Neuropsychol Rev (2011) 21:81–101
DOI 10.1007/s11065-011-9167-9

REVIEW

Fetal Alcohol Spectrum Disorders: Neuropsychological and Behavioral Features

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Received: 20 January 2011 / Accepted: 3 April 2011 / Published online: 19 April 2011

Abstract Heavy prenatal alcohol exposure can cause alterations to the developing brain. The resulting neurobehavioral deficits seen following this exposure are wide-ranging and potentially devastating and, therefore, are of significant concern to individuals, families, communities, and society. These effects occur on a continuum, and qualitatively similar neuropsychological and behavioral features are seen across the spectrum of effect. The term fetal alcohol spectrum disorders (FASD) has been used to emphasize the continuous nature of the outcomes of prenatal alcohol exposure, with fetal alcohol syndrome (FAS) representing one point on the spectrum. This paper will provide a comprehensive review of the neuropsychological and behavioral effects of heavy prenatal alcohol exposure, including a discussion of the emerging neurobehavioral profile. Supporting studies of lower levels of exposure, brain-behavior associations, and animal model systems will be included when appropriate.

Key Words Fetal alcohol syndrome (FAS) · Fetal alcohol spectrum disorders (FASD) · Neuropsychological outcome · Behavior · Neurobehavioral profile · Behavioral teratology

Of the many potential outcomes of prenatal alcohol exposure, alterations to the developing brain and resulting neurobehavioral deficits are of the most devastating. The term fetal alcohol spectrum disorders (FASD) has been used to emphasize the continuous nature of the effects of prenatal alcohol exposure, with the fetal alcohol syndrome (FAS) at the more severe end of the spectrum. Exposure to alcohol in utero is associated with cognitive impairment in various neuropsychological domains, including overall intellectual performance, executive function, learning and memory, language, visual-spatial ability, motor function, attention, and activity levels as well as behavioral problems including adaptive dysfunction, academic difficulties, and increased rates of psychiatric disorders. This paper will provide a comprehensive review of the neuropsychological effects of heavy prenatal alcohol exposure. Supporting studies of lower levels of exposure, brain-behavior associations, and animal model systems will be included when appropriate. Related topics, including structural (Lebel et al. 2011) and functional (Coles and Zhihao 2011) neuroimaging and diffusion tensor imaging (Wozniak and Muetzel 2011) as well as interventions (Kodituwakku and Kodituwakku 2011), also are included in this issue.

Diagnostic Terminology

The term FAS, or fetal alcohol syndrome, is used throughout this paper to refer to patients or subjects who meet the diagnostic criteria for FAS, as defined by the Institute of Medicine (IOM; Stratton et al. 1996) including modifications suggested by Hoyme et al. (2005). The term FASD, or fetal alcohol spectrum disorders, is used to refer to the larger group of patients who are affected by prenatal alcohol exposure and who may or may not meet diagnostic criteria for FAS (Bertrand et al. 2004). Individuals encompassed under this non-diagnostic umbrella term are those with diagnoses of FAS, partial FAS, or alcohol-related

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neurodevelopmental disorder (ARND) (Bertrand et al. 2004; Hoyme et al. 2005), as well as individuals affected by prenatal alcohol exposure who may not have any diagnosis.

One of the biggest challenges in understanding the considerable variability of neurobehavioral outcomes of prenatal alcohol exposure involves identifying the dose and pattern of alcohol consumption as well as developmental timing of exposure. In general, the amount of alcohol consumed is correlated with the severity of outcome (e.g., Sood et al. 2001; Streissguth et al. 1989b). However, pattern of alcohol exposure can often moderate these effects, with binge-like exposures resulting in more severe deficits than chronic exposure (Bailey et al. 2004; Bonthius et al. 1988). Timing of exposure is also important. Alcohol exposure during different periods of fetal development can greatly influence the pattern and severity of structural and functional abnormalities (Guerri et al. 2009). Unfortunately, this level of detail is often difficult to document, particularly in retrospectively recruited samples, and individual studies provide varying degrees of detail concerning levels and patterns of exposure. However, although criteria used to delineate heavy prenatal alcohol exposure may be inconsistent across studies, these samples generally include children of women who meet criteria for alcohol abuse and dependence (e.g., Coles et al. 1991; Mattson et al. 1998; Mattson et al. 2010). Prospectively recruited samples, by design, allow for a greater precision when describing dose, pattern, and timing effects of prenatal alcohol exposure, but exposure levels are generally lower than in retrospective samples. Lower levels of exposure are generally defined as one to three drinks per week (e.g., Fried and Watkinson 1988; Jacobson et al. 1993; Willford et al. 2004). Different criteria for moderate to low exposure are included when available. These issues highlight the complexity of conducting research on prenatal alcohol exposure and the many risk factors and moderating variables that contribute to the considerable range of phenotypes presented by individuals with FASD.

General Intelligence

One of the most common neurocognitive findings among those exposed to alcohol during pregnancy is diminished intellectual capacity. The majority of individuals diagnosed with FAS are not intellectually disabled (defined as overall IQ score <70 and adaptive disability), and intellectual disability is not a necessary criterion for the diagnosis of FAS. However, FAS is considered one of the leading identifiable causes of mental retardation (i.e., intellectual disability, Abel and Sokol 1987; Pulsifer 1996). Many affected individuals exhibit impaired intellectual abilities, even in the absence of facial features (i.e., smooth philtrum, short palpebral fissures, and thin vermillion) and growth retardation (Dalen et al. 2009; Mattson et al. 1997), although children with a diagnosis of FAS tend to have more severe impairments than those who were exposed prenatally to alcohol but do not have sufficient dysmorphic features for a diagnosis (Mattson et al. 1997). One study indicated that children with FAS have mean IQ scores significantly lower than those with partial FAS and ARND, who do not differ significantly from one another (Chasnoff et al. 2010), and another reported a significant relation between general cognitive function and degree of dysmorphic features and growth deficiency (Ervalahti et al. 2007). The average IQ estimate of individuals with heavy prenatal alcohol exposure is 70 for those with FAS (Streissguth et al. 1991) and 80 for nondysmorphic individuals (Mattson et al. 1997). Although a clinically significant difference between verbal and nonverbal intelligence scores is often present, the direction of this difference is not consistent (for review, see Mattson and Riley 1998). Furthermore, IQ score is significantly correlated with psychopathology; children with moderate and severe intellectual disability experienced greater psychiatric disturbance, and IQ scores below 50 indicated poor psychiatric outcome (Steinhausen et al. 1994).

Much less research has examined intellectual abilities among individuals with lower levels of alcohol exposure, and results have been conflicting. Early studies found moderate levels of prenatal alcohol exposure to be associated with decreases in intelligence scores in young children (Fried and Watkinson 1988; Streissguth et al. 1990; Streissguth et al. 1989a). A more recent study found that moderate alcohol exposure during first and second trimesters significantly affected intellectual ability, but only among African American children (Willford et al. 2006). However, another study reported that moderate levels of consumption are not associated with verbal, performance, or overall IQ scores in childhood (Alati et al. 2008). Although a weak effect of binge drinking (4 or more units of alcohol per occasion) was found, it was attenuated when mother's educational attainment was taken into account. The discrepancies among studies with lower levels of exposure highlight the need for additional research and importance of considering a variety of factors when evaluating studies.

Executive Function

Great interest has been shown in understanding higher-order cognitive processes in developmental psychopathologies, including FASD. Executive functions are related to frontal-subcortical circuits involving projections from the

frontal lobes to the basal ganglia and thalamic nuclei (Cummings 1993), which have been found to be vulnerable to prenatal alcohol exposure (Fryer et al. 2007b; Mattson et al. 1996c). Executive functions have been widely defined as "the ability to maintain an appropriate problem-solving set for attainment of a future goal" (pp. 201–202, Welsh and Pennington 1988). This complex construct encompasses a variety of cognitive abilities, such as planning, response inhibition, and working memory, and involves the integration of more basic processes such as attention, memory, sensation, perception, and motor activity (Pennington and Ozonoff 1996).

The Behavior Rating Inventory of Executive Functioning (BRIEF) is a parent report of executive function in children (Gioia et al. 2000). It includes eight subscales and two summary indices. Several studies have evaluated children with FASD using the BRIEF, however, many of these have not included a comparison group of children. In one study without controls, children with FASD had scores in the clinical range (>1.5 standard deviation from the population average) on all subscales, with greatest difficulty on the inhibitory control, working memory, and problem-solving subscales (Rasmussen et al. 2007), while another study revealed abnormal elevation on all but two subscales (Rasmussen et al. 2006). In a separate investigation, these executive function deficits (using the two BRIEF summary indices) were predictive of poorer social skills and greater problem behaviors (Schonfeld et al. 2006). Because these studies did not include a comparison group it is difficult to conclude whether the magnitude of the deficits persists when compared to a demographically matched control group. A later investigation of 43 adolescents (age 13–18 years) did include a comparison group and replicated these effects, revealing that children with prenatal alcohol exposure demonstrate poorer executive functioning than typically developing controls for all subscales and summary indices of the BRIEF (McGee et al. 2008a). However, parents of the children with FASD in this study were instructed to recruit another child similar to their own but without prenatal alcohol exposure. These unexposed children comprised the comparison group; as a result, the group may not have been representative of the population of typically developing children. While more research is needed in this area, these parent-report findings are further supported by neuropsychological data, which indicate that alcohol-exposed children are delayed on executive function tasks, including measures of problem-solving, planning, concept formation and conceptual set shifting, verbal and nonverbal fluency, response inhibition, and working memory, as detailed below.

Problem-Solving and Planning Various tower tasks have been used to demonstrate deficits in the domains of problem-solving and planning. In these studies, alcohol-exposed children display increased perseverations on incorrect strategies, increased rule violations, fewer passed items overall, and decreased initial time planning a strategy to complete each problem than typically-developing controls (Aragon et al. 2008b; Green et al. 2009b; Kodituwakku et al. 1995; Mattson et al. 1999).

Concept Formation and Set-Shifting Difficulties forming and identifying abstract concepts and shifting to new conceptual categories have also been reported. Alcohol-exposed children make more errors and complete fewer categories compared to controls on the Wisconsin Card Sorting Test (WCST), a task that requires abstract reasoning and the ability to shift cognitive strategies in response to feedback (Carmichael Olson et al. 1998; Coles et al. 1997b; Kodituwakku et al. 1995; McGee et al. 2008b; Vaurio et al. 2008). In one study using the WCST, children with FAS tended to perform more poorly than exposed children without FAS (McGee et al. 2008b), yet in another study, differences among groups of alcohol-exposed children—FAS, partial FAS, and ARND—were not significant (Chasnoff et al. 2010). Similarly, in a study using the California Card Sorting Test of the Delis-Kaplan Executive Functioning System (D-KEFS), children with and without a diagnosis of FAS completed fewer sorts than control children and received fewer points for their description of their sorts (McGee et al. 2008b). Not only were alcohol-exposed children less able to generate concepts independently, they were less able to recognize categories when cued by the examiner. Furthermore, on the California Word Context Test of the D-KEFS, a test that assesses concept formation and reasoning in the verbal domain, children with prenatal exposure to alcohol needed more sentences to form a correct response and made more set loss errors (Mattson and Riley 1999). Combined, these findings suggest that individuals with histories of prenatal alcohol exposure have difficulties forming and shifting concepts and thinking analytically, which in turn, impair their problem-solving abilities.

Fluency Another area of executive function that is compromised by prenatal alcohol exposure is fluency. Children exposed to alcohol during gestation demonstrate deficits on both traditional and set-shifting measures of verbal and nonverbal fluency. In one study, deficits on higher-order switching tasks were not accounted for by traditional fluency tasks, and deficits persisted when IQ was controlled statistically (Schonfeld et al. 2001). Within the verbal domain, four studies have demonstrated that although deficits are noted in both letter and category fluency, deficits are greater on letter fluency tasks (Kodituwakku et al. 2006b; Mattson and Riley 1999; Rasmussen and Bisanz 2009; Vaurio et al. 2008). Similar findings were also

reported within a sample of Native American Indian children: compared to controls, alcohol-affected children were impaired in letter fluency but unimpaired on category fluency (Aragon et al. 2008b).

Findings within the nonverbal domain have been less clear. While one study documented impaired design fluency amongst alcohol-exposed children compared to controls (Schonfeld et al. 2001), another found that children with FASD did not display deficits relative to normative data (Rasmussen and Bisanz 2009). This discrepancy in findings may be related to the two study designs. In the first study, scores of alcohol-exposed children were compared to a typically developing control group matched on demographic characteristics including age, sex, and race, whereas in the second study, they were compared to the normative mean (scaled score=10), possibly attenuating group differences.

Inhibitory Control Response inhibition is another area of weakness in alcohol-exposed children. On measures of inhibitory control, such as the Stroop Test, children with histories of heavy prenatal exposure to alcohol make more errors than typically developing children, particularly on the switching and interference conditions (Connor et al. 2000; Mattson et al. 1999). A study using event-related potentials to examine response inhibition processing found that children with FAS and partial FAS behaviorally inhibited responses as well as control groups on a Go/No-Go task; however, the level of neural activation was greater in children prenatally exposed to alcohol, suggesting greater cognitive effort (Burden et al. 2009). Similar findings have been described in a study using fMRI during a Go/No-Go task (Fryer et al. 2007b) (for further discussion, see Coles and Zhihao 2011). Poor inhibitory ability may be related to impaired theory of mind, as poor performance on theory of mind measures has been found to be correlated with a task of inhibition control in children with prenatal alcohol exposure (Rasmussen et al. 2009).

Working Memory Alcohol-exposed children show deficits in the ability to hold and manipulate information in working memory (Green et al. 2009b; Kodituwakku et al. 1995). A frequently used measure of working memory that has been found to be sensitive to prenatal alcohol effects is the backwards condition of the digit span subtest of the Wechsler Intelligence Scales for Children (WISC). Children with heavy prenatal alcohol exposure recall fewer digits on this condition than typically developing controls (Aragon et al. 2008b; Carmichael Olson et al. 1998; O'Hare et al. 2009). Furthermore, of all the WISC subtests, prenatal alcohol consumption was found to be most correlated with the digit span subtest as well as the arithmetic subtest, which also requires manipulation of information in working memory (Streissguth et al. 1990). In addition to verbal working memory, children with FASD also struggle with visual-spatial working memory. In one study, these children committed more errors and demonstrated poorer use of strategy on a computerized task of spatial working memory (Green et al. 2009b). In another study, children and adults with FASD provided fewer correct responses, greater incorrect responses and non-responses, and longer latencies during correct responses on an experimental visual-spatial *n*-back task (Malisza et al. 2005). Although less work has been done in this area, it appears that working memory abilities are impaired in alcohol-exposed children above and beyond global intellectual deficits. One investigation demonstrated that the association between prenatal alcohol exposure and performance on working memory measures remained significant even after IQ was statistically controlled (Burden et al. 2005b). Understanding of these impairments is particularly significant because these processes often underlie other executive control and attention skills (Burden et al. 2005b).

Learning and Memory

Animal research has established that the hippocampus is particularly sensitive to the teratogenic effects of prenatal alcohol exposure (e.g., Bonthius and West 1990; Livy et al. 2003; Maier and West 2001). While neuroimaging data in humans have been less conclusive, some studies have shown vulnerability of the hippocampus to prenatal alcohol insult (e.g., Autti-Rämö et al. 2002; Willoughby et al. 2008). Not surprisingly, a number of clinical studies have reported learning and memory deficits in children with heavy prenatal alcohol exposure. These impairments range across specific aspects of learning and memory, including verbal and nonverbal skills.

Verbal Learning and Memory Alcohol-exposed children display deficits in both learning and recall of verbal information (Mattson et al. 1996b; Mattson and Roebuck 2002). They learn fewer words on the learning trials of the California Verbal Learning Test-Children's Version (CVLT-C) and have greater difficulty recalling them on both free and recognition recall trials (Crocker et al. 2011; Mattson et al. 1996b). These deficits are present in both children with and without the physical features of FAS (Mattson et al. 1998; Mattson and Roebuck 2002). Interestingly, when the number of words initially learned was controlled, alcohol-exposed children displayed retention rates that were similar to typically developing controls (Mattson et al. 1998; Mattson and Roebuck 2002). These findings have been replicated in independent samples of children (Kaemingk et al. 2003; Willoughby et

al. 2008) and adults (Coles et al. 2010), and in a study of light to moderate levels of alcohol exposure (Willford et al. 2004). Of note, implicit learning strategies on tasks like the CVLT-C may positively influence the ability of alcohol-exposed children to retain verbal information, because spared retention was not detected on another task of word list learning without an implicit learning strategy (Roebuck-Spencer and Mattson 2004).

When given verbal tasks that involve a story rather than word list, children with FASD exhibit superior memory during both immediate and delayed recall compared to their performance on word list tasks. In one study, performance on story recall and word-list recall were compared in alcohol-exposed children (Pei et al. 2008). In comparison to the word-list task, subjects recalled more information on the story task but also recounted more inaccurate information. However, intrusions were only penalized on the word-list task, which may have affected the scores on these tasks. Because no control group was used, it is unclear in this study whether memory for stories in prenatal alcohol exposure is impaired compared to typically developing peers. Other studies, however, have reported deficits in this domain in children with heavy levels of exposure relative to comparison children (Willoughby et al. 2008). In light to moderate levels of exposure, prenatal alcohol exposure predicted poor memory for stories at 10 years of age (Richardson et al. 2002) but not 14 years (Willford et al. 2004) within the same cohort of children. These findings suggest that these abilities might improve with age, at least in less affected children.

Nonverbal Learning and Memory In the nonverbal domain, children with prenatal alcohol exposure also display learning and recall deficits: a lower rate of learning across acquisition trials and less recall of information after a delay period. However, it is less clear whether retention of nonverbal material is intact or impaired because results are mixed when initial learning is taken into account (Aragon et al. 2008b; Kaemingk et al. 2003; Mattson and Roebuck 2002). Differences may be due to task characteristics or length of delay, as described below.

Within the nonverbal domain, limited research has addressed visual-spatial memory, and current data reveal inconsistent results. One study described performance on a virtual Morris water maze task that is sensitive to hippocampal damage. Children and adolescents with histories of prenatal alcohol exposure exhibited poorer performance on the hidden and probe trials but not cued-navigation trials, suggesting that these place-learning deficits were not attributable to visual-motor or motivation deficits (Hamilton et al. 2003). In addition, these findings were consistent with those found in the animal literature (e.g., Johnson and Goodlett 2002). A second study used the Memory for 16 Objects test, a task also sensitive to hippocampal damage. In this study, children with FAS remembered the same average number of objects on immediate recall as control subjects but fewer objects in delayed recall (Uecker and Nadel 1996). In a subsequent study with the same subjects, deficits were noted in spatial but not object recall (Uecker and Nadel 1998). Because retention was not addressed directly in either of these studies, it is unclear whether the nature of the deficits was related to encoding or memory difficulties. Additional studies have also shown impaired spatial recall in alcohol-exposed children compared to controls (Aragon et al. 2008b) and a negative correlation between alcohol exposure and memory for nonverbal figures. In contrast, another research group found greater deficits in object relative to spatial recall in one study (Rasmussen et al. 2006), but no significant differences in spatial compared to object recall at either immediate or delayed time intervals in another study (Pei et al. 2008). Discrepancies may be due to differences in visual memory task design, including the objects participants are asked to remember (familiar everyday items vs. faces) and time delay intervals.

Furthermore, children with FASD have poor spatial recall on the Rey-Osterrieth Complex Figure task relative to controls (Willoughby et al. 2008). Because learning was not assessed in this study, it is difficult to conclude whether impairments are due to learning or memory deficits. A separate study found that light-to-moderate levels of prenatal alcohol exposure predicted poorer performance on a different design memory task (Richardson et al. 2002). Additional studies have demonstrated that when performance on visual perception and verbal memory tasks are taken into account with statistical analysis, group differences in spatial memory are no longer apparent, suggesting that impairments in spatial memory may be explained by deficits in lower order processes (Kaemingk and Halverson 2000).

Language

Research on the effects of prenatal alcohol exposure on language skills has been mixed. Case reports suggest that prenatal alcohol exposure is associated with speech and language disturbances, ranging from an absence of comprehensible speech to mild dysarthria or lisping (Abel 1990). Furthermore, indications of maternal problem drinking may be related to poor receptive language functioning (Russell et al. 1991). Retrospective group studies of language functioning in this population also have revealed language deficits. Impairments include word comprehension (Conry 1990; LaDue et al. 1992;

Mattson et al. 1998), naming ability (Mattson et al. 1998), articulation (Becker et al. 1990), grammatical and semantic abilities (Becker et al. 1990), pragmatics (Abkarian 1992), and expressive and receptive skills (Aragon et al. 2008a; Carney and Chermak 1991; Janzen et al. 1995; McGee et al. 2009b). Population studies with individuals in South Africa and Italy further reveal that exposed individuals have impaired grammar comprehension skills (Kodituwakku et al. 2006a).

While retrospective studies of language have shown fairly clear and consistent results, prospective studies have been more equivocal. Phonological processing deficits at age 14 years were related to prenatal alcohol exposure levels in a long-term prospective study (Streissguth et al. 1994a). Another series of prospective studies found lower levels of alcohol exposure to be associated with significantly lower language comprehension and expression in children at 13-months (Gusella and Fried 1984), 2 years (Fried and Watkinson 1988), and 3 years (Fried and Watkinson 1990). However, within the same cohort of children, deficits in language abilities were not detected later at 4 (Fried and Watkinson 1990), 5, and 6 years of age (Fried et al. 1992), and another prospective study found neither expressive nor receptive language impairments in children ages 1, 2, and 3 years (Greene et al. 1990). A more recent study also found no association between low levels of alcohol exposure and parent reports of language delay at age 2 years (O'Leary et al. 2009). A possible explanation for these discrepancies may be due to varying levels of alcohol exposure. Many of these prospective studies included samples of children who were exposed predominantly to low levels of alcohol; it may be that language deficits are more common in children with heavy prenatal alcohol exposure. It may also be that language deficits are secondary to overall intellectual deficits (McGee et al. 2009b) but further study is needed to clarify this relationship.

Beyond assessing language skills in standardized contexts, recent research has focused on understanding how children exposed to alcohol prenatally use language to achieve communicative goals and conceptualize their social environment. Findings suggest that in social interactions, children with FASD struggle to balance linguistic and social-cognitive task demands in order to produce contextually integrated discourse (Coggins et al. 2003). They provide insufficient organization and information for listeners in narratives (Coggins et al. 2007) and, according to caregiver reports, fail to consider the perspective of the listener during interaction (Timler et al. 2005). Using narrative analysis, one study examined semantic elaboration and strategic use of linguistic references to identify concepts in a group of children prenatally exposed to alcohol. Both normal controls and alcohol-exposed children varied in their extent of semantic elaboration in narrative telling, but children with FASD were significantly more likely to use ambiguous references and inappropriately distinguish concepts in their stories (Thorne et al. 2007).

Visual-spatial Ability

Although research is limited in this domain, deficits in visual-spatial perception and construction have been reported in children with histories of prenatal alcohol exposure. As previously discussed, prenatal exposure to alcohol has been found to be associated with abnormal development of hippocampal structure and functioning (e.g., Autti-Rämö et al. 2002; Barnes and Walker 1981; Berman and Hannigan 2000; Riikonen et al. 1999). Given that behavioral research with animals has shown that visual-spatial abilities depend on medial temporal lobe and hippocampal functioning (e.g., Morris et al. 1982; O'Keefe and Dostrovsky 1971), it is reasonable to expect visual-spatial abilities to be compromised in prenatally exposed individuals.

Multiple studies document impairments in simple visual-spatial construction on tests like the Beery-Buktenica Developmental Test of Visual Motor Integration, which requires individuals to copy drawings of geometric forms (Aronson and Hagberg 1998; Chiodo et al. 2009; Conry 1990; Janzen et al. 1995; Jirikowic et al. 2008a; Korkman et al. 1998; Mattson et al. 1998; Uecker and Nadel 1996). Performance on more complex visual-spatial tasks has been reported only rarely. On a clock-drawing task, although children with FAS were able to remember the essential features of a clock, they disregarded details like spacing between numbers. These observations, combined with reported simple visual-spatial construction deficits, suggest that alcohol-exposed individuals may demonstrate a form of constructional apraxia (Uecker and Nadel 1996). In one very small study of four boys with fetal alcohol effects, none of the subjects were able to successfully model the construction of a simple symmetrical block structure when shown a video of a peer building the same configuration (Meyer 1998). Additional research has shown that children with prenatal alcohol exposure differentially process specific features of visual stimuli. On a hierarchical processing task consisting of large symbols (the global feature) made up of smaller symbols (the local feature), alcohol-exposed children had significantly greater difficulty processing local features compared to global features (Mattson et al. 1996a).

Impairments in visual-spatial perception may account for some of the spatial memory deficits described above (e.g., Kaemingk and Halverson 2000; Uecker and Nadel 1996), as group differences on measures of spatial location are reduced once visual perception performance is statistically

controlled (Kaemingk and Halverson 2000). These results imply that visual-spatial perception deficits in children with FASD may influence spatial memory, but do not completely account for those impairments.

Motor Function

Many studies of FASD suggest an association between alcohol exposure and poor motor performance. The earliest reports by Jones and Smith (1973) described poor hand/eye coordination, weak grasp, tremors, and balance and gait difficulties. More recent studies have found that children prenatally exposed to heavy levels of alcohol exhibit impairment of both fine and gross motor skills. Young children with FAS show clinically important developmental delays in fine but not gross motor skills (Kalberg et al. 2006). Other findings of motor impairment in this clinical population include postural instability (Roebuck et al. 1998b), atypical gait (Marcus 1987), delayed motor reaction timing (Green et al. 2009b; Simmons et al. 2010; Simmons et al. 2002; Wass et al. 2002), impaired fine-motor speed and coordination (Chiodo et al. 2009; Jirikowic et al. 2008a; Mattson et al. 1998), increased motor timing variability (Simmons et al. 2009), poor hand/eye coordination (Adnams et al. 2001), poor bimanual coordination (Roebuck-Spencer et al. 2004), dysfunctional force regulation (Simmons et al. 2011), atypical trajectories in goal-directed arm movements (Domellof et al. 2010), impaired oculomotor control (Green et al. 2009a), poor sensory processing and sensorimotor performance (Jirikowic et al. 2008a), and weak grasp (Conry 1990). However, one study found that children with FASD exhibit deficits in static postural control (Kooistra et al. 2009), which is in contrast to a previous study (Roebuck et al. 1998a) reporting that these children perform as well as controls in stable environmental conditions. Another found no differences in gross motor functioning in FAS children (Adnams et al. 2001). Inconsistencies amongst these studies may be attributed to differences in the comprehensiveness of assessment of postural instability and insensitivity of the Griffith's Locomotor subscale to detecting more subtle motor deficits in this population.

These findings are not surprising considering the teratogenic effects of alcohol to brain regions associated with motor functioning such as the cerebellum and basal ganglia. Animal research has found that cerebellar neurons are sensitive to alcohol-induced damage (Goodlett et al. 1998; Hamre and West 1993; Thomas et al. 1998a), and neuroimaging research has documented significant volume and size reductions in the cerebellum and caudate nucleus of the basal ganglia (Archibald et al. 2001) (for detail, see Lebel et al., this issue). The causes of motor impairment observed in individuals with FASD are not limited to brain dysfunction. In addition to central nervous system abnormalities, peripheral motor nerve damage is also evident. Children prenatally exposed to alcohol show increased motor delay variability (Simmons et al. 2009) that is likely attributable to atypical muscle development (David and Subramaniam 2005), reduced motor neurons (Bradley et al. 1997; Heaton and Bradley 1995), poor peripheral nerve myelination (Zoeller et al. 1994), and slowed nerve conductivity (de los Angeles Avaria et al. 2004) that are associated with prenatal alcohol exposure. Furthermore, skeletal malformations of the hands and feet (e.g., tetraectrodactyly and camptodactyly) (Church et al. 1997; Herrmann et al. 1980) and delayed skeletal maturity (Naidoo et al. 2006) are evident in these individuals and may contribute to poor performance on motor tasks.

While the aforementioned studies used samples that included both young children and adolescents, subsequent research focusing specifically on motor function in older individuals are equivocal about whether the observed deficits persist into adolescence and adulthood. Young children with histories of heavy prenatal alcohol exposure exhibit slower motor reaction time on both simple and choice reaction time tasks (Simmons et al. 2002). However, in a subsequent study with adolescent subjects, group differences were not observed (Simmons et al. 2006). Another study investigating fine motor coordination and balance in two adult populations with FASD, including a prospective longitudinal sample of adults who were exposed to varying levels of alcohol, reported results to the contrary. Data revealed that adults with FASD perform worse than controls on tests of fine motor control and balance and that the dose-dependent effects of alcohol on motor coordination during childhood continued to be apparent in adulthood among individuals previously diagnosed with FAS or ARND (Connor et al. 2006). It is possible that the discrepancies between studies are because each examined different aspects of motor function. It is also possible that some types of motor impairment may represent developmental delays that eventually normalize with age, while others may be long lasting impairments in function. Additional research will help to discern the extent of motor impairment throughout the lifespan.

Attention and Activity Levels

Hyperactivity and attention deficits are frequently observed in individuals with heavy prenatal alcohol exposure. Early reports on FAS describe these children to be tremulous, hyperactive, and irritable (Hanson et al. 1976). Affected children show deficits in attention on neuropsychological tasks of vigilance, reaction time, and information processing (Burden et al. 2005a; Jacobson et al. 1994; Jacobson et

al. 1993; Streissguth et al. 1984, 1986, 1994b). Parent (Janzen et al. 1995; Mattson and Riley 2000; Nash et al. 2006) and teacher (Aragon et al. 2008a; Brown et al. 1991; Carmichael Olson et al. 1992) reports of attention difficulties are also common. More than 60% of children exposed to alcohol in utero exhibit deficits in attention (LaDue et al. 1992), and they demonstrate a significantly higher rate of attention-deficit/hyperactivity disorder (ADHD) (Fryer et al. 2007a) and hyperkinetic disorders (Steinhausen et al. 1993) than typically developing children. Like children with ADHD, children prenatally exposed to alcohol show impairments investing, organizing, and maintaining attention as well as inhibiting impulsive responses (Nanson and Hiscock 1990). Recent studies have focused on the comparison between FASD and ADHD, particularly in the domain of attention. These studies are described in detail in a following section.

Among children with histories of heavy prenatal alcohol exposure, deficits in attention are not global. Research suggests that prenatal alcohol exposure leads to differential deficits in visual and auditory attention; however, these findings have not been entirely consistent. Two studies revealed greater impairment in visual sustained attention in children and adolescents with prenatal alcohol exposure (Coles et al. 2002; Mattson et al. 2006). In contrast, another study described more severe deficits in the auditory modality in adults (Connor et al. 1999). Discrepancies may relate to the tasks used or to the age of the subjects in these studies. Additional studies of attention in adults may provide clarification in this domain.

Academic Impairments

Children with FASD also have difficulties with academic function. Studies demonstrate deficits in both verbal (i.e., reading and spelling) and mathematical domains (Carmichael Olson et al. 1992; Coles et al. 1991; Howell et al. 2006; Mattson et al. 1998; Rasmussen and Bisanz 2010; Streissguth et al. 1990, 1994a), and these deficits persist even after controlling for IQ (Goldschmidt et al. 1996). Mathematics has emerged as a specific area of weakness; however, little is known about the nature of these deficits. Alcohol-exposed children consistently perform lower than controls on measures of global mathematics achievement (Mattson et al. 1998; Streissguth et al. 1994a), and there is evidence suggesting that individuals with FASD may have particular deficits in basic numerical processing skills such as cognitive estimation (Jacobson et al. 2011; Kopera-Frye et al. 1996; Meintjes et al. 2010). Furthermore, recent neuroimaging studies support neuropsychological findings and have shown that children with FASD show abnormalities in regions thought to be important in mathematical processing, such as left and right parietal regions and the medial frontal gyrus (Lebel et al. 2010; Santhanam et al. 2009) (for detail, see papers by Coles et al. and Wozniak et al., this issue). One study that evaluated the effects of dose and timing of alcohol exposure on academic ability reported that the relationship between prenatal alcohol exposure and mathematics was best characterized by a linear dose-response relationship, whereas the relationships between alcohol-exposure and the verbal academic domains were better modeled as threshold effects (Goldschmidt et al. 1996).

Clinical and Behavioral Features

In addition to the neuropsychological deficits already described, children with FASD are likely to present with a wide range of maladaptive and clinically significant behavioral characteristics. Studies of individuals with FASD reveal marked deficits in parent and self-reports of behavior (Coles et al. 1997a; Coles et al. 1999; Mattson and Riley 2000; Nash et al. 2006; Sood et al. 2001; Steinhausen et al. 2003). In one study, children with histories of heavy prenatal alcohol exposure were compared to an IQ matched sample of controls using the Child Behavior Checklist (Mattson and Riley 2000). Children in the alcohol-exposed group had significantly more parent-reported behavioral and emotional disturbances than controls on five of the eight measure subscales. As a group, children with prenatal alcohol exposure had clinically significant scores on several externalizing behavior domains, such as the social problems, attention problems, and aggressive behavior scales of the measure. When examined individually, 90.1% of alcohol-exposed children in the sample had profiles with problem scores in the clinical range, whereas only 27% of controls had any clinically elevated scores. In this study, internalizing problem behaviors were also elevated in comparison to the control group, but the differences were not as large when compared with externalizing behavior domains. However, prenatal alcohol exposure has been associated with negative affect and increased risk for major depressive disorder in childhood (Fryer et al. 2007a; O'Connor 2001; O'Connor and Paley 2006; O'Connor et al. 2002). Thus, further examination of the association between FASD and internalizing behaviors is necessary to conclude whether one domain is relatively more affected than another.

Other studies have identified a dose-response effect between prenatal alcohol exposure and behavioral problems (Sood et al. 2001), and recent studies have begun to tease apart the effects of environmental factors from prenatal alcohol exposure when evaluating the association with behavioral difficulties in affected children (D'Onofrio et al. 2007; Hill et al. 2000; O'Connor and Paley 2006; Rodriguez et al. 2009; Staroselsky et al. 2009). Some findings suggest that maternal psychopa-

thology may be a better predictor of internalizing problems in children with FASD but that alcohol exposure is more directly related to externalizing problems (Staroselsky et al. 2009). However, other studies fail to find strong associations between prenatal alcohol exposure and externalizing difficulties once environmental factors are taken into account (D'Onofrio et al. 2007; Hill et al. 2000; Rodriguez et al. 2009). D'Onofrio and colleagues suggest that childhood conduct problems might be related to an environmentally mediated causal effect of prenatal alcohol exposure whereas impulsivity and attention difficulties might be accounted for by other factors that are correlated with maternal drinking during pregnancy (D'Onofrio et al. 2007). Differences in findings might be related to varied sample sizes and exposure levels between studies as well as discrepancies in methodologies used.

Increased levels of secondary disabilities and psychiatric diagnoses are other common consequences of heavy prenatal alcohol exposure (Burd et al. 2003; Famy et al. 1998; Fryer et al. 2007a; Lynch et al. 2003; O'Connor 2001; O'Connor and Kasari 2000; O'Connor and Paley 2006; O'Connor et al. 2002; Roebuck et al. 1999; Steinhausen and Spohr 1998; Streissguth et al. 1996). As mentioned, children with FASD often have increased rates of mood disturbance. One study used structural equation modeling to construct a model of the relationship between prenatal alcohol exposure and childhood depression (O'Connor and Paley 2006). This model considered both pre- and postnatal factors, and data suggested that higher levels of prenatal alcohol exposure are related to increased negative affect and depressive symptoms but that this relationship is mediated by mother-child interactions that occur over time, such as lower levels of emotional support and decreased expressions of positive affect from mothers. Because externalizing behaviors are also elevated in children with FASD, it is not surprising that rates of oppositional defiant disorder, conduct disorder, and ADHD are elevated (Burd et al. 2003; D'Onofrio et al. 2007; Disney et al. 2008; Fryer et al. 2007a; Steinhausen and Spohr 1998; Steinhausen et al. 1993). One study indicated that within FASD, male participants were significantly more likely than female participants (86% compared to 29%) to be diagnosed with ADHD (Herman et al. 2008). In the greater population of children with ADHD, the ratio of boys to girls is estimated at 2 to 1 (Merikangas et al. 2010), although higher ratios (4:1) have been reported (Cantwell 1996).

Other studies suggest that children with prenatal alcohol exposure are more likely to be rated as having delinquent behavior (Roebuck et al. 1999) and exhibit impaired moral decision-making abilities (Schonfeld et al. 2005). One study demonstrated that low IQ of children with FASD predicted lower moral maturity relative to their non-exposed peers and that these children exhibit a specific deficit in moral value judgments in their relationships with others. In this same sample of children, delinquency was higher in the FASD group, and half of non-dysmorphic alcohol-exposed children studied had probable conduct disorder (Schonfeld et al. 2005). Other studies have demonstrated that children with prenatal alcohol exposure are more likely (94.4% vs. 72.2%) to lie about their behavior and are more skilled lie-tellers at a younger age then typically developing controls (Rasmussen et al. 2008).

Evidence suggests that the behavioral difficulties and psychopathology of children with FASD persist into adulthood (Barr et al. 2006; Famy et al. 1998; Spohr et al. 2007) and often result in adverse life outcomes such as substance abuse problems (Alati et al. 2006; Alati et al. 2008; Baer et al. 1998; Baer et al. 2003) and trouble with the law (Fast et al. 1999; Streissguth et al. 2004). In one cohort of prospectively identified subjects, prenatal alcohol exposure was associated with alcohol-problems at 21-years of age, and these effects remained even after controlling for the effects of family history of alcohol use disorders, other prenatal exposures, and other environmental factors such as postnatal parental use of other drugs (Baer et al. 2003). These findings are supported by similar studies (Alati et al. 2006, 2008) and demonstrate that the behavioral effects of prenatal alcohol exposure are persistent and extend beyond childhood into adolescence and early adulthood. Furthermore, the host of clinical difficulties associated with prenatal alcohol exposure, such as impulsivity, mood disorder, and substance abuse, place affected individuals at high risk for suicide, and research suggests that individuals with FASD have an increase in lifetime suicide attempts relative to the general population (Baldwin 2007; O'Malley and Huggins 2005; Streissguth et al. 1996). In one account, 43% of adults with FASD reported suicide threats and 23% reported a history of suicide attempts throughout the lifetime (Streissguth et al. 1996).

The increase in adverse life outcomes in adults with prenatal alcohol exposure may also relate to deficits in adaptive functioning, which have been demonstrated in the domains of communication, daily living skills, and socialization (Crocker et al. 2009; Jirikowic et al. 2008b; Thomas et al. 1998b; Whaley et al. 2001). Convergent evidence suggests that socialization may be the most affected domain within adaptive functioning (Crocker et al. 2009; McGee et al. 2008a, 2009a; Thomas et al. 1998b; Whaley et al. 2001). More specifically, socialization abilities of children with FASD fail to improve with increasing age (Crocker et al. 2009; Thomas et al. 1998b; Whaley et al. 2001), suggesting an arrest in development of these skills rather than a delay. A similar arrest in development within the communication domain was documented in an investigation that compared children with FASD to children with ADHD and controls on adaptive ability (Crocker et al. 2009). Thus, children with prenatal alcohol exposure are likely to have increasing difficulty

meeting the greater demands in social and communication function as they become teenagers and adults. Importantly, poor social skills observed in children with FASD are associated with executive dysfunction, and problem solving and planning deficits appear to contribute to interpersonal difficulty in this population (Schonfeld et al. 2006).

Recent interest also has been shown in understanding sensory processing in children with FASD and the impact difficulties in this domain might have on behavioral problems in this population. Sensory processing is defined as the ability to integrate neurological processing of sensory input and appropriate behavioral responses and deficits are thought to negatively impact everyday functions, including behavior (Cosbey et al. 2010). Such deficits have been documented in alcohol-affected children and are associated with other neurobehavioral impairments (Franklin et al. 2008) and decreased adaptive and academic function (Carr et al. 2010; Jirikowic et al. 2008a). One study examined the occurrence of sensory processing difficulties in children with partial FAS, ARND, and alcohol-exposed children that did not meet any formal alcohol-related diagnosis (Carr et al. 2010). Though all subjects demonstrated sensory processing deficits, results suggested differences in severity of impairment among groups. In addition, the relationships between sensory processing difficulties and adaptive function and IQ differed depending on alcohol-related diagnosis, highlighting the importance of nontraditional assessment tools in order to fully understand the full range of deficits associated with prenatal alcohol exposure (Table 1).

Neurobehavioral Profile

The extant data, summarized previously, along with studies demonstrating similarities between individuals with FASD and controls, can be used to construct a neuropsychological profile of strengths and weaknesses useful for the identification of affected individuals as well as specific domains to target for clinical intervention. While the definition of this profile is far from complete and the possibility that multiple profiles will be described is likely, thus far, the profile of children with FASD is characterized by general deficits in intellectual ability (e.g., Mattson et al. 1997) and relative deficits in executive function (e.g., Kodituwakku et al. 1995, 2006b; Mattson et al. 1999; Vaurio et al. 2008), visual attention (e.g., Coles et al. 2002; Mattson et al. 2006), verbal (e.g., Mattson et al. 1996b; Mattson et al. 1998) and nonverbal (e.g., Kaemingk et al. 2003; Mattson and Roebuck 2002) learning, motor function (e.g., Roebuck et al. 1998a), social skills (e.g., Schonfeld et al. 2006), externalizing behaviors (e.g., Mattson and Riley 2000) and adaptive function (e.g., Crocker et al. 2009; Thomas et al. 1998b; Whaley et al. 2001). Relative strengths or lack of impairment are present in auditory attention (e.g., Coles et al. 2002; Mattson et al. 2006), retention of verbal information (e.g., Mattson et al. 1996b, 1998), and basic language function (McGee et al. 2009b). One recent investigation used latent profile analysis to statistically test the presence of a neurobehavioral profile of prenatal alcohol exposure. Findings demonstrated that there was a distinct profile of function for children with heavy prenatal alcohol exposure and that this resulting profile could accurately distinguish alcohol-exposed children from controls (Mattson et al. 2010).

Given the heterogeneity of outcomes, overlap in presentation with other clinical groups, and the lack of a definitive physical or biological marker with which to identify all children who have been prenatally exposed to alcohol, identification of affected children is often difficult, especially without confirmed maternal history of alcohol exposure. Focusing on domains that are particularly affected and continuing to develop the neuropsychological profile will assist in determining the expected pattern of deficits in children with prenatal alcohol exposure. A focus of more recent neuropsychological investigations is to compare individuals with prenatal alcohol exposure to those who manifest clinically similar behaviors in order to clarify the specificity of deficits to prenatal alcohol exposure and determine a pattern of performance that might distinguish the groups. Thus far, this literature has focused on comparisons between children with FASD and non-exposed children with ADHD as well as between children with FASD and non-exposed children with low IQ scores.

Comparisons with ADHD As stated, although children with FASD are at increased risk for ADHD, studies that have evaluated both clinical groups suggest that they can be characterized by separate neurobehavioral profiles. There is a small but growing literature aimed at understanding the specificity of deficits seen in children with heavy prenatal alcohol exposure through direct comparison with children with ADHD on specific cognitive and behavioral domains (Burden et al. 2010; Coffin et al. 2005; Coles et al. 1997b; Crocker et al. 2009; Crocker et al. 2011; Greenbaum et al. 2009; Jacobson et al. 2011; Kooistra et al. 2010; Kooistra et al. 2009; Nanson and Hiscock 1990; Nash et al. 2006; Vaurio et al. 2008). Results from these investigations suggest that the two clinical groups are similar on parent reports of attention (Nanson and Hiscock 1990), communication and socialization aspects of adaptive function (Crocker et al. 2009), and performance on the Wisconsin Card Sorting Test (Vaurio et al. 2008). However, children with FASD and ADHD also have been distinguished on several cognitive domains, as follows.

In the domain of attention, three studies have documented differences in the nature of the attention impairments seen in these two clinical groups. Coles and

Table 1 Summary of neuropsychological findings reported in individuals with fetal alcohol spectrum disorders (FASD) when compared to typically developing children, children without alcohol exposure but with a diagnosis of attention-deficit/hyperactivity disorder (ADHD) and children without prenatal alcohol exposure but with low IQ scores. See text for details

Cognitive domain	Compared to typically developing controls	Compared to children with ADHD	Compared to low IQ controls
Global deficits	The average IQ score of individuals with FAS is approximately 70 (Streissguth et al. 1991). Individuals with prenatal alcohol exposure who lack facial dysmorphia do not have as severe intellectual impairment as those with dysmorphic features, but they still exhibit lower IQ scores compared to nonexposed peers (Chasnoff et al. 2010; Mattson et al. 1997). General cognitive function is significantly associated with the degree of facial dysmorphia and growth deficiency. The average IQ of nondysmorphic individuals is approximately 80 (Mattson et al. 1997).	Children with FASD exhibit decreased IQ scores compared to children with ADHD but without prenatal alcohol exposure (e.g., Crocker et al. 2011; Vaurio et al. 2008).	N/A[a]
Executive function	Deficits have been noted on several executive abilities including planning (Aragon et al. 2008b; Green et al. 2009b; Kodituwakku et al. 1995; Mattson et al. 1999), set shifting (Carmichael Olson et al. 1998; Coles et al. 1997b; Kodituwakku et al. 1995; McGee 2008b; Vaurio et al. 2008), fluency (Aragon et al. 2008b; Kodituwakku et al. 2006a; Mattson and Riley 1999; Schonfeld et al. 2001; Vaurio et al. 2008), response inhibition (Burden et al. 2009; Connor et al. 2000; Mattson et al. 1999) and working memory (Green et al. 2009b; Kodituwakku et al. 1995).	Groups perform similarly on set shifting measures, such as the Wisconsin Card Sorting Test but only children with FASD display overall deficits on letter fluency and a relative weakness on the Trail Making Test–B versus the Trail Making Test–A (Vaurio et al. 2008).	When compared directly to an IQ-matched comparison group, children with FASD perform similarly on measures of set shifting and verbal fluency (Vaurio et al. 2011). However, deficits in nonverbal fluency persist when IQ is statistically controlled (Schonfeld et al. 2001).
Verbal learning and memory	Alcohol-exposed children show impaired initial learning but spared retention of verbal information (Kaemingk et al. 2003; Mattson 1996b; Mattson et al. 1998; Mattson and Roebuck 2002; Willford et al. 2004; Willoughby et al. 2008). Verbal recall deficits are accounted for by difficulties encoding information rather than retention of information already learned. However, spared retention may be due to implicit learning strategies of some word-list tests like the CVLT-C (Roebuck-Spencer and Mattson 2004).	Although verbal learning is impaired in both groups, children with FASD appear to have greater difficulties encoding information, whereas children with ADHD have deficits retrieving already learned material (Crocker et al. 2011).	Both groups of children show similar retention of verbal material that is encoded (Vaurio et al. 2011). However, deficits in some aspects of verbal learning and memory continue to persist even after IQ is controlled (Coles et al. 2010) and when children with FASD are compared to IQ-matched controls (Mattson et al. 1996b; Vaurio et al. 2011).
Nonverbal learning and memory	Impaired learning and memory of nonverbal information are apparent; however, findings about whether retention of nonverbal material is intact or impaired are inconsistent (Aragon et al. 2008b; Kaemingk et al. 2003; Mattson and Roebuck 2002). Some research suggests that spatial recall is impaired (Hamilton et	N/A[a]	Deficits in visual learning and recall persist even after IQ is controlled (Coles et al. 2010; Kaemingk et al. 2003).

Table 1 (continued)

Cognitive domain	Compared to typically developing controls	Compared to children with ADHD	Compared to low IQ controls
	al. 2003; Uecker and Nadel 1998), while others report that it is intact (Kaemingk and Halverson 2000; Rasmussen et al. 2006).		
Language	Retrospective studies show speech production deficits and difficulty with both expressive and receptive language skills (Aragon et al. 2008a; Carney and Chermak 1991; Janzen et al. 1995; McGee et al. 2009b), however, results from prospective studies of low to moderate alcohol exposure are mixed (O'Leary et al. 2009; Streissguth et al. 1994a)	N/A[a]	Both groups of children show similarities on measures of expressive and receptive language ability (McGee et al. 2009b).
Visual-spatial ability	Children with FASD show deficits on visual-motor tasks (Aronson and Hagberg 1998; Chiodo et al. 2009; Conry 1990; Janzen et al. 1995; Jirikowic et al. 2008a; Korkman et al. 1998; Mattson et al. 1998; Uecker and Nadel 1996) and on specific aspects of visual processing (Mattson et al. 1996a). Deficits in visual-spatial perception (Kaemingk and Halverson 2000) and motor ability (Janzen et al. 1995) may account for difficulties in these domains.	N/A[a]	In one investigation, children with FASD performed similarly to IQ-matched controls on the Beery-Buktenica Developmental Test of Visual Motor Integration (Vaurio et al. 2011).
Motor function	Deficits in fine and gross motor abilities have been documented in FASD (Chiodo et al. 2009; Green et al. 2009b; Jirikowic et al. 2008a; Mattson et al. 1998; Simmons et al. 2010; Simmons et al. 2002; Wass et al. 2002). However, some findings may be related to task demands (Adnams et al. 2001). In addition, the trajectory of these abilities is unclear as some studies report that deficits persist with age (Connor et al. 2006), while others fail to find differences in samples of adolescents (Simmons et al. 2006).	Motor competence and balance control are differentially affected between children with ADHD and FASD. Both clinical groups of children show similar levels of impairment on tasks targeting complex motor skills and static balance, but children with ADHD are more likely than children with FASD to show severe impairment on basic cerebellar motor control functions (Kooistra et al. 2009).	Children perform similarly to IQ-matched controls on measures of fine motor skills (Vaurio et al. 2011)
Attention and hyperactivity	Children with prenatal alcohol exposure show deficits in attention on neuropsychological tasks of vigilance, reaction time, and information processing (Burden et al. 2005a; Jacobson et al. 1994; Jacobson et al. 1993; Streissguth et al. 1984, 1986, 1994b). Parent (Janzen et al. 1995; Mattson and Riley 2000; Nash et al. 2006) and teacher (Aragon et al. 2008a; Brown et al. 1991; Carmichael Olson et al. 1992) reports of attention difficulties are common. Visual sustained attention appears to be more impaired than auditory attention (Coles et al. 2002; Mattson et al. 2006); however findings have not been entirely consistent (Connor et al. 1999).	Compared to children with ADHD, children with FASD show deficits shifting attention, encoding information, and problem-solving, while those with ADHD have more difficulties focusing and sustaining attention (Coles et al. 1997b) and controlling motor skills and static balance (Kooistra et al. 2009).	Alcohol-exposed children do not show significant impairment on sustained attention above and beyond that explained by IQ (Coles et al. 2002; Vaurio et al. 2011).

Table 1 (continued)

Cognitive domain	Compared to typically developing controls	Compared to children with ADHD	Compared to low IQ controls
Psychopathology and secondary disabilities	Children with FASD are likely to be classified as hyperactive, impulsive, disruptive, or delinquent and have increased rates of internalizing and externalizing behavior disorders (Mattson and Riley 2000; Nash et al. 2006). Alcohol-exposed children also have elevated rates of comorbid psychiatric disorders (Fryer et al. 2007a; O'Connor and Paley 2006), sensory processing difficulties (Carr et al. 2010; Jirikowic et al. 2008a), and deficits in adaptive (Crocker et al. 2009; Jirikowic et al. 2008b; Thomas et al. 1998b; Whaley et al. 2001) and academic (Carmichael Olson et al. 1992; Coles et al. 1991; Howell et al. 2006; Mattson et al. 1998; Streissguth et al. 1990, 1994a) functions.	Children with FASD and ADHD are similar on parent reports of attention and behavior (Coles et al. 1997b). However, on measures of adaptive function, only children with FASD display arrested development of socialization and communication skills with abilities failing to improve with increasing age (Crocker et al. 2009). Children with FASD also demonstrate weaker daily living skills (Crocker et al. 2009), social cognition, and facial emotion processing ability (Greenbaum et al. 2009) than do children with ADHD.	Alcohol-affected subjects are more impaired than IQ-matched controls on measures of externalizing behavior (Mattson and Riley 2000) and adaptive skills (Thomas et al. 1998b; Whaley et al. 2001)

[a] N/A: Research in this area are not yet available

colleagues (1997b) demonstrated unique attention profiles between these two clinical groups by assessing attention using the four factor model proposed by Mirsky (Mirsky et al. 1991): Focus, Sustain, Encode, and Shift. While children with ADHD had more difficulty in the Focus and Sustain components, children with FASD were more impaired in the Encode and Shift domains. These results indicate that ADHD is characterized by difficulties focusing and sustaining attention, whereas FASD is associated with deficits in shifting attention, encoding of information, and flexibility in problem solving. More recent studies using a Go/No-Go response inhibition task indicate that children with ADHD, regardless of prenatal alcohol exposure, exhibited poorer inhibitory control but only children with ADHD without prenatal alcohol exposure showed impaired neural processing, suggesting that the attention deficits in ADHD associated with prenatal alcohol exposure are qualitatively different than those in ADHD alone (Burden et al. 2010). Furthermore, in comparison to children with ADHD but without prenatal alcohol exposure, children with ADHD and prenatal alcohol exposure are more variable in their responding at different event rates (Kooistra et al. 2010).

Furthermore, differences in attention profiles between children with prenatal alcohol exposure with or without a diagnosis of ADHD have been found to vary depending on gender. In a study investigating the effect of ADHD diagnosis on a sample of boys and girls with prenatal alcohol exposure, girls with FASD and ADHD showed significantly impaired ability to sustain attention and encode information compared to other girls with FASD without a diagnosis of ADHD, while boys with FASD and ADHD were significantly better than their non-ADHD counterparts in sustaining attention (Herman et al. 2008).

Studies of other cognitive abilities have revealed further differences between these groups. In one study of executive function, different patterns of deficit were revealed: although the groups were similar on the Wisconsin Card Sorting Test, only children with FASD displayed overall deficits on letter fluency and a relative weakness on the Trail Making Test–B versus the Trail Making Test–A (Vaurio et al. 2008). In a study of verbal learning and memory using the CVLT-C, verbal learning was affected in both groups, although in different ways; performance of alcohol-exposed children appears to reflect inefficient encoding of verbal material, whereas performance of children with ADHD is better characterized by a deficit in retrieval of learned material (Crocker et al. 2011). Children with FASD and ADHD have also been distinguished using measures of mathematics and numerical processing (Jacobson et al. 2011). Results of this study suggest that mathematics difficulty in children with ADHD might be more related to impairments in general cognitive abilities important for proficient academic achievement whereas children with FASD display a specific impairment in basic numerical processing abilities, such as the ability to mentally represent and manipulate numbers and quantities.

Motor competence and balance control also appear to be differentially affected between children with ADHD and FASD. Although both clinical groups of children show similar levels of impairment on tasks targeting complex

motor skills and static balance, children with ADHD are more likely than children with FASD to show severe impairment on basic cerebellar motor control functions (Kooistra et al. 2009). These findings suggest that children with ADHD exhibit problems with both basic and complex motor and balance skills, while children with FASD have relatively intact basic motor skills but struggle to integrate these functions into coordinated, complex motor skills.

Tasks tapping more basic cerebellar functions also have been able to discriminate children with FASD and ADHD. In one study, children with FASD failed to learn a classically conditioned eyeblink response, producing longer latencies and poorly timed responses to the conditioning stimulus. Children with ADHD, on the other hand, were impaired on measures of adaptively timed responses but showed learning of the conditioned eyeblink response that was similar to controls (Coffin et al. 2005). In other studies of motor abilities, children with ADHD were more likely to be clinically impaired on measures of postural stability than were children with FASD (Kooistra et al. 2009).

Finally, the distinct behavioral phenotypes of children with FASD and ADHD have been evaluated and findings suggest that parent-reported behavioral measures are useful in detecting differences in clinical presentation between the two groups. On measures of adaptive function, only children with FASD display arrested development of socialization and communication skills with abilities failing to improve with increasing age. Although children with ADHD demonstrate impaired abilities on these domains, their difficulties appear to be characterized by a developmental delay with skills improving at a rate that is similar to controls (Crocker et al. 2009). Children with FASD also demonstrate weaker daily living skills (Crocker et al. 2009), social cognition, and facial emotion processing ability (Greenbaum et al. 2009) than do children with ADHD and typically developing controls. See Fig. 1 for a visual

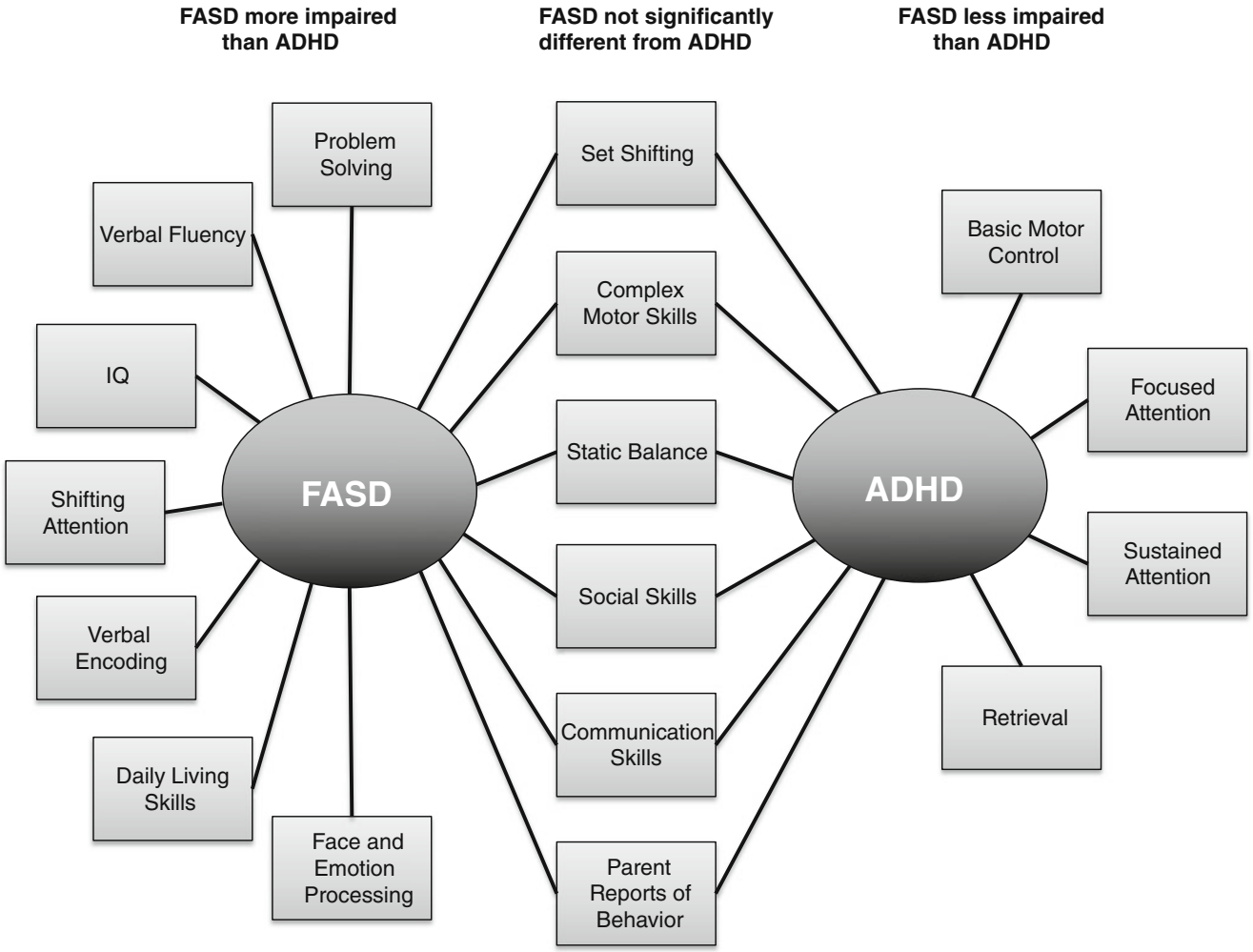

Fig. 1 Patterns of neuropsychological impairments in children with FASD and ADHD. Note that domains listed do not reflect absolute impairments (i.e., when compared to non-exposed, typically developing controls) but rather, relative impairment on domains on which the two clinical groups have been directly compared. See text and Table 1 for details and related references

representation of the patterns of impairments in FASD and ADHD populations.

Comparisons with IQ-Matched Samples When children with heavy prenatal alcohol exposure are compared to children without histories of alcohol exposure but who have similar IQ scores, similarities and differences in their neurobehavioral presentation are also noted. Both groups of children show similarities on measures of expressive and receptive language ability (McGee et al. 2009b), sustained attention, and retention of verbal material (Vaurio et al. 2011). However, alcohol-affected subjects are more impaired than IQ-matched controls on measures of externalizing behavior (Mattson and Riley 2000), adaptive skills (Thomas et al. 1998b; Whaley et al. 2001), and verbal learning (Coles et al. 2010; Mattson et al. 1996b; Vaurio et al. 2011). Parent reports of attention have indicated that externalizing behavior is more affected in alcohol-exposed children than in IQ-matched samples, but results of internalizing behavior are mixed (Mattson and Riley 2000; Vaurio et al. 2011), indicating that further study is needed.

Conclusion

Individuals exposed to alcohol during pregnancy exhibit a wide range of long-lasting impairments in neuropsychological and behavioral domains. Deficits include diminished intellectual function, poor learning and memory, impaired executive and visual-spatial function, delayed motor and language development, and attention difficulties. In addition, these children present with increased internalizing and externalizing behavior problems, poor academic achievement, and high rates of comorbid psychiatric disorders. Despite some inconsistencies, the extensive neuropsychological literature on children prenatally exposed to alcohol during pregnancy illustrates a pattern in which affected children perform relatively well on simple tasks but show greater impairment on more complex tasks that require processing of complex information and greater involvement of executive functioning (Kodituwakku 2007). Recent efforts have begun to examine the specificity of these deficits through development of a neuropsychological profile of prenatal alcohol exposure that will aid in distinguishing affected individuals from other clinical populations. Continuing research comparing alcohol-exposed children to similar clinical groups will assist in the refinement this profile. Furthermore, greater understanding of the neurobehavioral impairments in children with prenatal alcohol exposure will help tailor intervention programs aimed at improving outcomes for this population.

Acknowledgements The authors thank the members of the Center for Behavioral Teratology and the families who graciously participate in our studies. Preparation of this paper supported by NIAAA Grants R01 AA019605, R01 AA010417, U01 AA014834, T32 AA013525, and F31 AA020142.

Disclosure The authors have no financial relationship to the organization that sponsored the research.

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