicate that IIV indirectly affects levels of adaptive behavior through its effect on levels of attention. As noted in Figure 2 and Table 4, IIV has a negative effect on attention levels ($a = -2.949$), while attention levels have 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, does not include zero (-2.021 to -0.096), thus indicating a significant indirect effect. There is also evidence that IIV influences adaptive behavior independent of its effect through impacting attention ($c' = -2.882$).

Discussion

The present study investigates 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 TD children with no prenatal alcohol exposure, using two different tasks. Mean RT and IIV were calculated for each task, group, and condition. The results indicate 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 more slowly 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), the overall RT of both the clinical and control groups increases as the difficulty of the task increases, secondary to the greater cognitive processing required for response planning. For this study, not only is the mean RT of both tasks higher on average in the inhibition condition for each group, but it is higher overall for the Arrows Game, which requires 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 RT increase in motor tasks that require a response selection (such as the Arrows Game) may be due to alcohol-related changes affecting the CNS (related to planning time) and peripheral nervous system (related to motor response time).

It is 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 their age-matched TD peers on a go/no-go paradigm requiring a motor response. The higher IIV in the clinical groups compared to the controls possibly adds to the understanding of how prenatal exposure to alcohol can affect the developmental trajectory of the brain. The IIV findings indicate group effects for both tasks where the control group is typically less variable. Whereas Simmons et al. (2010) report that as the cognitive demands of a task increase so does the response variability within an FASD group, the present findings take this a step further in their indication that as the cognitive demand increases so too does the variability *within* an individual with FASD IIV. The present findings are consistent with those of Geurts et al. (2008), who note that both the mean RT and IIV of their clinical populations were higher than those of the controls. Visual inspection of the IIV data in the present study also reveals 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 groups.

To the authors' 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 have been reported in children with ADHD, ASD, and Tourette's syndrome (Geurts et al., 2008; Verté 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 is it possible to distinguish between 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 additionally be due to competition between the DMN and the task-oriented network in other populations (Castellanos et al., 2009; Kelly et al., 2008). Although the DMN in those with FASD has been investigated (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., Guerri et al., 2009; Wilhelm & Guizzetti, 2015) 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 carried out to determine whether IIV accounts for variability in adaptive behavior

above and beyond that due to poor attention. With regard to IIV, attention, and adaptive behavior, the initial regression results across all groups indicate that attention and IIV together account for 25.2% of the variance in adaptive behavior. Attention and IIV share approximately 6% of this variance, while they also contribute uniquely. Specifically, IIV accounts 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%) is removed, suggesting that IIV does in fact measure something different than basic attention deficits and is not simply a result of poor attention. While it has been suggested that attention and IIV are related (Gmehlin et al., 2014; Kelly et al., 2008), 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 et al. (2009) in an aging population, where higher IIV was determined to be a useful predictor of activities of daily living. If the RT IIV is related to disruptions in 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 (Bölte & Poustka, 2002; Duncan & Bishop, 2013; Liss et al., 2001). In the present study, when the impact of IQ on adaptive behavior is controlled (regressed out), neither attention nor IIV account 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 abilities such as being able to cope with environmental changes, learn new everyday skills and demonstrate independence, which to some extent likely overlap with the 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 the 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 undertaken to further explore the relationship between IIV and attention when predicting adaptive behavior. Both direct and indirect relationships were found where IIV directly accounts for variance in adaptive behavior and also indirectly accounts for variance in adaptive behavior through its influence on attention. While attention does not fully mediate the relationship between IIV and adaptive behavior, it does 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 researchers discuss IIV as a result of

impaired attention (Kelly et al., 2008), evidence of IIV being associated with developmental disorders such as ADHD (Castellanos & Tannock, 2002; Gmehlin et al., 2014) and aging (MacDonald et al., 2006) suggests that it may be due to a lack of development or breakdown of processes that are 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 previously been mentioned that IIV in a TD population presents in the form of a U-shaped curve over the life span (for a review, see MacDonald et al., 2006). The question remains 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 TD individuals will hold, which it is hypothesized—based on the findings in the present study—is likely.

Assessing longitudinally the outcome of a targeted intervention in clinical groups with varying levels of IIV would add more information with regard 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 and demands for daily living increase, which is where there tends to be a departure of clinical groups from TD 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 et al., 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 the 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 does not investigate specific contributors to IIV, this may be a future direction worthy of investigation.

A limitation of the current study is that IIV is measured from the motor RT of a basic task that is reflective of a continuous performance test of attention that indeed is similar to the way in which the measure of attention was administered. As a result, future investigations of IIV in this population may benefit from using an RT 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 TD children; however, this may also be the 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 undertaken 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 carried out in this study, which include 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

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

Acknowledgements

We wish to acknowledge our colleague Dr. Stuart MacDonald for his input on the IIV analyses used in this paper.

Disclosure Statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the NIAAA [grant number R01-AA12915-01A1]; Center on Human Development and Disability, University of Washington (National Institute of Child Health and Human Development grant P30 HD02274).

ORCID

Sheliza Ali  <http://orcid.org/0000-0002-7534-8680>

References

- Astley, S. J. (2004). *Diagnostic guide for fetal alcohol spectrum disorders: The 4-Digit Diagnostic Code* (3rd ed.). Seattle, WA: University of Washington Publication Services.
- Astley, S. J. (2013). Validation of the fetal alcohol spectrum disorder (FASD) 4-Digit Diagnostic Code. *Journal of Population Therapeutics and Clinical Pharmacology*, 20(3), e416–e467.
- Astley, S. J., Aylward, E. H., Olson, H. C., Kerns, K., Brooks, A., Coggins, T. E., . . . Richards, T. (2009a). Functional magnetic resonance imaging outcomes from a comprehensive magnetic resonance study of children with fetal alcohol spectrum disorders. *Journal of Neurodevelopmental Disorders*, 1(1), 61–80. doi:10.1007/s11689-009-9004-0
- Astley, S. J., Aylward, E. H., Olson, H. C., Kerns, K., Brooks, A., Coggins, T. E., . . . Richards, T. (2009b). Magnetic resonance imaging outcomes from a comprehensive magnetic resonance

- study of children with fetal alcohol spectrum disorders. *Alcoholism: Clinical and Experimental Research*, 33(10), 1671–1689. doi:10.1111/j.1530-0277.2009.01004.x
- Astley, S. J., Olson, H. C., Kerns, K., Brooks, A., Aylward, E. H., Coggins, T. E., ... Richards, T. (2009). Neuropsychological and behavioral outcomes from a comprehensive magnetic resonance study of children with fetal alcohol spectrum disorders. *The Canadian Journal of Clinical Pharmacology*, 16(1), e178–e201.
- Astley, S. J., Richards, T., Aylward, E. H., Olson, H. C., Kerns, K., Brooks, A., ... Maravilla, K. (2009). Magnetic resonance spectroscopy outcomes from a comprehensive magnetic resonance study of children with fetal alcohol spectrum disorders. *Magnetic Resonance Imaging*, 27(6), 760–778. doi:10.1016/j.mri.2009.01.003
- Bellgrove, M. A., Hester, R., & Garavan, H. (2004). The functional neuroanatomical correlates of response variability: Evidence from a response inhibition task. *Neuropsychologia*, 42(14), 1910–1916. doi:10.1016/j.neuropsychologia.2004.05.007
- Bielak, A. A., Hultsch, D. F., Strauss, E., MacDonald, S. W., & Hunter, M. A. (2010). Intraindividual variability in reaction time predicts cognitive outcomes 5 years later. *Neuropsychology*, 24(6), 731–741. doi:10.1037/a0019802
- Bölte, S., & Poustka, F. (2002). The relationship between general cognitive level and adaptive behavior domains in individuals with autism with and without co-morbid. *Child Psychiatry and Human Development*, 33(2), 165–172. doi:10.1023/A:1020734325815
- Burton, C. L., Strauss, E., Hultsch, D. F., & Hunter, M. A. (2009). The relationship between everyday problem solving and inconsistency in reaction time in older adults. *Neuropsychology, Development, and Cognition. Section B, Aging, Neuropsychology and Cognition*, 16(5), 607–632. doi:10.1080/13825580903167283
- Castellanos, F. X., Kelly, C., & Milham, M. P. (2009). The restless brain: Attention-deficit hyperactivity disorder, resting-state functional connectivity, and intrasubject variability. *The Canadian Journal of Psychiatry*, 54(10), 665–672. doi:10.1177/070674370905401003
- Castellanos, F. X., & Tannock, R. (2002). Neuroscience of attention deficit/hyperactivity disorder: The search for endophenotypes. *Nature Reviews Neuroscience*, 3, 617–628. doi:10.1038/nrn896
- Cicchetti, D. V., Carter, A. S., & Gray, S. A. (2013). Vineland adaptive behavior scales. In F. R. Volkmar (Ed.), *Encyclopedia of autism spectrum disorders* (pp. 3281–3284). New York, NY: Springer.
- Clark, C., Prior, M., & Kinsella, G. (2002). The relationship between executive function abilities, adaptive behavior, and academic achievement in children with externalizing behavior problems. *Journal of Child Psychology and Psychiatry*, 43(6), 785–796. doi:10.1111/1469-7610.00084
- Cook, J. L., Green, C. R., Lilley, C. M., Anderson, S. M., Baldwin, M. E., Chudley, A. E., ... Mallon, B. F. (2016). Fetal alcohol spectrum disorder: A guideline for diagnosis across the lifespan. *Canadian Medical Association Journal*, 188(3), 191–197. doi:10.1503/cmaj.141593
- Crocker, N., Vaurio, L., Riley, E. P., & Mattson, S. N. (2009). Comparison of adaptive behavior in children with heavy prenatal alcohol exposure or attention-deficit/hyperactivity disorder. *Alcoholism: Clinical and Experimental Research*, 33(11), 2015–2023. doi:10.1016/j.biotechadv.2011.08.021
- Dennis, M., Francis, D. J., Cirino, P. T., Schachar, R., Barnes, M. A., & Fletcher, J. M. (2009). Why IQ is not a covariate in cognitive studies of neurodevelopmental disorders. *Journal of the International Neuropsychological Society*, 15, 331–343. doi:10.1017/S1355617709090481
- Duncan, A. W., & Bishop, S. L. (2013). Understanding the gap between cognitive abilities and daily living skills in adolescents with autism spectrum disorders with average intelligence. *Autism: The International Journal of Research and Practice*, 0(0), 1–9. doi:10.1177/1362361313510068
- Dykiert, D., Der, G., Starr, J. M., & Deary, I. J. (2012). Age differences in intra-individual variability in simple and choice reaction time: Systematic review and meta-analysis. *PLoS One*, 7(10), e45759. doi:10.1371/journal.pone.0045759
- Geurts, H. M., Grasman, R. P., Verté, S., Oosterlaan, J., Roeyers, H., van Kammen, S. M., & Sergeant, J. A. (2008). Intra-individual variability in ADHD, autism spectrum disorders and

- Tourette's syndrome. *Neuropsychologia*, 46(13), 3030–3041. doi:10.1016/j.neuropsychologia.2008.06.013
- Gmehlin, D., Fuermaier, A. B. M., Walther, S., Debelak, R., Rentrop, M., Westermann, C., ... Aschenbrenner, S. (2014). Intraindividual variability in inhibitory function in adults with ADHD – An ex-gaussian approach. *PLoS One*, 9(12), e112298. doi:10.1371/journal.pone.0112298
- Guerra, C., Bazinet, A., & Riley, E. P. (2009). Foetal alcohol spectrum disorders and alterations in brain and behaviour. *Alcohol and Alcoholism*, 44(2), 108–114. doi:10.1093/alcalc/agn105
- Hausknecht, K. A., Acheson, A., Farrar, A. M., Kieres, A. K., Shen, R.-Y., Richards, J. B., & Sabol, K. E. (2005). Prenatal alcohol exposure causes attention deficits in male rats. *Behavioral Neuroscience*, 119(1), 302–310. doi:10.1037/0735-7044.119.1.302
- Hill, B. D., Rohling, M. L., Boettcher, A. C., & Meyers, J. E. (2013). Cognitive intra-individual variability has a positive association with traumatic brain injury severity and suboptimal effort. *Archives of Clinical Neuropsychology*, 28(7), 640–648. doi:10.1093/arclin/act045
- Hultsch, D. F., Strauss, E., Hunter, M. A., & MacDonald, S. W. S. (2008). Intraindividual variability, cognition, and aging. In F. I. Craik & T. A. Salthouse (Eds.), *The handbook of aging and cognition*, 2011 (pp. 492–556). New York, NY: Psychology Press.
- Jirakovic, T., Kartin, D., & Olson, H. C. (2008). Children with fetal alcohol spectrum disorders: A descriptive profile of adaptive function. *Canadian Journal of Occupational Therapy*, 75(4), 238–248. doi:10.1177/000841740807500411
- Kable, J. A., Connor, M. J. O., Olson, H., Paley, B., Mattson, S. N., Anderson, S. M., & Riley, E. P. (2016). Neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE): Proposed DSM-5 diagnosis. *Child Psychiatry & Human Development*, 47(2), 335–346. doi:10.1007/s10578-015-0566-7
- Kelly, A. M., Uddin, L. Q., Biswal, B. B., Castellanos, F. X., & Milham, M. P. (2008). Competition between functional brain networks mediates behavioral variability. *Neuroimage*, 39(1), 527–537. doi:10.1016/j.neuroimage.2007.08.008
- Kjellmer, L., & Olswang, L. B. (2012). Variability in classroom social communication: Performance of children with fetal alcohol spectrum disorders and typically developing peers. *Journal of Speech, Language, and Hearing Research*, 56, 982–993. doi:10.1044/1092-4388(2012/11-0345)
- Lebel, C., Mattson, S. N., Riley, E. P., Jones, K. L., Adnams, C. M., May, P. A., ... Sowell, E. R. (2012). A longitudinal study of the long-term consequences of drinking during pregnancy: Heavy in utero alcohol exposure disrupts the normal processes of brain development. *The Journal of Neuroscience*, 32(44), 15243–15251. doi:10.1523/JNEUROSCI.1161-12.2012
- Liss, M., Harel, B., Fein, D., Allen, D., Dunn, M., Feinstein, C., ... Rapin, I. (2001). Predictors and correlates of adaptive functioning in children with developmental disorders. *Journal of Autism and Developmental Disorders*, 31(2), 219–230. doi:10.1023/A:1010707417274
- MacDonald, S. W. S., Nyberg, L., & Bäckman, L. (2006). Intra-individual variability in behavior: Links to brain structure, neurotransmission and neuronal activity. *Trends in Neurosciences*, 29(8), 474–480. doi:10.1016/j.tins.2006.06.011
- MacDonald, S. W. S., & Stawski, R. S. (2014). Intraindividual variability—An indicator of vulnerability or resilience in adult development and aging? In M. Diehl, K. Hooker, & M. J. Sliwinski (Eds.), *Handbook of intraindividual variability across the life span* (pp. 231–257). New York, NY: Routledge.
- Malbin, D. V. (2004). Fetal Alcohol Spectrum Disorder (FASD) and the role of family court judges in improving outcomes for children and families. *Juvenile and Family Court Journal*, 55(2), 53–63. doi:10.1111/jfcj.2004.55.issue-2
- Mattson, S. N., Crocker, N., & Nguyen, T. T. (2011). Fetal alcohol spectrum disorders: Neuropsychological and behavioral features. *Neuropsychology Review*, 21(2), 81–101. doi:10.1007/s11065-011-9167-9
- May, P. A., Blankenship, J., Marais, A.-S., Gossage, J. P., Kalberg, W. O., Joubert, B., ... Seedat, S. (2013). Maternal alcohol consumption producing fetal alcohol spectrum disorders (FASD): Quantity, frequency, and timing of drinking. *Drug and Alcohol Dependence*, 133(2), 502–512. doi:10.1016/j.drugalcdep.2013.07.013

- Moore, E. M., Migliorini, R., Infante, M. A., & Riley, E. P. (2014). Fetal alcohol spectrum disorders: Recent neuroimaging findings. *Current Developmental Disorders Reports, 1*, 161–172. doi:10.1007/s40474-014-0020-8
- Mukherjee, R. A. S. (2015). Fetal alcohol spectrum disorders. *Paediatrics and Child Health, 25* (12), 580–586. doi:10.1016/j.paed.2015.09.008
- Nesselroade, J. R. (1991). The warp and the woof of the developmental fabric. In R. M. Downs, L. S. Liben, & D. S. Palermo (Eds.), *Visions of aesthetics, the environment, and development: The legacy of Joachim F. Wohlwill* (pp. 213–240).
- Olson, H. C., Feldman, J. J., Streissguth, A. P., Sampson, P. D., & Bookstein, F. L. (1998). Neuropsychological deficits in adolescents with fetal alcohol syndrome: Clinical findings. *Alcoholism: Clinical and Experimental Research, 22*(9), 1998–2012.
- Rasmussen, C., Andrew, G., Zwaigenbaum, L., & Tough, S. (2008). Neurobehavioral outcomes of children with fetal alcohol spectrum disorders: A Canadian perspective. *Paediatrics & Child Health, 13*(3), 185–191.
- Roozen, S., Peters, G. J. Y., Kok, G., Townend, D., Nijhuis, J., & Curfs, L. (2016). Worldwide prevalence of fetal alcohol spectrum disorders: A systematic literature review including meta-analysis. *Alcoholism: Clinical and Experimental Research, 40*(1), 18–32. doi:10.1111/acer.12939
- Santhanam, P., Coles, C. D., Li, Z., Li, L., Lynch, M. E., & Hu, X. (2011). Default mode network dysfunction in adults with prenatal alcohol exposure. *Psychiatry Research – Neuroimaging, 194* (3), 354–362. doi:10.1016/j.psychres.2011.05.004
- Schoenbaum, G., Roesch, M. R., Stalnaker, T. A., & Takahashi, Y. K. (2009). A new perspective on the role of the orbitofrontal cortex in adaptive behavior. *Nature Reviews Neuroscience, 10* (12), 885–892.
- Simmonds, D. J., Fotedar, S. G., Suskauer, S. J., Pekar, J. J., Denckla, M. B., & Mostofsky, S. H. (2007). Functional brain correlates of response time variability in children. *Neuropsychologia, 45*(9), 2147–2157. doi:10.1016/j.neuropsychologia.2007.01.013
- Simmons, R. W., Thomas, J. D., Levy, S. S., & Riley, E. P. (2010). Motor response programming and movement time in children with heavy prenatal alcohol exposure. *Alcohol, 44*(4), 371–378. doi:10.1016/j.alcohol.2010.02.013
- Sparrow, S. S., Balla, D. A., & Cicchetti, D. V. (1984). *The vineland adaptive behavior scales: Interview edition, survey form*. Circle Pines, MN: American Guidance Service.
- Streissguth, A. P., Barr, H. M., Sampson, P. D., & Parrish-Johnson, J. C. (1986). Attention, distraction and reaction time at age 7 years and prenatal alcohol exposure. *Neurobehavioral Toxicology & Teratology, 36*(6), 1387–1406.
- Streissguth, A. P., Bookstein, F. L., Barr, H. M., Sampson, P. D., O'Malley, K., & Young, J. K. (2004). Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. *Journal of Developmental & Behavioral Pediatrics, 25*(4), 228–238. doi:10.1097/00004703-200408000-00002
- Streissguth, A. P., Bookstein, F. L., Sampson, P. D., & Barr, H. M. (1995). Attention: Prenatal alcohol and continuities of vigilance and attentional problems from 4 through 14 years. *Development and Psychopathology, 7*(3), 419–446. doi:10.1017/S0954579400006611
- Streissguth, A. P., Sampson, P. D., Carmichael Olson, H., Bookstein, F. L., Barr, H. M., Scott, M., ... Mirsky, A. F. (1994). Maternal drinking during pregnancy: Attention and short-term memory performance in 14-year-old children: A longitudinal prospective study. *Alcoholism: Clinical and Experimental Research, 18*(1), 202–218. doi:10.1111/j.1530-0277.1994.tb00904.x
- Stuss, D. T., Murphy, K. J., Binns, M. A., & Alexander, M. P. (2003). Staying on the job: The frontal lobes control individual performance variability. *Brain, 126*(11), 2363–2380. doi:10.1093/brain/awg237
- Sulik, K. K. (2005). Genesis of alcohol-induced craniofacial dysmorphism. *Experimental Biology and Medicine, 230*(6), 366–375. doi:10.1177/15353702-0323006-04
- Tamnes, C. K., Fjell, A. M., Westlye, L. T., Ostby, Y., & Walhovd, K. B. (2012). Becoming consistent: Developmental reductions in intraindividual variability in reaction time are related to white matter integrity. *The Journal of Neuroscience, 32*(3), 972–982. doi:10.1523/jneurosci.4779-11.2012

- Timler, G. R., & Olswang, L. B. (2001). Variable structure/variable performance parent and teacher perspectives on a school-age child with FAS. *Journal of Positive Behavior Interventions*, 3(1), 48–56. doi:[10.1177/109830070100300107](https://doi.org/10.1177/109830070100300107)
- Tinius, T. P. (2003). The integrated visual and auditory continuous performance test as a neuropsychological measure. *Archives of Clinical Neuropsychology*, 18, 439–454. doi:[10.1093/arclin/18.5.439](https://doi.org/10.1093/arclin/18.5.439)
- Treit, S., Lebel, C., Baugh, L., Rasmussen, C., Andrew, G., & Beaulieu, C. (2013). Longitudinal MRI reveals altered trajectory of brain development during childhood and adolescence in fetal alcohol spectrum disorders. *The Journal of Neuroscience*, 33(24), 10098–10109. doi:[10.1523/JNEUROSCI.5004-12.2013](https://doi.org/10.1523/JNEUROSCI.5004-12.2013)
- Verté, S., Geurts, H. M., Roeyers, H., Oosterlaan, J., & Sergeant, J. A. (2006). The relationship of working memory, inhibition, and response variability in child psychopathology. *Journal of Neuroscience Methods*, 151(1), 5–14. doi:[10.1016/j.jneumeth.2005.08.023](https://doi.org/10.1016/j.jneumeth.2005.08.023)
- Wechsler, D. (1944). *The measurement of adult intelligence* (3rd ed.). Baltimore, MD: Williams & Wilkins.
- Wechsler, D. (1991). *Wechsler intelligence scale for children* (3rd ed.). San Antonio, TX: The Psychological Corporation.
- Wilhelm, C. J., & Guizzetti, M. (2015). Fetal alcohol spectrum disorders: An overview from the glia perspective. *Frontiers in Integrative Neuroscience*, 9, 1–16.