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SAN DIEGO STATE UNIVERSITY

Emotion-Based Decision-Making in Children with Fetal Alcohol Spectrum Disorders

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

Linnea Vaurio

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2011

The Dissertation of Linnea Vaurio is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Chair

University of California, San Diego

San Diego State University

2011

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ABSTRACT OF THE DISSERTATION

Emotion-Based Decision-Making in Children with Fetal Alcohol Spectrum Disorders

by

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Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2011
San Diego State University, 2011

Professor Sarah N. Mattson, Chair

Neurobehavioral outcomes associated with prenatal alcohol exposure range from severe intellectual deficiency to subtle attention and motor deficits. Diagnosis of individuals with fetal alcohol spectrum disorders (FASD) can be challenging especially when physical markers are absent or prenatal histories are unavailable. In addition, due to neurobehavioral similarities, individuals with FASD and those with attention-deficit/hyperactivity disorder (ADHD) can be confused clinically, making differential diagnosis difficult. Research has recommended that identification of

FASD be based on a neurobehavioral profile. However, some neurocognitive domains, including decision-making, have received little attention.

Emotion-based decision-making involves strategic adaptation of behavior based on uncertain information and is essential for everyday function. Deficits in decision-making in individuals with FASD are suggested by neuroanatomical abnormalities and difficulty with everyday function. The Iowa Gambling Task (IGT) is a widely used measure of decision-making, simulating unpredictable reward and loss contingencies of complex decision-making. The IGT, which has not been used in alcohol-exposed populations, was administered to children with FASD (n = 21), ADHD (n = 22), and typically developing controls (n = 21). Further, because working memory, the process of temporarily storing and manipulating information, may be related to decision-making, a measure of working memory was included in the test battery. A mixed-model ANOVA demonstrated that children with FASD chose significantly fewer advantageous cards than control children. In contrast, children with ADHD were distinguished from controls based on processing frequency of rewards/losses on the IGT. Group decision-making performance was not accounted for by working memory performance in either the FASD or ADHD group. Collectively, these results suggest that children with FASD and ADHD have aberrant decision-making processes, although their dysfunction may be due to distinguishable mechanisms. While children with FASD were deficient in making decisions based on learning from exposure to past contingencies, children with ADHD differed from controls in their ability to tolerate unpredictable reinforcement schedules. Decision-making was found to be independent of intellectual function and other high order

cognitive abilities, including working memory, and therefore should be a consideration in further research and clinical assessment of children with FASD and ADHD.

I. Introduction

Fetal Alcohol Spectrum Disorders

In utero exposure to alcohol can lead to extensive and lifelong consequences. While initial research on prenatal alcohol exposure focused on the characteristic facial dysmorphia and behavior associated with the Fetal Alcohol Syndrome (FAS), significant neurocognitive impairments exist in individuals with prenatal alcohol exposure with or without the physical features (Mattson, Riley, Gramling, Delis, & Jones, 1998). Outcomes associated with prenatal alcohol exposure range from subtle motor and attention deficits to reduction of overall intelligence. These outcomes depend on dose, timing, and frequency of alcohol exposure as well as a host of moderating factors such as maternal age and nutrition (May et al., 2004). The nomenclature of the disorder has evolved to reflect the range of potential outcomes. The non-diagnostic term fetal alcohol spectrum disorders (FASD) has been adopted by the National Task Force on Fetal Alcohol Syndrome and Fetal Alcohol Effect (Bertrand et al., 2004) and will be used herein to describe individuals with prenatal exposure to alcohol with or without the associated physical features of FAS. Researchers have recommended identification of children with FASD using a neurobehavioral profile rather than emphasizing physical effects of the disorder (Riley et al., 2003). A focus on neurocognitive outcomes may be appropriate because these consequences are most debilitating for alcohol-exposed individuals. In addition, improved conceptualization of the disorder may allow for more accurate and earlier diagnosis and determination of strengths and weaknesses in alcohol-exposed

populations, leading to improved intervention. Because identification of individuals with prenatal alcohol exposure does not necessarily hinge on the physical features that were delineated in FAS, confusion with similar clinical populations can occur. Specifically, children with heavy prenatal alcohol exposure have been shown to have attention deficits (Mattson, Goodman, Caine, Delis, & Riley, 1999) and frequently have a comorbid diagnosis of attention-deficit/hyperactivity disorder (ADHD; Bhatara, Loudenberg, & Ellis, 2006; Fryer, McGee, Matt, Riley, & Mattson, 2007). Neurobehavioral similarities between non-exposed children with ADHD and individuals with prenatal alcohol exposure and ADHD make these groups difficult to distinguish. However, few studies have compared children with FASD directly to children with ADHD (Coles et al., 1997; Crocker, Vaurio, Riley, & Mattson, 2009; Crocker, Vaurio, Riley, & Mattson, 2011; Nanson & Hiscock, 1990; Vaurio, Riley, & Mattson, 2008).

Attention-Deficit/Hyperactivity Disorder

ADHD is a behavioral syndrome that arises in early childhood, typically before the age of 7, and is characterized by poorly sustained attention and hyperactivity/impulsivity (American Psychiatric Association, 2000). Approximately 3-7% of the childhood population is affected by ADHD (American Psychiatric Association, 2000). Symptoms of ADHD, in general, persist into adolescence (Barkley, 1997), and a diagnosis of ADHD is associated with increased risk for low academic achievement, delinquency, early substance abuse, and difficulties in social relationships (Barkley, 2002).

Diagnostic criteria of ADHD and its subtypes are dependent on caregiver and/or teacher report of behaviors that are observed as "often present". Notably, unlike in children with heavy prenatal alcohol exposure, decrements in general intellectual function do not seem to be a common consequence of ADHD (Schuck & Crinella, 2005). There is increasing support for conceptualization of ADHD as a more heterogeneous group of disorders with different etiologies and outcomes. Recent research has focused on delineating causal mechanisms, based on neuropsychological and cognitive theory, that are observable "within-child," rather than based on third-party ratings (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). Much of the focus toward this goal is on sustained attention, behavioral inhibition and motivation, as well as executive function, state regulation, and temporal information processing (Nigg, 2005). Therefore, direct comparison of children with ADHD to those with FASD, specifically by use of executive function measures, may assist in clarifying diagnostic criteria for both populations.

Neuroanatomical Pathways of Cognitive and Emotion-Based Executive Function

Executive function is a higher-order cognitive ability associated with the frontal lobes of the brain. Executive function occurs across sensory modalities (e.g., auditory and visual) and can be measured by both verbal and nonverbal tasks. Executive function abilities integrate sub-processes such as planning, cognitive flexibility, and working memory to enable self-control and goal-directed behavior (Lezak, Howieson, Loring, Hannay, & Fischer, 2004). Conceptualizations of executive function suggest that there are dissociable factors within the overarching category (Miyake et al., 2000). Literature based on populations with brain lesions and

neuroimaging data provides support for the dissociation between emotion-based decision-making and cognitive-based executive function (Bechara, Damasio, Tranel, & Anderson, 1998; Damasio, 1995). Decision-making tasks are distinguished from cognitive-based executive function tasks, as they require modification of behavior based on emotionally salient information. More specifically, emotion-based decision-making tasks involve reward and loss as well as contingencies that cannot explicitly be predicted.

Cognitive executive function and emotion-based decision-making are thought to have dissociable neuroanatomical substrates. Emotion-based decision-making has been associated with the ventromedial area of the prefrontal cortex (VmPFC) and more generally with the overlapping orbitofrontal cortex (OFC) (Bechara, Damasio, & Damasio, 2000). Mediation of emotion-based decision-making is thought to rely primarily on a neuroanatomical loop involving orbitofrontal cortex, which is structurally distinct from other frontal-subcortial functional circuits (Alexander, DeLong, & Strick, 1986). In this closed loop, the orbitofrontal cortex projects to the ventromedial head of the caudate nucleus, the medial dorsomedial portion of the internal segment of the globus pallidus and the rostromedial aspect of the substantia nigra, projecting back to the orbitofrontal cortex through the thalamus (Alexander, et al., 1986). The amygdala, which is particularly associated with processing of emotion-related learning/processing is a primary direct input into the orbitofrontal cortex as well as a reciprocal output region (Kringelbach & Rolls, 2004). The orbitofrontal cortex, amygdala and cingulate cortex have been identified as being essential in representation and learning of reinforcers, and the orbitofrontal cortex is particularly

important in rapid processing of such information (Kringelbach & Rolls, 2004). Even within the orbitofrontal cortex, areas appear to be specialized to process different aspect of stimuli with reinforcing/aversive qualities. A metanalysis of neuroimaging data assessing the orbitofrontal cortex found that the medial orbitofrontal cortex is associated with learning and memory of rewarding information, while lateral orbitofrontal cortex is related to processing of punishing stimuli (Kringelbach & Rolls, 2004).

Somatic maker hypothesis. The somatic marker hypothesis (Bechara, et al., 2000) highlights the relationship between body signals and incorporation of these signals into decision-making. This theory postulates that for each emotion-related decision that an individual makes, somatic reactions (or markers) occur in the peripheral nervous system, including skeletal muscles, smooth muscles, and the viserca (Bechara, et al., 2000). These affective somatic states become associated with choices made in emotional situations and with the outcome, whether good or bad. When exposed to similar choices in the future, somatic markers serve as a biasing signal of the individual's emotional past experience with a situation, which, with integration of brain response, contribute to effective appraisal of situations that require affective processing (Bechara, et al., 2000). These signals are thought to be particularly significant in assessing situations with uncertain or complex contingencies by helping to simplify and reduce the situation and to appropriately bias the individual's interpretation (Hinson, Jameson, & Whitney, 2002). The relationship between somatic markers and decision-making typically has been assessed using skin conductance responses to measures physiological arousal in relation to exposure to

reward and punishment. In the somatic marker hypothesis, impaired decision-making is conceptualized as ineffective integration of peripheral (somatic) markers with central processing in the orbitofrontal/ventromedial regions, leading to inefficient learning of affective cues.

In contrast to emotion-based decision-making, working memory and planning skills (cognitive executive function) are related to dorsal and lateral areas of the prefrontal cortex. The neuroanatomical circuit for cognitive executive function is thought to proceed as follows: the dorsolateral prefrontal cortex projects to the dorsolateral head of the caudate, which projects to the lateral dorsomedial aspects of the internal segment of the globus pallidus and the rostrolateral aspect of the substantia nigra, returning to the dorsolateral prefrontal cortex through aspects of the thalamus (Alexander, et al., 1986). Measures of spatial, object and auditory working memory have been found to activate areas in the dorsolateral prefrontal region of the cortex (Casey, Tottenham, & Fossella, 2002; Goldman-Rakic, 1995; McNab & Klingberg, 2008). Emotion-related processing and integration of affective processing are thought to be relatively more involved in cognitive executive functioning.

As detailed above, distinct aspects of subcortical regions are preferentially involved in working memory and decision-making. Although the delineated small regions within the basal ganglia are difficult to distinguish using currently available neuroimaging techniques, recent investigations provide evidence of subcortical involvement more generally in working memory and emotion-based decision-making. In functional neuroimaging studies of nonclinical adults, the caudate nucleus (Haruno & Kawato, 2006; Haruno et al., 2004) and putamen (Haruno & Kawato, 2006) of the

basal ganglia were activated in decision-making tasks involving monetary rewards. In one study, magnitude of activity in the caudate nucleus was associated with short-term reward and reflected the magnitude of a subject's behavioral change in the decision-making task (Haruno, et al., 2004). On measures of spatial working memory, globus pallidus activity, which is the output region for the basal ganglia, has been found to be particularly associated with storage of relevant information (McNab & Klingberg, 2008).

Executive function and decision-making in FASD. Studies have demonstrated that heavy prenatal alcohol exposure is associated with deficient planning skills, as children with such exposure have significant difficulty solving problems that require mental manipulation of information (Kodituwakku, Handmaker, Cutler, Weathersby, & Handmaker, 1995; Mattson, et al., 1999) and exhibit more frequent rule violations than non-exposed peers on measures of planning (Mattson, et al., 1999). Alcohol exposure also is associated with impairments in conceptual set shifting (Mattson, et al., 1999; Vaurio, et al., 2008), concept formation (McGee, Schonfeld, Roebuck-Spencer, Riley, & Mattson, 2008), and the rapid generation of verbal and nonverbal responses (Kodituwakku et al., 2006; Kodituwakku, et al., 1995; McGee, et al., 2008; Schonfeld, Mattson, Lang, Delis, & Riley, 2001; Vaurio, et al., 2008). Some investigations have found evidence of response inhibition deficits in individuals with FASD (Mattson, et al., 1999) while other investigations have not found these deficits (Coles, et al., 1997; Kodituwakku, et al., 1995).

There are sparse data on the effects of prenatal alcohol exposure on emotion-based decision-making. One study of children and young adults with FASD used a

reward-based task to examine emotion-related learning. In this task, participants earn points by learning an initial rule. After becoming proficient with the original rule, the rule changes and participants are required to make an "affective shift" by learning the new rule in order to continue to earn points. Participants with FASD were impaired on the task (made less shifts) and these deficits were present after covarying their performance on the cognitive-based executive function test (WCST) (Kodituwakku, May, Clericuzio, & Weers, 2001). However, the degree of impairment observed in the alcohol group was similar for cognitive- and emotion-based executive function tasks. These data suggest that emotion-based executive function tasks can be used effectively in individuals with FASD. No other known study has examined emotion-based decision-making tasks in alcohol-exposed populations. More specifically, no published study has used a gambling task to measure emotion-based decision-making in alcohol-exposed individuals or attempted to determine the contributing factors to deficits in this domain.

Executive function and decision-making in ADHD. Initial conceptualizations of ADHD focused on impaired attention and hyperactivity. More recently, executive dysfunction (Nigg, 2005) and impaired behavioral inhibition (Barkley, 1997) have been considered as explanatory mechanisms of the disorder. A meta-analysis including investigations of executive function deficits in ADHD showed that children with ADHD had poorer group performance than controls on 13 tasks measuring response inhibition, vigilance, set shifting, planning, and verbal and spatial working memory (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Impairments on tasks of response inhibition and planning (Nigg, 1999; Nigg, Hinshaw, Carte, &

Treuting, 1998; Pennington & Ozonoff, 1996; Schachar, Mota, Logan, Tannock, & Klim, 2000; Willcutt et al., 2001) are found even after controlling for other comorbid conditions such as conduct disorder (Nigg, 1999; Nigg, et al., 1998; Pennington & Ozonoff, 1996). Impaired executive function or response inhibition do not appear to account for all deficits seen in this population, as only a subset of any ADHD sample demonstrates these deficits and some children diagnosed with ADHD perform in the average range on measures that assess behavioral inhibition or executive function (Nigg, et al., 2005).

Emotion-based executive dysfunction has been hypothesized as a possible primary impairment in ADHD (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006), and researchers have begun to examine emotion-based decision-making in this population. Some results show deficits in children with ADHD on the Iowa Gambing Task (IGT) (Garon, Moore, & Waschbusch, 2006; Toplak, Jain, & Tannock, 2005), however there are some conflicting results (Geurts, van der Oord, & Crone, 2006). There is evidence to suggest that brain response in children with ADHD is altered in the absence of behavioral differences when compared to controls (Ernst, Kimes et al., 2003). Other findings were mediated by subgroup characteristics. For example, in a modified version of the IGT, children with ADHD who were rated as anxious/depressed had performance that was comparable to controls, while children with ADHD who were not rated as anxious/depressed had impaired performance (Garon, et al., 2006). Impairments on the IGT in ADHD children have been related to an over-sensitivity to reward and under-sensitivity to punishment (Masunami, Okazaki, & Maekawa, 2009).

Relationship of Working Memory and Decision-Making

Emotion-based decision-making as measured by the IGT is a high-order cognitive function. Investigations have attempted to assess the relative independence versus inter-relationship of "cognitive" executive functions (including working memory) and emotion-based decision-making. The functional dissociations of working memory and decision-making that are hypothesized based on distinct brain circuitry also have been observed using behavioral measures and via brain imaging techniques. Individuals with orbitofrontal/ventromedial prefrontal lesions can have intact global intellectual function and can perform normally on tests of cognitive executive function but have difficulty making decisions, especially those involving uncertainty and processing rewards and losses (Bechara, et al., 2000). This difficulty in making decisions leads to significant impairment in everyday social function for these individuals. A recent review found that the majority of previous investigations examining the correlations between measures of working memory and summary scores of the IGT did not find significant relationships (Toplak, Sorge, Benoit, West, & Stanovich, 2010).

However, in addition to being a "closed loop" of functionality, neurostructural evidence suggests that frontal-subcortical systems are modulated by one another (Alexander, et al., 1986). Some evidence suggests that working memory ability mediates the relationship of emotion-based decision-making in that increasing working memory demands leads to poorer performance on gambling tasks (Hinson, et al., 2002). In order to examine the relationship between working memory and decision-making deficits, Bechara, et al. (1998) assessed individuals with acquired

dorsolateral prefrontal and orbitofrontal lesions on modified versions of delayed matching to sample and delayed nonmatching to sample tasks and the IGT. All patients with orbitofrontal lesions were impaired on the IGT, and approximately half of these patients were impaired on the working memory tasks. Patients with orbitofrontal lesions who demonstrated impaired decision-making and impaired working memory performance had lesions that extended to more posterior brain regions, and the investigators postulated that subcortical damage might be contributing to working memory deficits in those patients. Patients with right dorsolateral prefrontal lesions who had severe working memory impairments also had somewhat diminished performance on the IGT (low average range). In summary, all individuals who displayed working memory deficits demonstrated some impairment in decision-making performance; some patients with impaired decision-making did not have working memory deficits. Therefore, ventromedial damage was associated consistently with impaired decision-making, and inconsistently with working memory impairment. This pattern of performance suggests that individuals with impaired working memory performance may be more likely to have impairments in decision-making, while those with decision-making deficits do not necessarily have working memory deficits. An explanation that may resolve the independence versus interdependence of cognitive based executive functions and decision-making is that the relationship of the processes is “asymmetrical” in that the two functions have shared component processes, that, when interrupted will interfere with both cognitive based executive function and decision-making (Brand, Recknor, Grabenhorst, & Bechara, 2007). However, processing emotional feedback is a unique characteristic of

successful performance on the IGT and therefore, it is possible to have impairments on emotion-based decision-making with relatively intact cognitive executive functioning (Brand, et al., 2007).

Task demands of the IGT may, in part, explain conflicting evidence that suggests working memory and decision-making are not entirely independent processes. Working memory involves temporary storage and manipulation of information for use in cognitive tasks (Baddeley, 1995). Successful performance on the IGT requires the ability to consider past and present contingencies effectively, which, in turn, requires maintenance of a representation (i.e., working memory) of these contingencies temporarily. Memory of advantageous deck location is important for proficient performance and thus, a spatial working memory component may be particularly significant (Bechara, Damasio, Damasio, & Anderson, 1994). Working memory ability therefore has been considered as a component process in effective IGT performance (Bechara, et al., 2000).

Working memory in FASD. While working memory deficits have been hypothesized in individuals with FASD (Rasmussen, 2005), available research on working memory impairments in alcohol-exposed individuals is sparse and conflicting, with some results finding no significant differences between exposed and control groups on common measures of working memory (Kodituwakku, et al., 1995) and others suggesting impairments after controlling for IQ (Burden, Jacobson, Sokol, & Jacobson, 2005). A recent investigation suggested that when compared to controls, children with FASD were more error-prone and adopted an inefficient strategy on a computerized measure of spatial working memory (Green et al., 2009). It is unclear if

findings of working memory impairment might relate to the tasks included, which were not exclusively working memory tasks, or the lack of attention to lower order deficits, which might account for the observed findings. In a preliminary study, children with prenatal alcohol exposure were compared to controls on a computerized version of the Delayed Matching to Sample Task to examine object working memory ability (Vaurio, Repp, McGee, Riley, & Mattson, 2006). This task has a hierarchical component so that lower-order deficits can be examined simultaneously with trials of increasing demand. On this task, while alcohol-exposed participants demonstrated poorer performance overall, lower-order deficits (attention, comprehension of instructions or visual perceptual ability) accounted for these differences. This investigation also demonstrates that when examining higher-order processing deficits in alcohol-exposed populations, using a well-matched lower-order task can illuminate the level of deficit. Available literature on working memory deficits in FASD is equivocal and so inclusion of a working memory task could add significant information to an area that has received little attention in this population.

Working memory in ADHD. In contrast, deficits on working memory tasks have been found consistently in studies of ADHD (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005) and have been hypothesized to be a central deficit in this disorder (Barkley, 1997). Studies of emotion-based decision-making tasks have demonstrated that ADHD group gambling task deficits are not correlated with working memory performance (Drechsler, Rizzo, & Steinhausen, 2008), or remain after covarying performance on working memory tasks (Toplak, et al., 2005), suggesting that two abilities may be relatively independent in this population.

Neuroanatomical Findings in FASD and ADHD

Individuals with FASD and ADHD typically do not have localized brain abnormality. Prenatal alcohol exposure is associated with widespread and sometimes severe brain alterations, while ADHD is associated with more subtle alterations. However, both populations show specific abnormalities in cortical and subcortical areas thought to mediate emotion-based decision-making and working memory. In a structural magnetic resonance imaging (MRI) study of alcohol-exposed participants, the ventral aspect of frontal cortical areas showed reduced brain growth when compared to controls (Sowell et al., 2002). Tissue abnormalities have also been observed in the frontal lobe. Analysis of cortical thickness comparing children with FASD to controls showed relatively thicker right dorsal frontal regions in the FASD individuals, which was associated with impaired verbal recall (Sowell et al., 2008). Aberrant white matter microstructure has been observed in the bilateral medial frontal lobes (Fryer et al., 2009) suggesting reduced connectivity and tissue integrity in this region.

Evidence from functional neuroimaging also suggests abnormalities in the frontal lobes in children with FASD and those with ADHD. One study found that while controls had an expected asymmetrical pattern of blood flow in the frontal lobe, children with FAS had a pattern of abnormal functional symmetry with similar blood flow in the right and left frontal lobes (Riikonen, Salonen, Partanen, & Verho, 1999). Functional deficits also were seen in an investigation examining response inhibition, using a Go/No-Go task. Despite similar task performance, subjects with FASD displayed increased BOLD response in the prefrontal cortex and decreased BOLD

response in the caudate nucleus relative to controls (Fryer et al., 2007). Similarly, children with FASD have shown increased activation in frontal regions and decreased activation in medial and lateral temporal regions when compared to controls when performing a task of verbal learning (Sowell et al., 2007).

In addition, frontal-striatal impairments are found commonly in individuals with ADHD (Biederman, 2005). In a review of structural imaging studies of children and adults with ADHD, all studies focusing on the dorsolateral prefrontal region found reduced size of the region (Seidman, Valera, & Makris, 2005). While many of the studies in ADHD focus on prefrontal dysfunction, a dearth of specific findings of brain abnormalities in the orbitofrontal regions may be due to methodological difficulties in using MRI in areas proximal to the eyes and nose (Kringelbach & Rolls, 2004).

Volumetric reductions in the basal ganglia also have been reported in FASD populations. The caudate nucleus is disproportionately reduced in size in individuals with FASD, even after controlling for microcephaly (Archibald et al., 2001; Mattson et al., 1994). One study using magnetic resonance spectroscopy demonstrated abnormal brain metabolism in the left caudate nucleus of children exposed prenatally to alcohol, suggesting functional abnormality also exists in this region (Cortese et al., 2006).

Volumetric abnormalities also have been noted in ADHD. In a meta-analysis of neuroimaging studies, reductions in the right caudate nucleus were among the most consistently observed brain abnormalities (Valera, Faraone, Murray, & Seidman, 2007) and converging functional neuroimaging studies implicate abnormal frontal-

subcortical circuits, (Bush, Valera, & Seidman, 2005; Dickstein, Bannon, Castellanos, & Milham, 2006) especially on tasks of cognitive control (Vaidya et al., 2005). When performing decision-making tasks, adults with ADHD have been found to have less extensive or lack of brain activation in the ventral and dorsolateral prefrontal cortex, insula, anterior cingulate, and hippocampus when compared to controls (Ernst, Kimes, et al., 2003). Therefore, there is evidence to suggest that frontal and basal ganglia regions, which are substrates of working memory and decision-making, are abnormal in both FASD and ADHD populations.

Neuropsychological Comparison of FASD and ADHD

Ongoing investigations show that children with ADHD and FASD can be compared and distinguished based on neuropsychological measures. In one preliminary study (Mattson, Vaurio, & Riley, 2007), 84% of an FASD group and 77% of an ADHD group were correctly classified using the Wechsler Intelligence Scale for Children-III (Wechsler, 1991) Freedom from Distractibility Index and the Attention scale from the Child Behavior Checklist (Achenbach, 1991a). The measures used for the classification scheme originally were identified based on a sample of typically developing controls versus children with prenatal exposure to alcohol (Lee, Mattson, & Riley, 2004). While children with ADHD and children with FASD have been noted to have difficulties on measures of visual sustained attention, different mechanisms have been hypothesized to explain the deficits. Children with FASD had difficulty attending to visual stimuli when presented at a fast rate, while children with ADHD-combined type had difficulty on trials with slow rate of presentation (Kooistra, Crawford, Gibbard, Ramage, & Kaplan, 2009). Authors of the study therefore

hypothesized that while children with ADHD had difficulty attending to understimulating material, children with FASD had more difficulty attending to overstimulating stimuli. Differential patterns of performance in the two clinical groups also have been observed on tasks of verbal learning and memory. Children with FASD have show deficits in encoding verbal material, but did not demonstrated difficulty in retrieving material that is successfully encoded (Crocker, et al., 2011). In contrast, performance in the ADHD group was characterized by deficient retrieval of material that was encoded.

Direct comparison of the populations also shows that children with FASD and children with ADHD are impaired on cognitive executive function tasks, although their patterns of deficits are different (Vaurio, et al., 2008). In this investigation, the FASD and ADHD groups displayed deficits on set shifting as measured by the Wisconsin Card Sort Test (WCST) when compared to controls. Additionally, based on within-group comparisons, both ADHD and FASD groups demonstrated a relative weakness on letter vs. category fluency. Letter fluency is thought to be more directly related to executive processes than category fluency, providing support for a relative weakness on a verbal executive function measure for each group. Only the FASD group displayed overall deficits on letter fluency and a relative weakness on psychomotor sequencing (trail making B), versus a measure of motor function and processing speed (trail making A). This pattern of results suggests that individuals with FASD may have difficulty with executive measures of psychomotor ability, while this may not be a specific deficit in children with ADHD. In addition, WCST performance was significantly lower than expected based on IQ in the ADHD group

and significantly higher than expected in the FASD group. In sum, both groups demonstrated impairment on cognitive executive function tasks; however the FASD group had overall impairment in several domains, while the ADHD group had overall deficits only on the WCST and relative deficits on verbal fluency. Additional data from measures of adaptive ability suggest that while children with ADHD and children with FASD are impaired on aspects of adaptive function, including communication, daily living skills and socialization, the two groups differ in the nature of their deficits across development (Crocker, et al., 2009). With increasing age, children with ADHD had a pattern characterized as delayed adaptive ability (i.e. improving with at increasing ages but at a slower rate than controls) while children with FASD have an arrest in development of adaptive abilities. These investigations demonstrate that even in areas of shared deficit, children with ADHD and FASD show different patterns and levels of performance and can be distinguished from one another using neuropsychological measures.

Introduction to the Current Project

Since the identification of the Fetal Alcohol Syndrome (FAS) nearly 40 years ago, a multitude of deleterious neurocognitive outcomes associated with prenatal alcohol exposure have been documented. However the neurocognitive profile of alcohol-affected individuals is not clearly defined as research only recently has begun to proceed in this direction and some domains have received little attention. One understudied cognitive function is emotion-based decision-making, which requires modification of behavior based on uncertain information and emotionally salient reward and punishment contingencies. Deficits in emotion-based decision-making tasks are associated with poor real world social function (e.g., inability to make realistic future plans, engaging in risky behavior). Such deficits in individuals with prenatal alcohol exposure are suggested by both neuroanatomical abnormalities and difficulty with everyday function. Successful decision-making may require functional working memory, the process of temporarily storing and manipulating information (Baddeley, 1995). While working memory function has not been examined thoroughly in individuals with fetal alcohol spectrum disorders (FASD), deficits in this area may relate to impairments in emotion-based decision-making. Therefore, consideration of working memory ability in children with FASD may illuminate the nature of the higher-order decision-making deficit. In order to successfully perform and be engaged on the IGT, children must have an appreciation for numerosity, understanding what is "more" and "less" and able to read dollar amounts. Therefore, a Quantity Task was developed to assure that participants had these basic abilities. Finally, very little research has compared individuals with prenatal alcohol exposure directly to

clinically-related groups on any cognitive domain. Due to neurobehavioral similarities, children with FASD and children with Attention-Deficit/Hyperactivity Disorder (ADHD) may be clinically confused. Children and adults with ADHD have demonstrated behavioral impairments in working memory and emotion-based decision-making tasks and neuroanatomical abnormalities typically associated with both of these functions have been noted. Inclusion of individuals with FASD and ADHD in research studies may assist in distinguishing patterns of performance between these clinically comparable populations. The goal of this comparison is to improve diagnostic specificity rather than simply to outline deficits of individuals with prenatal alcohol exposure when compared to typically developing controls. Therefore the aim of the current study was to investigate emotion-based decision-making in children with FASD as compared to children with ADHD and typically developing controls and to consider the relative contribution of working memory function to decision-making.

Primary aim 1. *To compare performance of children with prenatal alcohol exposure to children with attention-deficit/hyperactivity disorder on emotion-based decision-making*

Emotion-based decision-making of children with FASD, children with ADHD, and typically developing controls were examined using The Iowa Gambling Task (IGT; Bechara, et al., 1994) as modified by Hooper et al. (Hooper, Luciana, Conklin, & Yarger, 2004). Because children with FASD and children with ADHD demonstrate impaired performance on cognitive executive function tasks, and have

neuroanatomical abnormalities in frontal and subcortical areas associated with emotion-based decision-making, it was hypothesized that both ADHD and FASD groups would have deficient performance on an emotion-based decision-making task when compared to controls. When compared directly, children with FASD have impairments in several domains of high order ability, while children with ADHD have relatively less severe impairments and are equal to controls on some domains. Therefore, an additional expectation is that the FASD group will have poorer performance than the ADHD group on emotion-based decision-making.

Primary aim 2. *To examine the relationship of working memory and emotion-based decision-making*

A task of working memory (Delayed Response Task, Bechara, et al., 1998)) was administered in conjunction with the IGT and included in analyses to examine if deficits in emotion-based decision-making are independent of spatial working memory deficits. Previous research has demonstrated that in children with ADHD, emotion-based decision-making deficits were not correlated with working memory performance and remained after covarying working memory (Toplak, et al., 2005). Therefore, it was hypothesized that working memory deficits would not significantly predict emotion-based decision-making deficits in the ADHD group. However, a different pattern of performance was anticipated in children with FASD. Children with FASD are more significantly impaired across selected cognitive executive function tasks when compared to children with ADHD (Vaurio, et al., 2008), and compelling evidence for the independence of emotion-based decision-making and executive

functions in FASD is lacking in currently available literature (Kodituwakku, et al., 2001). Therefore, for the FASD group, it was hypothesized that working memory deficits will significantly predict the IGT performance.

II. Methods

Participants

Three groups of children were included: children with heavy prenatal alcohol exposure (the FASD group), children with ADHD without prenatal alcohol exposure (the ADHD group), and a control group of children with neither prenatal alcohol exposure nor ADHD (the CON group). Descriptions of the groups are below. All races or ethnicities and both sexes were eligible. Parents were asked not to administer stimulant medication on the day of testing although children were not excluded if their parents declined to do so. Total testing time was less than 60 minutes per child including breaks, which was completed in one day. The San Diego State University Institutional Review Board and the University of California, San Diego School of Medicine Human Research Protections Program approved all procedures.

Recruitment. All children were recruited as part of a larger ongoing study of the behavioral teratogenicity of alcohol. Alcohol-exposed children and children with ADHD were recruited into this larger study via several mechanisms, including professional referral, caregiver self-referral and community outreach at various agencies and child-related venues. Control subjects were recruited via caregiver self-referral and community outreach at various agencies and child-related venues. Groups were matched on age, sex, and race/ethnicity.

Inclusion criteria. The following criteria were required for inclusion in the proposed project: aged 8:0 to 16:11, speak English as primary language and meet requirements for one of the groups detailed below.

Exclusion criteria. The following criteria were used for exclusion from the project: significant head injury with loss of consciousness for more than 30 minutes or significant physical (e.g., uncorrected visual impairment, hemiparesis) or psychiatric (e.g., psychosis) disability that would preclude participation. Children were excluded from the FASD group based on other known causes of mental deficiency (e.g., congenital hypothyroidism, neurofibromatosis, chromosomal abnormalities). Children were excluded from the CON and ADHD groups if greater than minimal prenatal alcohol exposure (> 1 drink per week on average or > 2 two drinks on any one occasion during pregnancy) was known or suspected or if information was unavailable.

Alcohol-exposed group. Mothers of children in the FASD group consumed at least 4 drinks per occasion at least once per week or 14 drinks per week during pregnancy. All children were identified retrospectively. Teratogenic exposure history was determined through multisource collateral report, including review of available medical, social service, and adoption agency records or maternal report, when available. Direct maternal report generally was unavailable, as many children with heavy prenatal alcohol exposure no longer reside with their biological families. These procedures are in agreement with normative standards for retrospective confirmation of maternal alcohol use within the field of clinical behavioral teratology.

Alcohol-exposed children received a dysmorphology examination by Dr. Kenneth Lyons Jones and IQ/neuropsychological testing as part of their participation in other CBT projects. Standard criteria were used to determine alcohol-related diagnoses (Jones et al., 2006; Mattson et al., 2010). Children with FAS had two of

three key facial features typical of FAS (short palpebral fissures, smooth philtrum, thin vermillion) and either microcephaly or growth deficiency or both.

ADHD group. Children in the ADHD group met the criteria for ADHD, as defined by the DSM-IV (American Psychiatric Association, 2000), using the procedure described by Nigg, Blaskey, Huang-Pollock, & Rappley (2002), as follows. Children were considered as "possible ADHD" based on parent or teacher versions of the Child Behavior Checklist or Teacher's Report Form (Achenbach, 1991a, 1991b), a DSM-IV symptom checklist, or a previous diagnosis of ADHD by a physician or psychologist in the community. Diagnosis was confirmed with parents by means of a structured diagnostic parent interview, the Diagnostic Interview Schedule for Children (DISC-IV; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000), and supplemented by teacher-reported symptoms on the DSM-IV symptom checklist. These procedures are consistent with the DSM-IV field trials validity data (Lahey et al., 1994). The majority of children in the ADHD group reside with their biological mothers. Therefore, screening for exposure to alcohol or other teratogens in this group was determined through direct maternal report.

Control group. Non-exposed controls were recruited as described above and did not meet criteria for either of the other two subject groups. Further, all children were screened for ADHD using the screening methods described above, and subjects who met criteria for ADHD currently or in the past, or had intermediate features of ADHD were excluded from the control group. Similar to procedures for the ADHD group, screening for exposure to alcohol or other teratogens in these groups was determined through direct maternal report (see above).

Procedure

Decision-making task. The Iowa Gambling Task (IGT; Bechara, et al., 1994) was developed originally by Bechara, Damasio, Damasio and Anderson to examine deficits observed in patients with ventromedial prefrontal cortical lesions. Despite normal performance on standard neuropsychological measures, these individuals had significant impairments in everyday function, demonstrating difficulty in making realistic plans, maintaining social relationships, and managing finances. Therefore the IGT was developed as a laboratory measure to reflect uncertain contingencies that occur in complex everyday decision-making and to address emotional aspects of decision-making by including rewards and losses. The original task uses a hypothetical bank loan of $2000 that participants use to "gamble" on four decks of cards with unknown reward and loss schedules. While the original task used playing cards, a computerized version has been used extensively as a measure of emotion-based decision-making in diverse groups, including pediatric populations (Blair, Colledge, & Mitchell, 2001; Ernst, Grant et al., 2003; Hooper, et al., 2004). This study employed a slightly modified version of the IGT, which was used successfully in a large sample of children aged 9-17 (Hooper, et al., 2004). In this version, the same reward and loss schedule and card decks are used as Bechara's computerized IGT, although hypothetical rewards have been scaled down from the original $2000 so that children can earn actual money, with a maximum gain of $5. Although several gambling tasks have been modified for use in child populations, these modifications can unintentionally introduce additional explanatory factors. For example, in one version, punishments and rewards similar to those in Bechara's task were used,

although children were told that they were earning apples for a hungry donkey (Crone, Vendel, & Van der Molen, 2003). While children may be engaged by the stimuli and demands of this task, the effect of earning rewards for oneself versus another (altruistic behavior) may vary. In addition, the IGT has been used successfully in clinical and typically developing child and adolescent populations (Blair, et al., 2001; Ernst, Grant, et al., 2003; Hooper, et al., 2004), so a computerized version most similar to Bechara's task was used.

Working memory task. To examine the relative contribution or independence of working memory and emotion-based decision-making, Bechara and colleagues (1998) used modified versions of a delayed matching to sample task, and compared performance on these measures to performance on the IGT. In the original study, Bechara et al. combined data from two measures of working memory (spatial and object), with the goal of capturing a wide range of impairment. However, patients with ventromedial prefrontal lesions were relatively more impaired on the spatial versus object working memory, suggesting the spatial task may be more sensitive in detecting working memory deficits. In addition, in the Delayed Response Task (the spatial working memory task), the goal of the task is to attend to the location of a card, and the type, position and number (A, B, C, and D) of cards can be matched to the IGT. On the object working memory task included in the original study, only one card appears initially and the goal of the task is to attend to the color of the card. Because effective performance on the IGT is contingent on attending to the location of decks rather than appearance of the card, spatial working memory as assessed by the

Delayed Response (Spatial Working Memory) Task was deemed most appropriate for the current study.

Also in Bechara et al.'s (1998) original study, participants were asked to read semantically meaningless sentences during the delay of the Delayed Response Task. However, it is uncertain if this distracter would be most appropriate for children and for the current populations of interest. More specifically, both FASD and ADHD populations have shown difficulties with language and/or reading tasks (McGee, Bjorkquist, Riley, & Mattson, 2009; Seidman, Biederman, Monuteaux, Doyle, & Faraone, 2001), so it is possible that the reading requirements of the delay would introduce unintended differential effects across the groups who are not likely to be matched on reading ability. Therefore, a motor distracter task was used rather than a language-based measure (see below for description).

Quantity task. Successful performance on the IGT is contingent on understanding comparisons of quantities as well as the ability to understand numerosity as represented by Arabic numerals. To assure that the subjects had sufficient understanding of these concepts, a measure was included which asked subjects to judge "Which one is more?" to demonstrate: basic understanding of Arabic numeral (9 or 3), understanding numerical place value (7,000 or 800), and understanding monetary value as represented in Arabic numerals ($5.75 or $7.00). In addition, because tokens were used as an additional tangible indicator of reward, children were asked to judge "Which one is more?" between a stack of 5 and 10 tokens. Finally, because motivation to earn more money may be partially related to understanding the value of money as applied to acquiring objects, the child was asked

to judge “Which one costs more?” and was shown a picture of a video gaming system and a candy bar. All participants included in the investigation were able to complete this task with 100% accuracy. This measure is included in the Appendix.

Additional measures. In addition to the measures detailed below, the majority children in the study received a standard neuropsychological battery administered at the CBT, including either the Wechsler Intelligence Scale for Children Fourth Edition, Integrated (WISC-IV, Wechsler, 2004), measures from the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer) as well as the Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition, 2006). Two children included in the investigation had not received the WISC-IV at the time of IGT testing and so these participants’ Weschler Intelligence Scale for Children Third Edition (WISC-III; Wechsler, 1991) scores were substituted for each of the indices. Exploratory analyses were conducted with a subgroup of children including these measures. All children were tested on the IGT and the Spatial Working Memory Task in a quiet testing room at the CBT by a single examiner who was blind to group assignment and prenatal history.

Reward. Traditional gambling tasks use “play money” or points as a reward (Bechara, et al., 1994). Other studies have used tangible rewards in the form of actual money (Hooper, et al., 2004) or small toys (Garon, et al., 2006) to motivate younger participants. Emotion-based decision-making relies on salience of the reward (Kringelbach, 2005) and there is some indirect evidence that hypothetical money may not be sufficiently motivating for individuals with FASD. Adults with FASD have

difficulty managing money (Streissguth, Barr, Kogan, & Bookstein, 1996) and children with FASD have impairments in math (Kable, Coles, & Taddeo, 2007).

Therefore, in order to increase motivation for reward, participants chose between tangible rewards. Prior to beginning the tasks, the child chose to earn actual money or the equivalent in small toys. During each task, points were awarded and displayed on the screen. In addition, tokens were used to represent the "money" earned on the screen, with each token representing $0.10. As the child won or lost "money" on the screen, the examiner updated the child's "bank" (transparent glass jar) of tokens so that they would have an additional tangible reminder of wins and losses. The total value of the reward for participation did not exceed $5 for each task and children earned the equivalent of their points if they concluded the task with a positive point balance. Following testing, participants were provided with a financial incentive for participation ($10/hour of testing), and the reimbursement was offset by the amount earned on the task (i.e., all participants actually received the same reward regardless of their performance). In order to allow for future use of tangible incentives in incentive-based tasks, participants were not informed that they did not earn money specifically for the gambling task.

Iowa Gambling Task description. This is a computerized version of the task originally developed by Bechara et al. (1994) that is designed to simulate real life contingencies by delivering uncertain rewards and punishments. The task is an extensively used measure of emotion-based decision-making and has been used successfully in typically developing (Hooper, et al., 2004) and clinical (Blair, et al., 2001; Ernst, Grant, et al., 2003) populations of children. The task has four virtual

decks of cards (A, B, C, and D). Each deck has a pre-determined schedule of both reward and loss that is not communicated to the participant. Two decks (A and B) are composed of cards with high rewards and high losses (disadvantageous decks) and two decks (C and D) are composed of cards with low rewards and low losses (advantageous decks). In addition, the decks vary by frequency of loss: two decks (B and D) have infrequent larger losses and two decks (A and C) have frequent smaller losses. On each card choice, the participant "wins" some money, and on some card choices the participant also "loses" money. After each deck choice, the "win" and "loss" for that choice is displayed in text on the screen and a cumulative tally of money earned is displayed on the screen for the duration of the task. The task has been modified as described by Hooper et al. (2004) to scale down play money so that participants can earn actual money, with a maximum payout of $5 or an equivalent in toys.

Over a period of 20 deck choices, consistent selection from deck A or B would result in negative $1.25 in earnings (disadvantageous decks), while deck C or D would result in positive $1.25 net earnings (advantageous decks). See Figure 1. The goal of the task was to maximize money earned. Participants made 100 card selections, but were not told ahead of time how many selections they would be required to make. The participant selected one card at a time from any deck and could select the same deck or a different deck with every choice. The decision to select from one deck or another is largely influenced by schedules of reward and punishment (Bechara, et al., 1994; Bechara, et al., 1998).

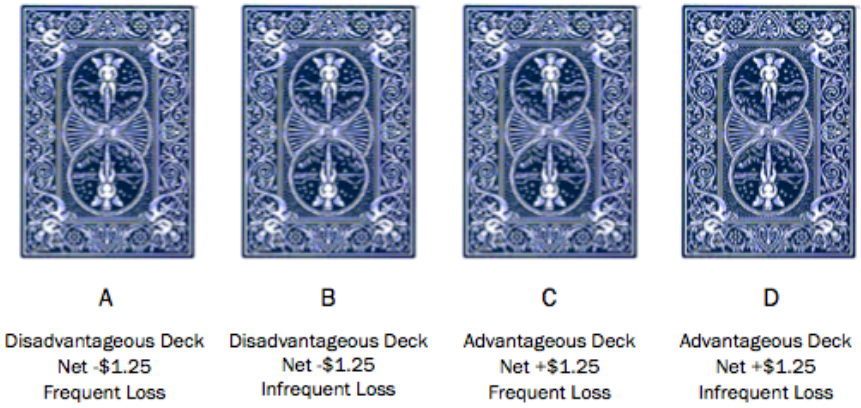


Figure 1. Image of Iowa Gambling Task decks, summary of deck characteristics.

Across time, normal adult controls alter their choice gradually to make more selections from advantageous decks and fewer selections from the disadvantageous decks. Typically developing children have a similar pattern of performance, although there is a significant effect of age on performance (Hooper, et al., 2004). Older children (aged 14-17) have performance comparable to adults, while younger children (aged 9-10) make less advantageous deck choices overall and require more trials to make relatively more advantageous versus disadvantageous choices.

***Iowa Gambling Task administration*.** First, the children were oriented to the computer screen, the display of cards and the keyboard used to choose each card. Standardized instructions were read to each child, indicating that they are going to play a card game and the goal is to win as much money as possible. They were told that they needed to choose many cards, one at a time, from any of the four decks until they are told to stop. They were also told that they had a chance to "win real money (or toys)" and that their total winnings would be displayed on the screen. The tangible

reward was pre-selected by the participant (money or toys) in order to increase participant motivation. Including orientation to the keyboard and computer screen and the trial, approximate length of the task was 15 to 20 minutes.

Rationale for Iowa Gambling Task outcome variables. The IGT consists of 100 deck selections. Consistent with the vast majority of previous investigations using the IGT, primary analyses for decision-making performance in this investigation examined performance across time by looking at 5 blocks of 20 deck selections each. In order to determine net advantageous performance within each block, calculations are made of advantageous deck choices (total chosen from deck B + C) minus disadvantageous deck choices (total chosen from A + B). Assessment of performance as related to by frequency/magnitude of punishment was also calculated as infrequent loss deck choices (total chosen from deck B + D) minus frequent loss deck choices (total chosen from A + C), again calculated for each 20 card selections (5 blocks).

For some analyses involved in this project, the goal was to determine the relationship of other neuropsychological domains and overall IGT performance. Developing a single outcome variable therefore was necessary. Some previous studies have examined overall IGT performance by collapsing across blocks and looking at net advantageous deck selections (e.g. total deck selections from C+D – A+B). However this approach may lead to inconsistent and/or inappropriate conclusions (Buelow & Suhr, 2009). In many investigations, performance by typically developing adults and children is characterized by initial net disadvantageous (i.e. negative) deck choices and net advantageous deck choices (i.e. positive) in later trials (e.g., Bechara, et al., 2000; Brand, et al., 2007; Hooper, et al., 2004). Therefore, summarizing data

without considering change in patterns over time is likely to mask the significant effect that is seen in typically developing teens and adults. For illustration, if an individual (participant A) selects an equal number of advantageous and disadvantageous cards across all five blocks (i.e. participant A has a scores of 0, 0, 0, 0, 0) and participant B has the following net scores (-10, -5, 0, 5, 10), a summary score for both participants would be 0, although based on past research the performances are consistent with different levels of proficiency. Effective performance on the IGT is characterized by a positive slope over the 100 deck selections, rather than a net positive total number of cards. For analyses examining overall IGT performance, the outcome variable was therefore calculated as the slope between advantageous minus disadvantageous card selections in trials 1-40 (early) versus trials 61-100.

Delayed response task description. The delayed response task was programmed based on Bechara et al. (1998). It is a version of a delayed matching to sample task, commonly used in humans and nonhuman primates to assess spatial working memory. Administration of this task along with the IGT, allowed for comparison of emotion-based decision-making with spatial working memory. The delayed response task is matched to the IGT on sensorimotor demands, however it is not matched on the unpredictable contingencies of the IGT or on exposure to gains and losses. This allows for isolation of the spatial working memory component from the emotion-based decision-making component. A spatial working memory task was chosen because it most closely matches the working memory aspects of the IGT, as noted above.

To begin the task, the child was told that he/she would play a card game. Standardized instructions were used. Practice trials preceded testing to assure that the children understood instructions, were able to use the keyboard appropriately, and understood the memory portion of the task. At the beginning of the task, four standard playing cards appeared face down on the computer screen in the same locations as those in the IGT. The task proceeded as follows. For each trial, two cards were illuminated with a green border for one second. After a motor delay (described below) participants were told to select the two original (green-bordered) cards with a corresponding computer key. Delays between the initial exposure to the green-bordered cards and the recall of the green-bordered cards' location were 0, 4, 8, and 12 seconds. On trials with no motor distracter (i.e. 0 second delay), participants' identification of the two green-bordered cards occurred immediately after exposure to those bordered cards. The location of the bordered cards randomly changed between trials. Length of delay varied randomly between trials. The task consisted of 10 trials of each delay length (40 trials total).

A motor distracter task occurred during trials of the spatial working memory task that had delays of 4, 8, and 12 seconds. During the distracter motor task, one card at a time was illuminated with a yellow border. The child pressed the key that corresponded with the deck location, which caused the next card to be illuminated with the yellow border. The order in which the cards are illuminated during the motor task was random. Dependent variables for the delayed response task were: total number of correct trials and number of correct trials for each delay length. For some analyses, a summary variable of working memory performance was needed. A Spatial

Working Memory Difference Score (SWMDiff) was calculated as performance accuracy at the longest delay (12-second delay) minus performance accuracy in the perceptual condition (0-second delay). Each participant therefore served as his/her own control and the effect of delay could be summarized in this variable. Including training trials and experimental trials, task length was approximately 15 minutes.

Data Analysis

Prior to any statistical analyses (described in detail below) multivariate outliers were removed based on Mahalanobis Distance > critical χ^2 value, $p < .001$. Alpha levels of .05 were used to determine statistical significance. Alpha levels less than .10 were considered marginally significant. Effect sizes also were examined when appropriate to determine practical significance. Statistically significant omnibus and interaction effects were followed up by pairwise comparisons. Age was assessed to determine if it was a significant predictor and was included in the model as a covariate when appropriate. Normality was examined through visual examination of histograms. The majority of variables included in the study did not have marked deviations of normality. Spatial working memory task variables were positively skewed and so data were re-analyzed after applying an arcsine transformation. Other variables that mildly deviated from normality (IED, CWI) were analyzed using nonparametric techniques (Spearman's ρ).

Decision-making performance – Primary analyses.

Aim 1. To examine the hypothesis that both ADHD and FASD groups would have deficient performance on the IGT when compared to controls and that the FASD group will have poorer performance than the ADHD group, mixed-model ANOVA

were used, as follows: To examine the effect of choice over time, the task was divided into five blocks of twenty cards each. The number of advantageous cards minus the number of disadvantageous cards was calculated for each block. These scores were examined using mixed-model ANOVA with block (five levels) as the within-subject factor and group (three levels) as the between-subjects factor. Follow up simple effects analyses and pairwise comparisons were conducted as appropriate.

Aim 2. To examine the hypotheses that emotion-based decision-making deficits observed in the ADHD group would remain after taking into account performance on tasks of working memory, and that emotion-based decision-making deficits would no longer be apparent after taking into account working memory deficits in the FASD group, linear regression was used, as follows: Hierarchical linear regression was conducted with overall IGT performance (calculated as the slope of advantageous cards minus disadvantageous cards chosen on gambling task for selections 1-40 versus 61-100) as the outcome variable and group working memory (SWMDiff) as explanatory variables. Linear regressions also were conducted within each group with IGT Slope as the outcome variable and SWMDiff as the explanatory variable

Possible outcomes. Three outcomes of these analyses were possible:

1. Both clinical groups would be impaired on emotion-based decision-making when compared to controls and in the ADHD group these deficits remain after taking into account working memory deficits. In the FASD group, no decision-making deficits would be apparent after accounting for working

memory deficits. This was the hypothesized outcome. This would be evidenced by a significant group by time effect on mixed-model ANOVA, described above, with follow-up pairwise comparisons showing that the ADHD group selected significantly fewer advantageous deck choices than controls on later trials and that the FASD group selected significantly fewer advantageous deck choices on later trials than the ADHD group. In a linear regression analysis within the ADHD group, working memory performance would not significantly predict IGT performance whereas in an analysis within the FASD group, working memory performance would be a significant predictor of IGT performance.

2. Both clinical groups would be impaired on emotion-based decision-making when compared to controls (seen in Aim 1 analyses) and these impairments are present after taking into account working memory deficits. This would indicate a specific deficit in emotion-based decision-making both for individuals with ADHD and those with FASD. For this outcome, mixed-model ANOVA would be as described in possible outcome 1. Within group regression analyses for FASD and ADHD groups would show that working memory performance was a significant predictor of IGT performance.
3. Both clinical groups would be impaired on emotion-based decision-making when compared to controls (seen in Aim 1 analyses) but these impairments are explained by working memory deficits. This would suggest that while decision-making is impaired, impairments might be better accounted for by

working memory deficits. For this outcome, mixed-model ANOVA would be as described in possible outcome 1. However, within the hierarchical linear regression, group membership would not be associated with IGT performance but working memory performance would be a significant predictor.

Exploratory analyses. IGT deck choice based on frequency/magnitude of loss, comparing across group was examined. Individuals with generalized anxiety disorder have been found to avoid decks with low frequency large losses (i.e., decks B and D) and preferentially select cards based on high frequency small losses (i.e. decks A and C), although these individuals had relatively better performance than controls on selections of advantageous deck selections (Mueller, Nguyen, Ray, & Borkovec, 2010), suggesting that these two dimensions of the IGT can be dissociated. Therefore, to determine the effect of frequency of loss on participant behavior, selections in the five blocks were also calculated based on number of cards selected from infrequently punishing decks minus cards from frequently punishing decks.

IQ data were available for all participants. The relationships between verbal and nonverbal intellectual function (WISC-III/WISC-IV VCI, POI) and IGT performance were examined. Data from larger batteries conducted at the CBT including D-KEFS and CANTAB data were available for the majority of participants included in the larger investigation (CON n = 20, FASD n = 19, ADHD n = 21). For these participants, correlational analyses were conducted to examine the relationship between the IGT slope variable and individual cognitive executive function components within each group. Executive function variables were selected to

represent the domains of inhibition (D-KEFS Color Word Interference, Inhibition Scaled Score; CWI), planning (D-KEFS Tower Test, Total Achievement Scaled Score, TT) verbal concept formation (D-KEFS Twenty Questions Test, Initial Abstraction Scaled Score, TQ), nonverbal problem solving (CANTAB Intra-Extra Dimensional Set Shift Stages Completed Z-score; IED) and working memory (Delayed Response Task; SWMDiff (described above)).

To determine the ability of cognitive executive function measures (CWI, TT, TQ, IED, SWMDiff) to distinguish children with prenatal alcohol exposure from the other two groups, two backward stepwise procedures (FASD vs. CON; FASD vs. ADHD) were conducted to identify the set of independent variables that best predicted group membership. Full models were reduced according to *p*-values and the final models included only variables that significantly ($p < .05$) predicted the outcome.

III. Results

Participant Characteristics

Demographic characteristics and IQ characteristics for the three groups are presented in Table 1. As expected based on previous research, the groups differed in on the WISC Verbal Comprehension Index (*p*s < .001), such that the average IQ score in the CON group was significantly higher than the ADHD group, which was significantly higher than the FASD group. Group differences were also noted on the Perceptual Organizational Index (POI, $p = .002$), Processing Speed Index, (PSI, $p = .001$) and Working Memory Index (WMI, $p = .001$). For the POI, PSI, the FASD group had significantly lower scores than the ADHD and CON groups. On the WMI, the FASD group had marginally poorer WMI scores than the ADHD group, which had significantly lower scores than the CON group. In addition, groups differed significantly on socioeconomic status ($p = .021$), with the FASD group having lower SES than the other groups. The groups did not differ in terms of years of age, race, ethnicity, sex or handedness (all *p*s > .10). One participant was excluded due to computer failure. This child was re-administered all tasks on a later date, though the participant data were found to be a multivariate outlier. Therefore, it was determined the data weren't representative and the participant data were excluded from analyses.

Table 1. Demographic and IQ characteristics for non-exposed control participants (CON), children with fetal alcohol spectrum disorders (FASD) and children with attention-deficit/hyperactivity disorder (ADHD).

	CON	FASD	ADHD	*p*	Group Comparisons[a]
N	21	21	22		
Age [N(years)]	12.82 (2.44)	12.08 (1.84)	12.04 (2.10)	.403	-----
Race [N(% White)]	14 (66.7)	12 (57.1)	19 (86.4)	.101	-----
Ethnicity [N(% Hispanic)]	6 (37.5)	5 (23.8)	5 (22.7)	.896	-----
Sex [N(% female)]	9 (34.6)	11 (52.4)	6 (23.1)	.238	-----
Handedness [N(% right)]	21 (100)	19 (90.5)	20 (90.9)	.352	-----
Socioeconomic Status (HH) [a] [Mean (SD)]	53.79 (7.18)	44.53 (12.99)	54.33 (13.54)	.021	FASD < ADHD = CON
Verbal Comprehension Index[a] [Mean (SD)]	111.19 (11.98)	89.19 (13.97)	103.59 (10.33)	< .001	FASD < ADHD < CON
Perceptual Organization Index[a] [Mean (SD)]	104.71 (13.42)	87.43 (17.46)	99.86 (14.57)	.002	FASD < ADHD = CON
Processing Speed Index [a] [Mean (SD)]	94.24 (11.52)	80.19 (12.98)	90.68 (11.39)	.001	FASD < ADHD = CON
Working Memory Index [a] [Mean (SD)]	100.81 (9.28)	84.05 (15.04)	92.73 (14.71)	.001	FASD = ADHD < CON

[a] $p < 0.05$.

Decision-Making Performance - Advantageous Deck Choices

A mixed-model ANOVA was conducted with block (five levels of 20 choices each) as the within-subject factor, group (three levels) as the between-subjects factor and number of advantageous minus disadvantageous card choices as the dependent variable. A marginally significant group X block effect was observed, $F(2, 61) = 2.64$, $p = .080$, partial $\eta^2 = .080$. A significant main effect of block was observed $F(1, 61) = 17.927$, $p < .001$, and no significant main effect of group was observed ($p > .10$). To follow up the interaction, univariate ANOVAs were conducted with group as the predictive variable and advantageous IGT performance as the outcome variable for each block (1-5). The only significant differences were on Block 1, $F(2, 63) = 5.03$, $p = .010$. Follow up pairwise comparisons demonstrated that the FASD group differed from both the CON group, $F(1, 40) = 10.20$, $p = .003$ and the ADHD group, $F(1, 40) = 4.40$, $p = .042$. There were no significant differences between the ADHD and CON group on any block. See Table 2 for effect sizes.

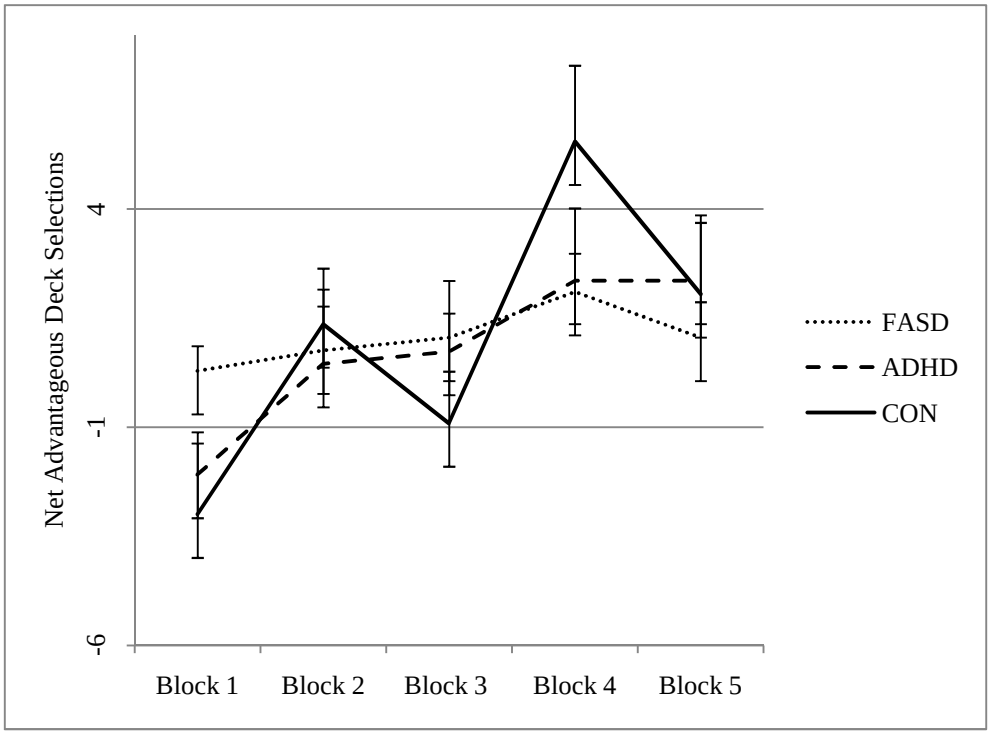
Table 2. Iowa Gambling Task Variables, Effect sizes (Cohen's *d)* for comparisons of net advantageous for non-exposed control participants (CON), children with fetal alcohol spectrum disorders (FASD) and children with attention-deficit/hyperactivity disorder (ADHD) across 5 blocks.

	CON vs. FASD	CON vs. ADHD	ADHD vs. FASD
Block 1 (Selections 1-20)	-0.97	-0.38	-0.63
Block 2 (Selections 21-40)	-0.06	0.00	-0.05
Block 3 (Selections 41-60)	-0.35	-0.17	-0.06
Block 4 (Selections 61-80)	0.45	0.32	0.04
Block 5 (Selections 81-100)	-0.06	-0.09	0.04

[a] $p < 0.05$.

To determine the nature of performance (learning) across time, a within-group, repeated measures ANOVA with block (five levels of 20 choices each) was conducted, with number of advantageous minus disadvantageous card choices as the outcome variable. Within the FASD group, no significant effect of block was observed $F(1, 20) = 2.45$, $p = .133$. However, a significant effect of block was observed for both the ADHD group, $F(1, 21) = 5.09$, $p = .035$, and the CON group, $F(1, 20) = 11.60$, $p = .003$. Follow up analyses indicated that children with ADHD selected significantly more advantageous cards in block 4 and block 5 than block 1 ($p < .05$) and children in the CON group selected significantly more advantageous cards in block 2, 3, 4, and 5 than block 1 ($p < . 05$). See Graph 1.

Graph 1. Iowa Gambling Task, number of advantageous minus disadvantageous card selections by block. Data represent mean values +/- standard error of the mean.



Spatial Working Memory Performance

Task validity. Because the delayed response task was developed by the candidate for this project, outcome variables were examined to assure that task difficulty was appropriate for children included in this investigation and that performance was a valid representation of working memory ability. The lowest average percentage within a group for this task occurred within the FASD group at the 12-second delay. The score was 65% accurate. The percentage that corresponds to chance/random responding would be equivalent to a 20% accurate response rate. Because group performance did not approach this cutoff in the most challenging condition, it was assumed that children were able to understand task demands. Therefore, it was determined that the participants were able to perceive the stimuli and respond accurately to computer stimuli with the keyboard. For working memory task analyses, all groups were anticipated to have less accurate performance with longer delays and so the 12-second delay (longest) should show the most significant degradation of performance.

Group results. On the delayed response working memory task, a significant main effect of delay was observed, $F(1, 61) = 106.11$, $p < .001$, partial $\eta^2 = .635$, with overall lower accuracy observed across longer delays, collapsed across groups. A significant main effect of group was also observed, collapsed across the four delays, $F(2, 61) = 4.89$, $p = .011$, partial $\eta^2 = .138$. No significant group X delay relationship was observed ($p > .10$, partial $\eta^2 = .071$). Because scores in this analysis were raw scores, age was examined as a possible covariate, but did not account for a significant amount of variance of the dependent variable and therefore was not included in the

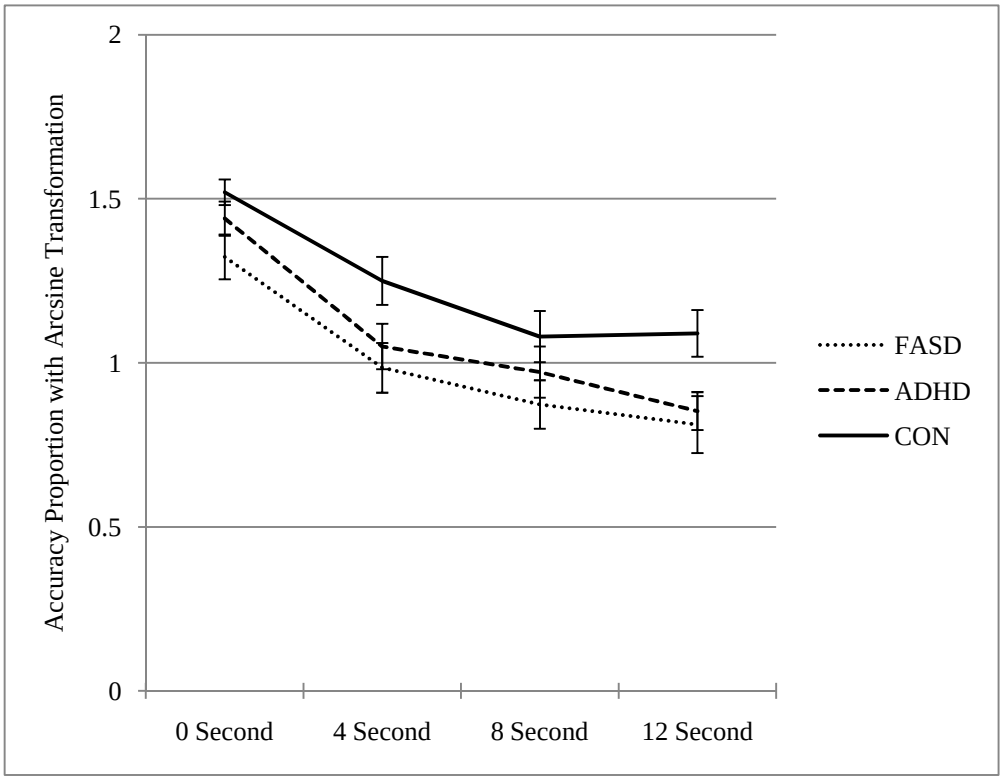
model. To follow up the main effect of group, pairwise group comparisons were conducted, collapsed across delays. When compared with the CON group, accuracy levels were significantly lower in both the FASD group, $F(1, 40) = 9.84$, $p = .003$, and the ADHD group, $F(1, 41) = 4.14$, $p = .048$. No significant group effects were observed when the FASD group was compared directly with the ADHD group ($p > .10$).

Transformed working memory analyses. Histograms of working memory variables were inspected and percentages across all delays tended to be positively skewed. Therefore, an arcsine transformation was applied to working memory outcome variables and normality significantly improved. Analyses were repeated with the transformed variables. Results showed a significant main effect of delay $F(1, 61) = 137.51$, $p < .001$, partial $\eta^2 = .693$, and a significant main effect of group $F(2, 61) = 5.62$, $p = .006$, partial $\eta^2 = .156$, but no significant group X delay interaction, *(*$p = .499$, partial $\eta^2 = .023$). To follow up the main effect of group, pairwise group comparisons were conducted, collapsed across delays. When compared with the CON group, accuracy levels were significantly lower in both the FASD group, $F(1, 40) = 10.95$, $p = .002$, and the ADHD group, $F(1, 41) = 4.93$, $p = .032$, which did not differ from each other ($p > .10$). See Graph 2.

Post hoc analysis of working memory performance. Because of the lack of published studies regarding working memory performance in FASD, post hoc analyses were conducted comparing FASD directly to the CON group. The ADHD group was not included in this analysis. Data were analyzed in a similar fashion as above, using transformed data. Results indicated significant main effects of group $F(1, 40) = 10.95$,

p = .002, and delay $F(1, 40) = 61.91$, $p < .001$. The group x delay interaction was not significant $F(1, 40) = .275$, $p = .603$. The main effect of delay was followed up with pairwise comparisons of the delay intervals, collapsed across group, which revealed, as above, that performance at each interval was significantly different from the next longest interval (0 > 4 > 8 > 12). To further examine these data, effect sizes (Cohen's *d)* were calculated, comparing the FASD group to the CON at each delay length and the following effects were observed at the 0, 4, 8 and 12-second delay, respectively: 0.79, 0.78, 0.59, 0.76. Large effect sizes were observed on the perceptual condition and medium to large effect sizes were observed across all delay trials.

Graph 2. Spatial working memory task, percent accuracy across delay conditions, by group. Data were transformed using arcsine transformation and are presented here as mean transformed values +/- standard error of the mean.



Relationship of Decision-Making and Working Memory Performance

A hierarchical linear regression was conducted with group and working memory task performance predicting overall IGT slope. As described above, working memory was defined for this analysis as the difference in performance between the 12s delay and the 0s delay, using raw, untransformed, data. In the first step that included Group, the model accounted for a significant amount of variance in IGT performance, $R^2 = .072$, $F(1, 62) = 4.79$, $p = .032$. In the next step, the subsequent inclusion of Working Memory difference score did not result in a significant increase in the proportion of IGT performance variance explained, $R^2 = .082$, $\Delta R^2 = .010$, $p = .418$ and thus the model including only group was retained. Follow up analyses for the retained model indicated that the significant relationship was driven by a significantly flatter slope in the FASD group than the CON group, $F(1, 41) = 6.43$, $p = .015$. No significant differences in IGT slope were observed when the ADHD group was compared directly with the FASD or CON groups ($p > .10$). See Table 3.

Table 3. Hierarchical Linear Regression Predicting Variance in Decision-Making (IGT Slope) Performance for non-exposed control participants (CON), children with fetal alcohol spectrum disorders (FASD) and children with attention-deficit/hyperactivity disorder (ADHD).

Step 1	B (Unstandardized)	β	*p*
Group	2.024	0.268	.032
	$R^2\Delta = .072$, $p = .032$		
Step 2			
Group	1.810	0.240	.065
SWM, Difference Score	3.626	0.104	.418
	$R^2\Delta = .010$, $p = .418$		

Group Coded as follows: FASD = 1, ADHD =2, CON=3

The relationship between working memory performance and IGT performance was also examined within each group. Working memory performance was not a significant predictor of IGT slope within the FASD group, the ADHD group or CON group ($p >$ 0.10).

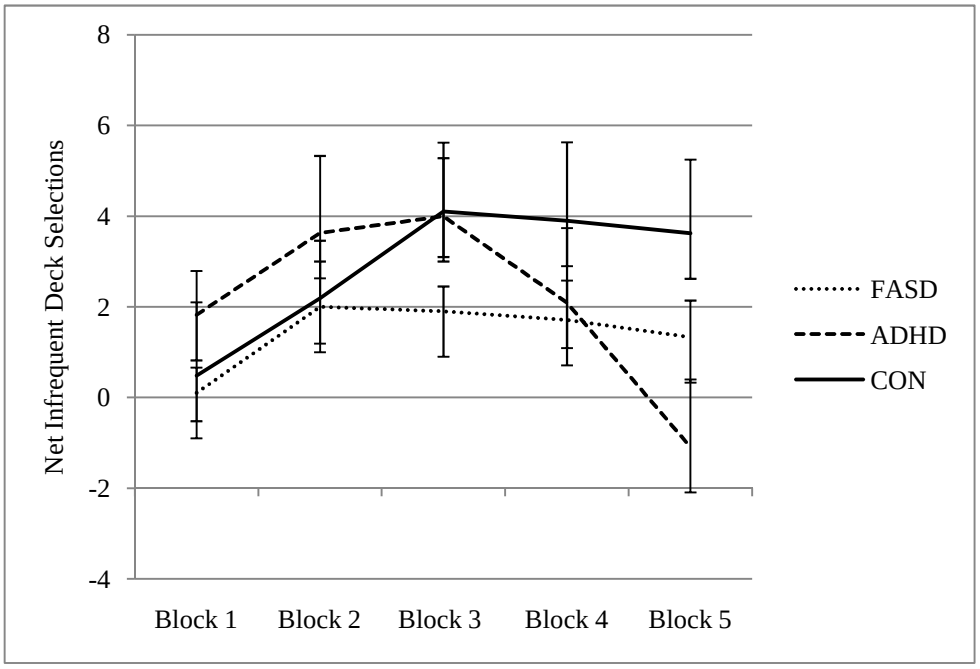
Decision-Making Performance: Frequency of Loss

To examine the influence of reinforcement contingencies (i.e. decks with infrequent versus frequent loss), a mixed-model ANOVA was conducted with block (five levels of 20 choices each) as the within-subject factor, group (three levels) as the between-subjects factor and number of cards with infrequent loss minus frequent loss as the dependent variable. A significant group X block effect was observed, $F(2, 61) = 3.86$, $p = .026$, partial $\eta^2 = .112$. To follow up the significant interaction, group effects were examined at each level of block. A marginal group effect was observed on block 5, (2, 63) = 2.88, $p = .064$. Follow up pairwise comparisons showed that only the ADHD vs. CON comparison was significant ($p < .05$) with the ADHD group selected significantly fewer infrequent loss deck choices than the CON group on this block. The group effect was not significant on any other block.

In order to examine the influence of frequency of loss for each group across time, simple main effects were conducted examining the influence on block within each group. Within the FASD group, participants selected significantly *more* cards from decks with infrequent large losses in block 2 than in block 1 ($p = .042$). The number of cards selected from decks with infrequent loss versus frequent loss was similar for the remainder of the task (i.e. Block 1 < 2 = 3 = 4 = 5). Within the ADHD group, participants selected significantly *fewer* cards from decks with infrequent large

loss in block 5 than in block 2 (p = .029) and also in block 5 than block 3 (p = .031). Within the CON group, participants selected significantly *more* cards from decks with infrequent larger losses in block 3 than in block 1 (p = .022) and also in block 3 than block 2 (p = .023). See Graph 3.

Graph 3. Iowa Gambling Task, number of choices from infrequently punishing decks minus number of choices from frequently punishing decks by block. Data represent mean values +/- standard error of the mean.



Cognitive Executive Function, Intelligence and Decision-Making Performance

To explore the underlying cognitive mechanisms of decision-making performance, correlational analyses (i.e., nonparametric Spearman's ρ correlation coefficient) were used, examining the relationship between IGT Slope and CWI, TT, TQ, IED, and SWMDiff (variables described above). Correlations were conducted separately within each group, as it is important to determine if relationships in the clinical samples differ from those in the control group. Correlations between verbal intellectual function (WISC VCI) and nonverbal intellectual function (WISC POI)

with IGT Slope were also examined within each group. Within the FASD group, IGT slope did not correlate significantly with any of the cognitive executive function measures or with the intelligence measure ($p > .05$). IGT performance was significantly associated with verbal concept formation as measured by TQ (Spearman's $\rho = 0.478$; $p = .033$) within the CON group and with nonverbal problem solving as measured by the IED (Spearman's $\rho = 0.440$; $p = .046$) in the ADHD group. Thus of 21 correlations examined, only 2 were significant. Table 4.

Table 4. Bivariate correlations between IGT learning variable and individual cognitive measures for non-exposed control participants (CON), children with fetal alcohol spectrum disorders (FASD) and children with attention-deficit/hyperactivity disorder (ADHD). Data are presented as Spearman's ρ correlation coefficient and *p*-value.

	CON (n=20)		FASD (n=19)		ADHD (n=21)	
	Iowa Gambling Task Slope					
	ρ	*p*-value	ρ	*p*-value	ρ	*p*-value
WISC Perceptual Organization Index Score	-.036	.878	.115	.618	-.039	.862
WISC Verbal Comprehension Index Score	.103	.657	.256	.262	-.087	.701
Spatial Working Memory, difference score	.069	.766	.273	.231	-.105	.641
D-KEFS Color Word Interference Inhibition, z-score	.112	.637	-.159	.515	-.140	.534
D-KEFS Twenty Questions Initial Abstraction	.478[a]	.033	.272	.247	-.062	.784
D-KEFS Tower Test Total Achievement Score, standard score	.156	.512	.070	.768	-.111	.624
CANTAB Intra-Extra Dimensional Set Shift, Stages Complete, z-score	.271	.248	.129	.587	.440 [a]	.046

[a] $p < 0.05$.

Group Prediction

A binary logistic regression was conducted to determine the combination of "cognitive" executive function (IED, CWI, TT, TQ, SWMDiff) and decision-making (IGT Slope) variables that would best distinguish children with FASD from the CON

group and the FASD versus ADHD group. See Table 5 for descriptive statistics and group comparisons for measures included in logistic regression analyses.

A backward stepwise procedure was used to identify the set of independent variables that best predicted group membership. Models were reduced according to *p*-values and the final model included only variables that significantly ($p < .05$) predicted the outcome. Prior to conducting the logistic regression, bivariate correlations were examined for evidence of multicollinearity in the independent variables. Tabachnick and Fidell (2001) propose that variables with a bivariate correlation of greater than .70 provide redundant information to an analysis, which can cause problems of multicollinearity. Because all bivariate correlations were < 0.64, the initial analysis included all six variables.

In the first analysis, group membership (FASD or CON) was the dependent variable and the six measures, described above, served as the independent variables. Two independent variables (IGT Slope, CWI) were retained in the final model, which was shown to reliably discriminate children in the FASD group from children in the CON group, $\chi^2 (2, n = 40) = 15.91$, $p < .001$. Overall group membership was predicted at an accuracy rate of 74.4%, with 78.9% accurate prediction of the FASD group and 70% accurate prediction of the CON group. These analyses were repeated to determine if children in the FASD and ADHD groups could be distinguished using cognitive executive function and decision-making measures. A useful model could not be established with the variables included in the analysis.

Table 5. Descriptive statistics and group comparisons for variables included in logistic regression for non-exposed control participants (CON), children with fetal alcohol spectrum disorders (FASD) and children with attention-deficit/hyperactivity disorder (ADHD).

	CON	FASD	ADHD	Group Comparisons[a]
N	20	19	21	
Color-Word Interference Scaled Score [a] [Mean (SD)]	10.70 (2.15)	7.32 (3.79)	8.59 (4.00)	FASD < CON, ADHD < CON
Twenty Questions Initial Abstraction Scaled Score [a] [Mean (SD)]	10.40 (3.08)	8.25 (2.42)	10.14 (2.59)	FASD < ADHD = CON
Tower Test Total Achievement Scaled Score [Mean (SD)]	9.90 (1.65)	8.55 (3.02)	9.32 (2.64)	----
Intra-Extra Dimensional Set Shift Stages Completed Z-score [Mean (SD)]	0.40 (0.64)	-0.17 (1.32)	0.14 (0.71)	----
Spatial Working Memory Difference Score (12-second – 0 second delay accuracy) [Mean (SD)]	-14.13 (12.81)	-25.93 (23.42)	-23.74 (13.42)	FASD < CON, ADHD < CON
IGT Slope [Mean (SD)]	5.10 (6.76)	1.05 (2.80)	3.18 (7.42)	FASD < CON

[a] $p < 0.05$.

Power

A power analysis was conducted after analyzing the data, focusing on the primary analyses of advantageous deck selection on the IGT and spatial working memory analyses. To detect a significant group X block interaction effect within a mixed-model ANOVA with 5 blocks and 3 groups, given the sample size obtained in this investigation (n = 66), the observed effect size (partial $\eta^2 = .080$), and observed intercorrelations of measures, power to detect significant interaction was calculated to be .99. Power for a group X delay interaction effect on the measure of spatial working memory, based on observed effect size (partial $\eta^2 = .071$) was also calculated to be .99.

IV. Discussion

Decision-Making

When children with heavy prenatal alcohol exposure were compared directly to typically developing controls, different patterns of performance were observed on the IGT, although results should be interpreted with some caution because overall group analyses did not reach statistical significance. Control children selected significantly more net advantageous decks on later trials when compared to earlier trials, which is consistent with performance seen by typically developing children in previous investigations. In contrast, children with prenatal alcohol exposure maintained a similar proportion of advantageous to disadvantageous deck selections across the 100 deck selections. These results suggest that children with prenatal alcohol exposure may have inefficient processing of rewards or lack of understanding of complex contingencies that could contribute to difficulty utilizing complex information. No known investigations have examined performance of children with prenatal alcohol exposure on emotion-based decision-making tasks although one study demonstrated that children and young adults with heavy prenatal alcohol exposure had difficulty incorporating rewards to effectively learn a rule reversal task (Kodituwakku, et al., 2001). While task requirements of the IGT and the reversal learning task are not equivalent, underlying brain mechanisms of the two functions have been found to overlap (Clark, Cools, & Robbins, 2004). Therefore, the only two currently known investigations that have examined processing of reinforcements suggest that individuals with heavy prenatal alcohol may be deficient in this domain.

Abnormal performance on the IGT can be characterized by many different patterns of performance. For example, participants with ventromedial lesions (Bechara, et al., 2000) and fronto-temporal dementia (Torralva et al., 2007) tend to select *increasing* numbers of *risky* cards across time (i.e. have increasingly negative scores across the 5 blocks), which may be due to insensitivity to punishment. As in the current group of subjects with FASD, individuals with amnesia due to bilateral hippocampal damage (Gupta et al., 2009) and female patients with anorexia nervosa, bulimia and obesity (Brogan, Hevey, & Pignatti, 2010) have abnormal performance characterized by a relatively flat slope and selection of similar proportion of advantageous and disadvantageous cards across the later trials of the IGT. Net advantageous scores in the FASD group were above zero, indicating that, to some degree, there was a response to losses/punishment unlike patterns of performance that were observed in individuals with ventromedial brain lesions or fronto-temporal dementia, who do not appear to be sensitive to losses/punishment. The flat learning curve evidenced by children with FASD indicates that they were did not maximize immediate reward (by choosing increasingly from disadvantageous decks) or maximize long-term reward (by choosing increasingly from advantageous decks).

These results may have implications for secondary disabilities noted in FASD. Similar to difficulties with interpersonal/financial spheres that are observed in individuals with ventromedial/orbitofrontal damage (Bechara, et al., 2000), individuals with prenatal alcohol exposure are often found to have deficits in everyday functioning. More specifically, children and adults with FASD have been identified as being at increased risk for participating in inappropriate sexual behavior, having

disruptions to school experience, legal trouble, confinement and drug and alcohol problems (Streissguth, et al., 1996). Future investigations are necessary to determine directly the relationship between difficulties with everyday functioning and decision-making ability, to assess the ecological validity of these observed deficits within the FASD population.

Unlike the FASD group, the ADHD group tended to choose significantly more advantageous cards in later blocks than in earlier blocks, as evidenced by a significant effect of block. These results indicate children with ADHD are able to effectively adapt their strategy in relation to rewards and losses. Previous data examining performance of individuals with ADHD on the IGT are mixed. Adults (Malloy-Diniz, Fuentes, Leite, Correa, & Bechara, 2007) and adolescents (Toplak, et al., 2005) with ADHD have been found to choose significantly fewer cards from advantageous vs. disadvantageous decks when compared with controls. However these significant group differences were not replicated in other child samples on modified versions of the IGT (Geurts, et al., 2006; Masunami, et al., 2009). One study including adolescents with ADHD and conduct disorder found poorer performance than controls on IGT performance only when the task was administered a second time (Ernst, Kimes, et al., 2003).

These mixed results suggest several possibilities for the lack of group differences observed with children with ADHD were compared to controls. One is that while children with ADHD may process rewarding/punishing stimuli differently at the level of physiological/brain function, behaviorally they are able to compensate for their aberrant processing. An additional explanation might be that while group

differences are observed in adulthood, these differences are not yet observable earlier in development. Because the frontal lobes continue to develop through early adulthood (Casey, Giedd, & Thomas, 2000) and IGT performance may not reach adult-level proficiency until after age 17 (Hooper, et al., 2004), it may be that the difficulty in decision-making in children with ADHD may not be evident until these functions are fully developed in peers. In addition, it is not clear that samples of children and adolescents with ADHD are comparable to adult samples and 40 to 69% of individuals with ADHD in childhood no longer meet criteria for the diagnosis in adulthood (Faraone & Biederman, 2005). Therefore, adults with the diagnosis may be more severely affected or a qualitatively different sample than children with ADHD and this may lead to increased likelihood in detecting group differences on gambling tasks in older samples.

Spatial Working Memory

Overall group differences were observed on the delayed response task. In designing the task, participant performance was expected to decline with longer exposure to the motor distracter (i.e. lower accuracy would be seen at longer delays), as this increased interference was expected to be more cognitively taxing. This expectation was supported by a significant effect of delay, with longer delays being associated with lower accuracy, indicating the task worked as a measure of working memory.

On follow up analyses, children with prenatal alcohol exposure in general, had lower accuracy than the control children. However, these results are somewhat equivocal regarding whether children with FASD in this sample demonstrate working

memory deficits. Because an interaction effect was not observed, it is possible that the poorer performance in FASD participants was due to problems with perceptual deficits and not to a specific deficit in working memory. Children in the ADHD group demonstrated similar performance, with overall performance lower than controls. As in the FASD group, deficits did not worsen with increasing delay suggesting a lack of a specific deficit in working memory. Thus, these results are inconsistent with previous studies supporting the presence of working memory deficits in children with ADHD (Nigg, 2005). Very little research has been devoted to this domain in children with FASD and results are conflicting. A recent investigation demonstrated children with FASD were more error prone and had poorer strategies than controls on a computerized measure of spatial working memory (Green, et al., 2009). However, in this investigation, children with FASD had poorer performance on a separate perceptual task, which was not considered in the analysis of working memory. Univariate comparisons at each delay were conducted and found to be significantly poorer in children with prenatal alcohol exposure, however interaction effects were not examined and so it is unclear if deficits in this sample are specific working memory impairments, after taking into account perceptual deficits. Therefore, continued investigation of working memory in children with FASD is necessary, including examination of other modalities (e.g. verbal working memory) and controlling for lower order tasks. Identifying parametric tasks, which could be adjusted so that children with FASD are able to perform at the same level as controls on low order (e.g. perceptual) conditions would help to illuminate the level and nature of performance in working memory.

Relationship of Decision-Making and Working Memory

Hierarchical linear regression analyses were conducted, including group and working memory performance to predict overall decision-making performance. Group was found to be an independent predictor of IGT slope performance, however IGT was not predicted by or associated with working memory performance. The lack of relationship between working memory and decision-making was observed in both clinical groups as well as in the control participants. Although the pattern of results were not those that were originally hypothesized, previous literature is mixed regarding the relationship between working memory and decision-making performance. The original conceptualization when creating the IGT was that the measure captured a cognitive ability that was unique and dissociable from working memory and other "cognitive" executive function measures. Models of frontal-subcortical circuitry provide neuroanatomical support for this proposed behavioral dissociation. Closed loops involving primarily orbitofrontal/ventromedial functions have been shown to mediate emotion-based decision-making, while dorsolateral-subcortical loops are activated for working memory and other "cognitive" executive functions. The data from the current investigation demonstrated that although the children in the FASD group had poorer overall performance on measures of working memory and decision-making separately, that these functions are not significantly correlated. A recent review determined that across 15 studies, which included 25 correlations of overall IGT performance with a measure of working memory and both clinical and control child and adult subjects, only 4 of 25 correlations were significant (Toplak, et al., 2010). Based on correlations that were reported in these investigations,

a median value of $r = 0.06$ was calculated, which authors emphasize may an overestimate, because values for nonsignificant correlations typically were not reported. These results were observed in samples similar to those included in this investigation, as non-significant correlations were observed in samples including typically developing children (Crone & van der Molen, 2004) and in adult samples of ADHD (Malloy-Diniz, et al., 2007). Therefore, while these results were not hypothesized, they are consistent with the majority of results finding a lack of relationship between working memory and IGT performance from recent investigations. In addition, the inclusion of the working memory task in the current investigation allowed for examination of the relationship between cognitive functions, rather than examining decision-making, a high order cognitive function, in isolation. Adopting this cognitive process approach allowed for examination of the mechanism of deficit and interrelationships of cognitive functions in children with ADHD and FASD and that decision-making performance cannot be accounted for by working memory performance.

These results may provide support for the dual-pathway model of ADHD as proposed by Sonuga-Barke (2003, 2005). This model suggests that symptoms observed in ADHD may be explained by dual routes: executive dysfunction as mediated by frontal dorsolateral-striatal circuits and altered reward processes as mediated by frontal ventral-striatal pathways. In some previous literature these two pathways have been posed as competing models to explain a singular “core deficit” leading to ADHD. In the dual-pathway model, both circuits are included to explain the range of deficits observed in ADHD that have not been sufficiently addressed by

either model alone. Recent investigations have demonstrated that within a group of children with a diagnosis of ADHD, some children were better categorized as having deficits in executive functions, while children who did not demonstrate executive dysfunction were better characterized by difficulty with delay aversion (Lambek et al., 2010).

While the dual-pathway model was developed as an explanatory mechanism for deficits in ADHD, it may be useful to examine deficits in alcohol-exposed populations. Children with FASD have been found to be impaired on measures of "cognitive" executive function in relation to controls (Kodituwakku, et al., 2006; Kodituwakku, et al., 1995; Mattson, et al., 1999; McGee, et al., 2008; Schonfeld, et al., 2001; Vaurio, et al., 2008). In the current study, performance on the working memory task was not significantly correlated with deficits on a measure of decision-making. Similar results were observed in the only known previous investigation to simultaneously examine cognitive and emotion-related processing in children with FASD, where working memory and decision making skills were found to be relatively independent of one another (Kodituwakku, et al., 2001). Neuropsychological and behavioral dysfunction that are currently viewed as overlapping in children with ADHD and those with FASD potentially could be distinguished using this model. Investigations comparing children with ADHD and FASD on multiple measures of reward processing and executive function may have clinical utility in contributing to developing neurobehavioral profiles of these disorders. This information also may contribute to identification of appropriate targets for behavioral therapy (e.g. planning/organization versus tolerance of delay aversion/processing of future

rewards/consequences). Pharmacological interventions in both populations may be informed by further delineation of the relative functioning of reward processing and executive dysfunction. While altered processing of reinforcements have been theorized to arise from hypofunction of the mesolimbic dopamine branch, executive dysfunction may be attributable to hypofunction of the mesocortical dopamine branch (Sagvolden, Johansen, Aase, & Russell, 2005). Specifically targeting altered neurotransmitter networks may allow for more efficient intervention.

Frequency of Reward

Previous investigations have demonstrated that some clinical groups have aberrant processing of reinforcements that relates to the frequency of reward and punishment. Therefore IGT results were analyzed to determine if performance by children with FASD or ADHD could be characterized based on approach or avoidance of reward. Children in the FASD group had a pattern of performance that was similar to the control group. Over time, children with FASD and control children preferentially selected from decks with infrequent larger losses versus those with frequent smaller losses. When compared directly, a marginal effect of group was observed, indicating that controls demonstrated preference for decks with infrequent (i.e. less predictable), large losses to a greater degree than did children with FASD. The approach adopted by controls allowed them to select significantly more advantageous cards than children with FASD. Control participants' overall strategy showed they tended to select more cards from decks with unpredictable (infrequent, large loss) contingencies. Therefore, these findings may indicate that the ability to tolerate unpredictable contingencies can be an advantage in effective decision making.

Children with FASD also demonstrated this tendency to select from decks with infrequent, large losses, to a lesser degree when compared to controls. The decreased approach of unpredictable losses observed in the FASD group may have contributed to lower overall advantageous strategy.

While results of advantageous deck choices were not effective in distinguishing children with ADHD from either group, examination of performance based on frequency of reinforcement revealed that children in the ADHD group had a significantly different pattern of performance when compared to controls. Across the task, typically developing controls selected similar proportions of cards with frequent and infrequent loss across the majority of trials (after trial 40), indicating a relatively consistent approach in relation to frequency of punishment. However, over time, children in the ADHD group began to select preferentially from decks that had smaller, more frequent rewards and smaller, more frequent losses. Previous investigations that have used tasks involving reinforcement have demonstrated that children with ADHD have a preference for small immediate rewards in comparison to larger delayed rewards (for review, see Luman, Oosterlaan, & Sergeant, 2005). The results from this study are consistent with these findings, and suggest that after children with ADHD were sufficiently exposed to the task to have some familiarity with contingencies, they selected significantly more cards from decks with frequent small rewards and frequent, small losses. In contrast, Toplak et. al (2005) found that on the IGT, children with ADHD selected significantly more cards from deck B (large reward, infrequent large punishment), while in this study the ADHD group tended to select *fewer* cards from both decks with infrequent punishment (deck B + D). Other

results find that performance of children with ADHD is better characterized by dysregulation when processing magnitude and not predicted by processing frequency of reward and loss (Luman, Oosterlaan, Knol, & Sergeant, 2008). It appears that further investigations that covary both frequency of reward/loss and magnitude of reward/loss will help to clarify the presence and nature of deficient reward processing in individuals with ADHD.

Individuals with ADHD and FASD often have comorbid mood symptoms and previous investigations demonstrate that affective disorders contribute to processing frequency of rewards in the IGT. On a modified version of the IGT, performance of individuals with generalized anxiety disorder (GAD) was better predicted by analysis of frequency of loss than advantageous deck choices. In fact, adult participants with GAD actually outperformed matched controls (Mueller, et al., 2010). When compared to controls, participants with GAD tended to avoid decks with large infrequent loss, suggesting that anxiety may have increased sensitivity to unpredictable long-term loss. In a separate investigation, when children with an ADHD diagnosis with and without comorbid symptoms of depression and anxiety were compared on a modified version of the IGT, those without elevated internalizing symptoms had impaired performance, while children rated high on depression and anxiety had performance comparable to controls (Garon, et al., 2006). Internalizing symptoms may lead to a somewhat protective approach to the IGT. It may be that the contingencies involved in the IGT do not capture an element in everyday life for which a riskier approach could be beneficial. Paradigms that reward for varying levels of risk may be interesting to use in populations with primary or comorbid affective disorders.

Relationship of Decision-Making, Executive Function and Intellectual Function

Similar to the analyses demonstrating that working memory was not significantly related to decision-making performance, the vast majority of results in the current investigation demonstrated a lack of relationship between cognitive executive function measures and gambling task performance for any of the groups included in the investigation. Measures were selected to represent processes that might be related to effective gambling task performance and included domains of inhibition, nonverbal planning, verbal concept formation, nonverbal problem solving and reversal-learning. These results add to the growing literature that suggests that the IGT may capture an ability that is relatively independent of measures of more "cognitive" executive function.

The findings again may relate to the dual-pathway model (described above) and also could converge with evidence from the somatic marker hypothesis. Although overall group differences were observed on some measures of executive function (e.g. Color-Word Interference), these impairments were not significantly correlated with IGT performance. Physiological data, such as skin conductance measures, were not collected in this investigation to directly assess the relationship of peripheral nervous system functioning and behavioral performance. However, the lack of association between emotion-based decision-making and executive function using behavioral data suggests that some aspect of the IGT may tap a unique cognitive process. Further examination of the relationship between peripheral and central nervous system function on the IGT in contrast other cognitive domains would illuminate if the somatic marker hypothesis is supported in these populations.

Groups were not matched on intellectual function. However, analyses suggested that verbal and nonverbal intelligence were not significantly correlated with decision-making performance. This finding is consistent with previous investigations examining the relationship of IQ with IGT performance (Toplak, et al., 2010). It should be noted that IQ scores in children with heavy prenatal alcohol exposure are often diminished (for review see Mattson & Vaurio, 2010), and the mean IQ index scores fell in the in the low average range in this sample, while index scores for the CON and ADHD group generally fell within the average range (with the exception of high average verbal comprehension index in the control group), indicating that differences in intellectual function are likely to be clinically significant in children with FASD versus ADHD or typically developing controls. Analyses in this investigation were conducted within groups rather than collapsed across clinical and control groups, as interrelationships of cognitive function can differ in clinical samples. This approach was adopted to better specify within-group relationships and increase likelihood that significant relationships between cognitive functions would be detected. The general lack of significant correlations and suggests that a significant relationship between IQ and decision-making may not exist in children with FASD or ADHD. In addition, because the current findings are consistent with the majority of previous investigations, they provide added support for the relative independence of emotion-based decision-making and intellectual function more generally.

Group Classification

Results of analyses from logistic regression analyses indicated that measures of executive function and decision-making are useful in distinguishing typically

developing controls from children with heavy prenatal alcohol exposure. More specifically, when measures of inhibition, planning verbal concept formation, nonverbal problem solving, working memory and decision-making were entered as predictors, decision-making and inhibition were retained as tasks that differentiated children with FASD from typically developing controls. Despite significantly poorer FASD performance when compared with controls on measures of verbally mediated concept formation (Twenty Questions) and spatial working memory, these scores were not found to distinguish groups on logistic regression. One explanation for the exclusion of the Spatial Working Memory variable from our model may be the variability within the measure, as indicated by somewhat larger standard deviation values. The variables retained in the model are those that account for unique variance and so it is possible that variance captured by the working memory and concept formation tasks were overlapping with those seen on other measures. Interestingly, decision-making performance, which has not been previously assessed in children with prenatal alcohol exposure, was found to be particularly useful in predicting FASD versus control group membership, suggesting the IGT may be a clinically useful tool to include in future investigations. A useful model to distinguish children with FASD from those with ADHD did not emerge using measures of executive function and emotion-based decision-making. One possibility for the lack of a distinguishing model is that the overlapping behavioral problems noted in populations of ADHD and FASD are captured by executive dysfunction and impaired decision-making. Rather than being domains of significantly different functioning, executive function and decision-making may be domains of shared deficit. It may be useful to

apply the dual-pathway model at the level of the individual in ADHD and FASD populations to determine if children with co-morbid executive dysfunction and impaired decision making are a distinguishable subgroup from children who have impairments in only one or the other domain. Alternatively, it is possible that the measures applied in this investigation are not sufficiently sensitive or focused on the correct aspect of executive dysfunction to detect the mechanisms of deficits in clinical populations with overlapping symptomatology. Comparison of other aspects within the domain of reward processing/decision making (e.g. delay aversion) as well as inclusion of other cognitive domains (e.g. attention) may help elucidate comparable and dissociated neuropsychological domains.

Summary

Collectively, these results suggest that children with FASD and those with ADHD demonstrate a different pattern of performance on the IGT in comparison to controls when assessed across the dimensions of advantageous deck choices and frequency of deck choice. While children with FASD adopted a significantly less advantageous approach and did not appear to be able to adjust their strategy to maximize reward, children with ADHD did not differ significantly in their approach to the IGT versus controls, and to some degree selected increasing numbers of advantageous cards over time. When compared to controls in card selection based on frequency of reward/punishment, children with FASD had a similar (if less pronounced) pattern when compared with controls, with both groups adopting a fairly consistent style and preferentially selecting from decks with infrequent losses, an approach that has been interpreted to be risk-taking. In contrast, over time children

with ADHD altered their strategy and selected fewer cards from decks with infrequent losses, a pattern of performance that suggests children with ADHD in this sample avoided choices that had unpredictable contingencies. Decision-making appears to be a relatively independent process in these populations, as working memory, other executive functions and intellectual function were not predictive of or associated with gambling task performance in any of the groups.

Limitations

Marginal effects were observed on outcomes related to advantageous deck selection on the IGT. These results were followed up despite trend-level significance. The lack of an overall group by block effect appears to be related to the pattern of performance observed in the ADHD group, as significant effects were observed upon direct comparison of the FASD and control groups. ADHD group performance was not found to be significantly different on selection of advantageous cards on the IGT when compared to either the typically developing controls or children with prenatal alcohol exposure. Combined measures of executive function and decision-making also were not useful in distinguishing the ADHD and FASD groups from one another and only marginal effects were observed in relation to processing frequency of reward. In addition, in most analyses, corrections for multiple comparisons were not employed and if utilized, some effects currently interpreted as significant would be re-classified as marginal. This raises the possibility that the investigation was underpowered in its ability to detect differences between clinical groups on the IGT. A previous investigation from our lab was able to detect differences in ADHD versus FASD group performance on measures of executive function with similar, and even smaller,

sample sizes (Vaurio, et al., 2008). Based on post-hoc power calculations, our sample size should have allowed for very good power to detect of significant overall differences. On some measures, significantly different variability was observed (e.g IGT block 5 net advantageous deck selections) when comparing clinical and control group performance. While violations of homogeneity of variance are typically considered less problematic when sample sizes are equal (as they are in this investigation), it may have decreased sensitivity to detect group differences. This may explain why only marginal effects were observed on the omnibus comparisons of advantageous deck choices on the IGT and spatial working memory analyses. Regarding the lack of differences between the clinical groups more specifically, effect sizes when comparing the FASD group directly to the ADHD group on the IGT were small. Based on power analyses, a required sample size of 77 per clinical group would be necessary to detect group differences on IGT advantageous deck choices. Therefore, increasing sample size may allow for either detection of small effect sizes between the ADHD and FASD groups, and/or could determine if ADHD participant behavior with regards to advantageous decision-making is different from or comparable to typically developing peers. A larger sample size in the control group also is likely to increase power to detect significant differences by reducing within-group variance. That sample size is not feasible for the current investigation but could be considered as a target for future studies.

The analytic strategy adopted in this investigation to examine decision-making performance as measured by the IGT was selected in order to allow for comparability with previous investigations. The IGT has high sensitivity to impaired decision-

making but low specificity as to underlying mechanisms of the deficit (Brand, et al., 2007). Therefore, while it appears that children with prenatal alcohol exposure adopted an ineffective decision-making strategy, the mechanism of this dysfunction is unclear. Recent investigations using the expectancy valence model as developed by Busemeyer and Stout (2002) have suggested that assessing participant performance on a trial-by-trial basis may allow for distinguishing component processes that lead to poor performance on the IGT. Using this model, three processes have been identified as factors that might explain poor performance on the IGT: 1. motivation (degree to which individual focuses on gains versus losses), 2. ability to adjust for current performance based on previously observed contingencies (attention to recent versus past trials), and 3. consistency of the individual's choices (possibly related to boredom, fatigue) (Yechiam, Busemeyer, Stout, & Bechara, 2005). The expectancy valence model been useful in distinguishing clinical populations' performance across these dimensions and may allow for increased sensitivity to detect different strategies in ADHD and alcohol-exposed children.

It is possible that the involvement of the ventromedial/orbitofrontal cortex in decision-making is related to increased complexity of a task, rather than related to integration of emotional response into the task. In a previous case study, an individual with ventromedial brain injury was error-prone on complex measures of memory and executive function (Cato, Delis, Abildskov, & Bigler, 2004), indicating that damage to the VM-PFD may lead to various cognitive deficits and sensitive, high order measures are necessary to detect such deficits. Incorporation of neuroimaging and other physiological measures may allow for determination if there is a distinct brain

response and body-brain relationship on measures of emotion-based decision-making that is not observed on complex high order measures of executive function without an affective component.

Future Directions

Follow up investigations using neuroimaging techniques to examine brain-behavior relationships may illuminate if underactive or overactive brain activity is associated with poor performance on the IGT as observed in children with FASD. Additionally, as in previous studies, comparison of peripheral nervous system response in both groups of children may help determine the nature of the relationship between somatic markers and behavioral response and to test the validity of the somatic marker hypothesis in individuals with FASD.

It does not appear that deficits on the IGT can be accounted for by deficits in cognitive executive function or differences in intelligence. Sample size precluded sub-group analysis of matched-IQ participants. Future investigations using a sample well-matched on IQ may elucidate further the relationship between intellectual function and decision-making in children with FASD. A recent investigation from our center adopted this approach and demonstrated that after controlling for IQ deficits, children with FASD have elevated rates of problematic behavior including social problems, rule-breaking behavior and aggressive behavior, although executive dysfunction was no longer apparent when IQ deficits were taken into account (Vaurio, Riley, & Mattson, 2011). Adding laboratory measures of emotion-based processing and determining their relationship to reported behavioral problems in matched IQ samples

may identify an additional domain that is affected independent of intellectual function in individuals with FASD.

Heavy prenatal alcohol exposure is associated with increased risk for comborbid diagnoses, including oppositional defiant disorder, conduct disorder, depressive disorders, specific phobias, substance abuse and personality disorders (Barr et al., 2006; Fryer, McGee, et al., 2007). Common comborbidities observed in individuals with ADHD include oppositional defiant disorder, conduct disorder, depressive disorders, and anxiety disorders (Gillberg et al., 2004). In this investigation it was not possible to examine or control for the effect of all co-occurring diagnoses on decision-making in either sample. It would be improbable to identify large groups of individuals with heavy prenatal alcohol exposure who did not meet criteria of a DSM diagnosis, or samples of individuals with ADHD-only diagnoses, and it seems this approach would limit generalizability because the samples would not be representative. Future investigations with larger samples should consider the relative contribution of comorbid psychiatric symptoms and syndromes that may provide additional explanatory power to patterns of decision-making performance in these populations.

While commercially available standardized gambling tasks have recently become accessible, currently available research on clinical populations, especially including children, is based on varied experimental paradigms and differing analytic approaches. As with any experimental task, increased generalizability across investigations is likely to emerge with standardized instructions, normative samples and further data on optimal use of outcome variables in analyses.

V. Appendix

Which is more?

9 or 3

7,000 or 800

$5.75 or $7.00





Which costs more?

Figure 2. Images of Quantity Task Stimuli

VI. References

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