DESCRIPTION: State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This abstract is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

The current proposal is in response to RFA-AA-03-002 and is part of the consortium application, entitled "Cross-Cultural Assessment of FASD." This RFA calls for, in part, "research to better define and characterize the description of FASD" including identification of core deficits in this population. The current application meets this goal by proposing research aimed at identifying core neuropsychological and neuroanatomical features in children with fetal alcohol syndrome and fetal alcohol spectrum disorder (FASD) in two samples of children in two countries, the United States and Russia.

Thirty years of research and practice have confirmed that (1) alcohol is a teratogen, (2) the brain is the organ most sensitive to alcohol's effects, and (3) the effects are of a continuous nature. Questions that remain pertain to whether a profile of core deficits and strengths exists, what this profile tells us about the underlying function of the brain, and whether effects can be accounted for by other environmental circumstances like living environment or general intellectual functioning. The current proposal includes both neuropsychological and brain imaging studies and is aimed at characterizing an FASD phenotype. Importantly, two distinct populations will be assessed, children in San Diego, California, and children in Moscow, Russia. The inclusion of these two populations will allow us to answer important questions relating to the role of environment, culture, and general intellectual functioning in the phenotype of FASD. Children in Moscow will primarily be ascertained from boarding schools and orphanages that house children with subnormal intellectual functioning. We have previously determined the rates of FAS in this population are very high. Children in San Diego will be ascertained from ongoing studies of FASD at the SDSU Center for Behavioral Teratology. Thus, we have the unique opportunity to examine the relationship between FASD, IQ, and living environment in large groups of children.

In addition to the unique aspects mentioned above, the current application dovetails with other applications in the consortium, allowing large groups of children with FASD to be examined in several international sites using consistent measures. The opportunity for convergence of data from these multiple sites provides tremendous power to test specific hypotheses regarding the phenotype of FASD.

PERFORMANCE SITE(S) *(organization, city, state)*
San Diego State University, San Diego, CA
Institute of Psychiatry, Moscow

KEY PERSONNEL. See instructions. *Use continuation pages as needed* to provide the required information in the format shown below. Start with Principal Investigator. List all other key personnel in alphabetical order, last name first.

Name	Organization	Role on Project
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Disclosure Permission Statement. Applicable to SBIR/STTR Only. See instructions. ☐ **Yes** ☐ **No**

a. Specific Aims

The teratogenicity of heavy prenatal alcohol exposure is well documented. However, many important questions remain to be answered. Most studies on the effects of such exposure have been done in the United States, in spite of the fact that the first published report of such effects was from France. In the 35 years since that report, it has become clear that (1) alcohol is a teratogen, (2) the brain is the organ most sensitive to alcohol's effects, and (3) the effects are of a continuous nature. Questions that remain to be answered include whether the neurobehavioral effects seen in children with fetal alcohol syndrome are specific to this disorder, whether a profile of core deficits and strengths exists, and whether effects can be accounted for by other intrinsic (general intellectual function) or extrinsic (poverty or living environment) factors.

The current study has one main goal: to determine whether a phenotype exists in children with fetal alcohol spectrum disorders (FASD). This goal will be addressed by examining children in two populations: children living in orphanages and special schools in Moscow, Russia and children in San Diego, CA. The inclusion of these two populations will allow us to address the role of general intellectual functioning as well as environment in the phenotype of FASD. Several previous studies have been criticized for including control groups that are mismatched to the FAS group on these two important factors. The population in Moscow represents an ideal opportunity to address both of these issues because children with and without FASD are available from the same population: children living in orphanages or special boarding schools both specifically designed for children with below average intelligence or other special needs. Both the FASD group and the control group will be selected from these institutions and thus will have similar general intellectual abilities and living environments. These children will be compared to children with FASD and controls from an ongoing U.S. study (San Diego, CA) to determine whether the effects seen in this special population are consistent across sites and to strengthen the generalizability of the presumed phenotype. We also anticipate that the addition of the Moscow and San Diego samples to the consortium project will greatly strengthen our ability to determine whether a profile of functioning can be revealed in this population.

Two types of evaluation will be conducted as part of this proposed project: neuropsychological and neuroanatomical. Previous studies have examined the brain in children with FASD and have revealed a pattern of brain changes that appear to be consistent across studies. The areas most often affected include the corpus callosum. However, most studies conducted thus far have had small sample sizes. The current study will include neuroanatomical studies in both sites. In addition, the relationship between the neuroanatomical and neuropsychological data will be examined with the same goal as above: to determine whether a phenotype exists in this population.

The specific aims of this proposal are:

1. To determine whether a phenotype exists in children with fetal alcohol spectrum disorders (FASD).
    a. Children with FASD (with and without FAS) and controls from Moscow, Russia and San Diego, California will be compared using the methodology proposed by the neurobehavioral core and neuroimaging core of the consortium application.
    b. The specificity of this phenotype will be tested by including children, ages 7-18 years, from two countries, and controls with similar living environments and general intellectual level.

b. Background and Significance

Fetal alcohol syndrome (FAS) is a serious public health concern, affecting 0.3-3/1000 live births [1] and the effects of heavy prenatal alcohol exposure reach beyond the diagnosis of FAS. While the incidence of FAS in children of alcoholic women is on the order of 10-40%, the number of children born with other alcohol-related effects is likely to be 10 times as high [2], suggesting that nearly 1 in 100 children may be affected by heavy prenatal alcohol exposure. Like children with FAS, children of alcoholic women (who drank heavily during pregnancy) who do not exhibit the facial features of FAS show deficits on a wide variety of neurobehavioral measures [3]. Many different labels for this non-dysmorphic group exist, including fetal alcohol effects (FAE), alcohol-related neurodevelopmental disorder (ARND), and prenatal exposure to alcohol (PEA). Most recently, the idea that the teratogenic effects of alcohol are continuous has led to the use of the term “fetal alcohol spectrum disorder (FASD)” to identify children affected by prenatal alcohol exposure who may or may not meet the traditional criteria for FAS.

Attention has focused recently on determining if a specific pattern of neuropsychological strengths and weaknesses (a functional “profile”) is caused by prenatal alcohol exposure and whether the nature of this pattern can be defined. Thus, rather than evaluate and describe deficits in this population, the current impetus is to define a profile of strengths and weaknesses, to identify “core deficits” in children affected by heavy prenatal alcohol exposure. In March 2000, a joint meeting of the Interagency Coordinating Committee on Fetal Alcohol Syndrome and the NIAAA aimed to identify such a pattern or profile. Two follow-up meetings in September 2001 and June 2002 continued this line of work and the overall goals of this consortium stem from this line of inquiry. The importance of the identification of such core deficits is fourfold. First, by identifying core deficits and thus a profile of functioning, we will be able to better identify children who have been affected by heavy prenatal alcohol exposure but who do not have FAS. These children are at risk for behavioral and brain alterations but may go completely undetected and are therefore at greater risk for secondary disabilities [4]. Second, a profile of functioning will help us develop rational treatment approaches specific to the effects of alcohol on brain development. Third, by identifying relative strengths as well as weaknesses, we can improve treatment strategies by developing programs in which the individual can participate. This may also reduce the rates of secondary disabilities, such as legal or mental health problems common in adults with FAS or other alcohol-related disorders [4]. Finally, by developing a profile of strengths and weaknesses, we will continue to increase our knowledge of alcohol’s effects on the brain, as well as normal brain development and function. Recent brain imaging work has identified areas of the brain specifically targeted by prenatal alcohol exposure. We hope to use this information to identify the functional consequences of such brain changes and proceed with focused and hypothesis-driven research.

This proposal involves assessment of children with FASD from two sites, the Center for Behavioral Teratology at San Diego State University, and the Institute of Psychiatry in Moscow, Russia. The benefits of utilizing two data-collection sites include increased sample sizes and the ability to make cross-cultural comparisons using common measures. An added benefit specific to the Moscow site is that children tested there all reside in the same system of orphanages and boarding schools, providing a level of environmental control not previously available. Thus, we will be able to match our controls on both intrinsic (intelligence) and extrinsic (living environment) factors. Children with FASD often have IQ scores below the average range [3]. Any attempt at developing a profile is hindered by the question of whether deficits seen on neuropsychological measures are secondary to general intellectual deficits or represent core deficits. Previous studies have attempted to address this “IQ problem” in several ways. Most often, statistical control of IQ is suggested, either by researchers or by reviewers. While popular, the use of covariance is not recommended in the cases where groups differ on the potential covariate [5, 6]. We have argued that when IQ interacts with group

membership, it cannot be used as a covariate. Such an analysis would be overly conservative and would greatly reduce the chance of finding significant group effects when they, in fact, exist (i.e., an increase in Type II error). However, while this argument against covarying IQ is on solid statistical ground, it does not provide a solution to the original question: whether core deficits exist in FASD?

Alternative strategies to address this complex issue have been to truncate the IQ range of FASD participants [7] or to match controls for IQ score [8, 9]. Both strategies limit the generalizability of results and the latter strategy also may bias results based on the specific characteristics of the selected control. The great strength of the current proposal is that we are able to test large numbers of children with and without FASD from the same population, children in orphanages and boarding schools in Moscow who are similar in terms of their overall level of intellectual ability. Importantly, not all participants in the current study will have low IQ scores. Although low IQ scores are common in children with FASD, this is not a universal feature of this disorder. We will include children with FASD of any intellectual level. Approximately 18% of the children with FAS and 48% of the children with FASD in our potential sample have IQ scores within the average range. Thus, we should be able to test the relationship between IQ and other performances within a range of ability levels.

Research on other developmental disabilities has taken up this idea of core deficits and provides the framework for this proposal. In an evaluation of early-onset hydrocephalus, Barnes and Dennis [10] note the qualifications for core deficits as (1) relatively independent of general cognitive level, and (2) not accounted for by other limitations. They suggest that the identification of core cognitive processes within developmental neuropathology may be important for establishing brain-behavior relationships. When applied to the study of FASD, these qualifications suggest that first, a core deficit must occur in children with a range of IQ scores. This does not mean that IQ scores are best controlled statistically, but rather that the deficit exists in children with FAS regardless of their IQ score. By testing children with a range of IQ scores, we hope to address this issue. Second, a core deficit must not be accounted for by other more basic deficits. For example, we have reported that deficits exist on complex executive function tasks even when deficits on more basic tasks are accounted for [11, 12]. In the current study, children with a range of IQ scores, in both the FASD and control groups will be assessed, and assessment will incorporate both higher order cognitive tasks and more basic component tasks.

Finally, this proposal incorporates both neuropsychology and neuroimaging. By including both domains of study, we hope to address a key issue in the field: how does neuropsychological function relate to neuroanatomical changes seen in children with FASD? We have previously evaluated children with FASD using brain magnetic resonance imaging (MRI). Some of these results are summarized in the Preliminary Studies section, below. Overall, results suggest that, contrary to previous beliefs, the effects of heavy prenatal alcohol exposure are not global in nature but instead are characterized by specific changes. We have found these specific changes in the cerebellum, caudate nucleus, corpus callosum, and parietal lobe and have correlated some of these changes with behavioral measures. However, our sample sizes have been small and thus, we hope that the cross-cultural study we are proposing will enable us to correlate brain-behavior relationships in a larger group of children.

c. Preliminary Studies

Neuropsychological Comparisons Across Sites

The two primary research sites for this proposed project are San Diego, CA and Moscow, Russia. Projects related to fetal alcohol syndrome are in place at both locations. Since 1990, we have been evaluating children with FAS and controls in San Diego using a comprehensive neuropsychological test battery, results of which have been published [9, 13-17]. In 1999, we entered into collaboration

with Dr. Galina Marintcheva of the Institute of Psychiatry in Moscow, Russia. As part of this project, children in boarding schools and orphanages in Moscow were evaluated using a three-pronged approach. First, family information was obtained for each child from school and orphanage records. As part of this information, alcoholism in the mother was determined. Second, each child was seen by a team of two pediatricians to determine whether the child met criteria for FAS. As a result of these evaluations, the pediatricians gave each child a preliminary diagnosis of FAS, Deferred, or Not FAS. Cases with Deferred diagnoses required additional information. Positive (FAS) or Deferred diagnoses and cases where diagnoses were not clear (i.e., the pediatricians disagreed) were confirmed or clarified by an American dysmorphologist, either Kenneth Lyons Jones, MD or Luther K. Robinson, MD. Final diagnoses were based on the decisions of Drs. Jones and Robinson. Finally, children were tested by one of four psychologists, using a neuropsychological test battery that included tests given in San Diego as well as some unique tests developed by the Russian psychologists. Thus far, 3805 children have been evaluated by the pediatricians and 318 received a preliminary diagnosis of FAS or Deferred. Of these, 272 were seen by either Dr. Jones or Dr. Robinson and 211 children received a confirmed diagnosis of FAS. The psychologists have tested 378 children, of whom 184 have a confirmed diagnosis of FAS. An additional 41 children have yet to be evaluated by either Dr. Jones or Dr. Robinson. Sixty-eight children tested qualified for the control group (see below). The remaining children were either unconfirmed controls (due to missing data), Deferred, not FAS but have alcohol exposure, or had some other diagnosis. Analysis of the neuropsychological test data is underway and preliminary comparisons with the San Diego dataset are presented below.

The samples presented here include children from the Moscow sample who have been administered the neuropsychological test battery and either have FAS (MOS-FAS) or are controls (MOS-CON). These controls were selected from the same boarding schools and orphanages as the children with FAS but have (1) family data negative for maternal alcoholism and (2) were seen by at least one pediatrician who indicated they did not have FAS. If they had a diagnosis of Deferred or FAS by either pediatrician, they were not included in the control group. There were 61 children who qualified for the control group who had neuropsychological test data. Sixty-one children with FAS were selected randomly (specifying the desired sex ratio) for the purposes of analysis. Children from the San Diego sample were selected for analysis if they had a confirmed diagnosis of FAS (by KLJ) or were in our control group of non-exposed children. A total of 54 children were selected for analysis, 27 of which had FAS (SD-FAS). The control group from San Diego (SD-CON) was selected from the larger sample based on the following matching criteria: age, sex, social status, ethnicity, and handedness. Unlike the Moscow sample, children in our control group are not matched with the FAS group on IQ score, thus the two control groups represent a wide range of intellectual functioning. The demographic information for the groups is listed in Table 1.

Table 1. Demographic information for FAS and CON groups in Moscow and San Diego

	MOSCOW		**San Diego**	
	CON	FAS	CON	FAS
N	61	61	27	27
Age [Mn (SD)]	13.4 (1.95)	12.4 (1.80)	11.8 (2.34)	11.2 (2.46)
Sex (%Female)	37.7	37.7	70.4	70.4
Ethnicity (%White)	100	100	66.7	55.6
Handedness (%Right)	85.2	83.6	96.3	77.8

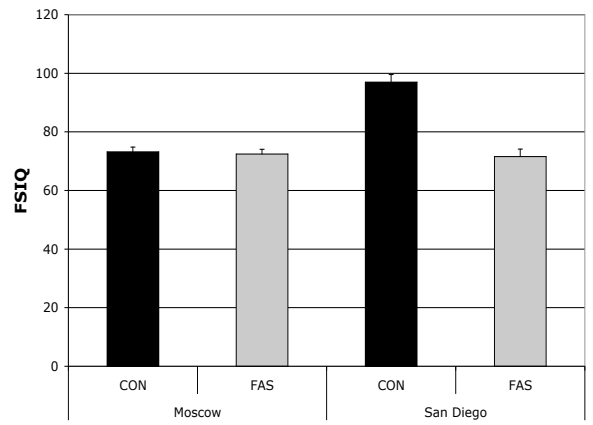

Figure 1. Full Scale IQ scores

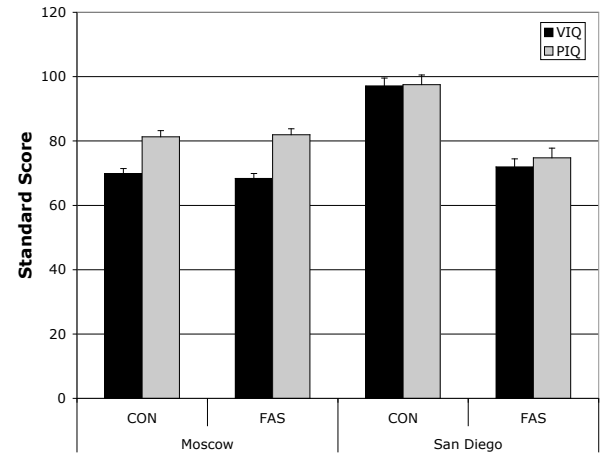

Figure 2. Verbal (VIQ) and Performance (PIQ) IQ scores

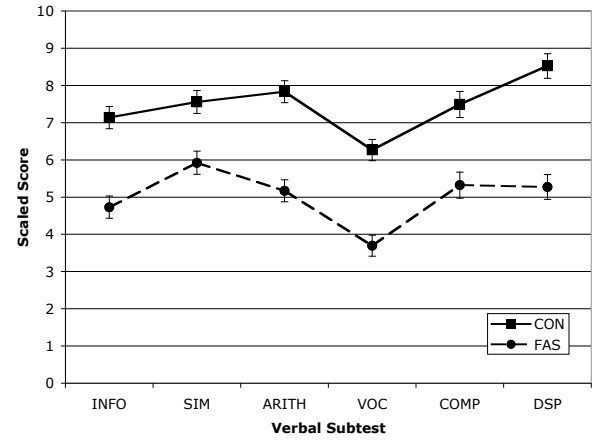

Figure 3. Verbal subtests scores, collapsed over site

Children in Moscow and San Diego were administered the appropriate version of the Wechsler Intelligence Scale for Children, resulting in full scale, verbal, and performance IQ scores as well as scores for the individual subtests. Because all children in the Moscow sample were drawn from the same special orphanages and boarding schools, the groups had similar IQ scores. These schools house children who have previously been identified as having subnormal intellectual functioning. Interestingly, the average IQ score for the Moscow FAS group (MOS-FAS) was similar to that of the San Diego FAS (SD-FAS) group. These data are presented in Figure 1. Analysis of these data revealed a significant group x site interaction, F (1,172) = 39.3, $p < .001$, as well as significant main effects of group, F (1,168) = 45.2, $p < .001$ and site, F (1,168) = 31.8, $p < .001$. Pairwise LSD comparisons revealed that the SD-CON group differed from the MOS-CON group ($p < .001$) but the two FAS groups were similar. For the Verbal and Performance IQ scales, the results were the same, and these data are illustrated in Figure 2. Analysis of these data revealed a significant group x site interaction, F (1,172) = 39.1, $p < .001$, as well as significant main effects of group, F (1,172) = 42.9, $p < .001$ and site, F (1,172) = 26.8, $p < .001$. Pairwise LSD comparisons revealed that overall, the SD-CON group differed from the MOS-CON group ($p < .001$) but the two FAS groups were similar. In addition, there was a significant site x IQ scale interaction, F (1,172) = 34.7, $p < .001$. Follow-up pairwise LSD comparisons indicated that in Moscow, PIQ>VIQ, whereas in San Diego, PIQ=VIQ. The VIQ-PIQ difference in the Moscow sample may relate to living environment.

Comparison of subtest scores was also informative and revealed a similar pattern of results. For the verbal subtests, there were significant group x subtest, F (5,168) = 2.5, p = .03, and group x site, F (1,172) = 48.0, $p < .001$, interactions, as well as significant main effects of group, F (1,172) = 63.9, $p < .001$ and site, F (1,172) = 53.4, $p < .001$. Follow-up pairwise comparisons across site indicated that for all subtests, the CON group outperformed the FAS group, although the magnitude of the differences varied from subtest to subtest with the largest differences on the digit span subtest (Figure 3). Interestingly, this is consistent with a recent study that utilized data from San Diego, Moscow, and South Africa, suggesting that in addition to a composite IQ score, the digit span subtest was the subtest that best predicted FAS diagnosis [18]. In addition, as in the previous analyses, follow-up pairwise LSD comparisons revealed that the SD-CON group differed from the

MOS-CON group ($p < .001$) but the two FAS groups were similar. There was also a site x subtest interaction, F (5,168) = 21.6, $p < .001$. Follow-up pairwise comparisons suggested that although the sites differed on all subtests, the difference on the Vocabulary subtest was the largest. The group x site x subtest interaction was not significant, thus the data presented are collapsed across site (Figure 3).

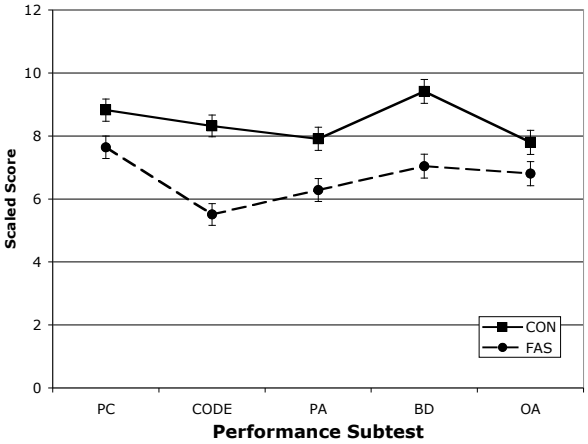

Figure 4. Performance subtest scores collapsed over site

For the performance subtests, there were significant group x subtest, F (4,169) = 4.2, $p = .003$, and group x site, F (1,172) = 29.8, $p < .001$, interactions, as well as a significant main effect of group, F (1,172) = 25.2, $p < .001$. Follow-up pairwise comparisons indicated that for all subtests, the CON group outperformed the FAS group, although the magnitude of the differences was larger for the Block Design and Coding subtests. In addition, as in the previous analyses, the SD-CON group differed from the MOS-CON group ($p < .001$) but the two FAS groups were similar. There was also a site x subtest interaction, F (4,169) = 3.0, $p = .018$, however follow-up pairwise comparisons suggested that the interaction was likely due to a difference between the subtests rather than differences between the groups. The group x site x subtest interaction was not significant, thus the data presented are collapsed across site (Figure 4).

Several other tests were also given to both the San Diego and Moscow samples. These include the Judgment of Line Orientation Test (JLO), Visual-Motor Integration Test (VMI), and the Grooved Pegboard Test (Pegs), which are all measures of visual-spatial and visual-motor skill. For all three measures, the main effects of group were significant (p's $\leq .002$). For JLO and VMI, the group x site interaction was also significant (p's $< .001$) and for JLO and Pegs, the main effect of site was significant (p's $< .01$).

The value of the collaborative efforts between Moscow and San Diego is best illustrated in the analysis of data from the Wisconsin Card Sorting Test (WCST). Prior to embarking on our collaboration in Moscow, we had investigated the relationship between FSIQ and WCST performance [19], since the WCST is proposed to be sensitive to fetal alcohol effects [20]. Our results suggested that although the alcohol-exposed group was impaired on the WCST relative to a non-exposed control group, their performance was better than expected based on their FSIQ. We were limited in the extent to which we could prove this hypothesis because we could not test it in control children with lower IQ scores. With the Moscow sample, we had the opportunity to test whether this apparent strength was a function of the test or whether it represented a specific strength in this population. We have now compared WCST performance in the FAS and CON groups from Moscow and San Diego. A composite score reflecting the average WCST performance was calculated for each child. This score and Full Scale IQ were analyzed using a 2 x 2 x 2 ANOVA

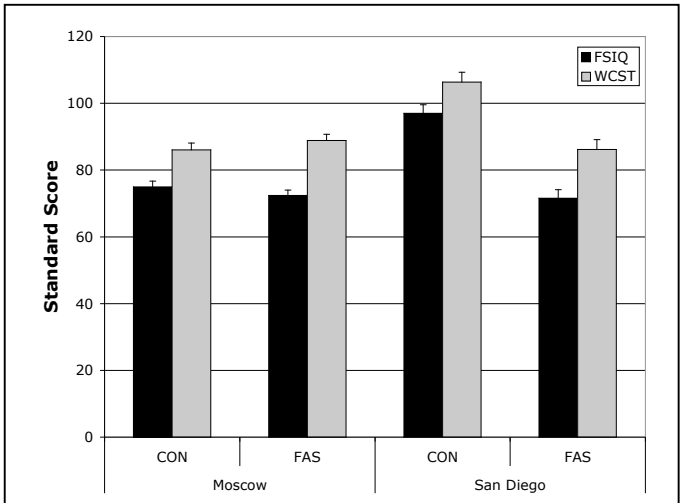

Figure 5. FSIQ and composite WCST Scores

with repeated measures on the last factor. Group (FAS/CON), and site (Moscow/SD) served as the between-subjects variables and test (FSIQ, WCST) served as the within-subject measure. The results revealed a significant group x test interaction, F (1,162) = 7.8, p = .006, suggesting differential performance on these measures by group. Follow-up comparisons revealed that both groups scored lower on FSIQ than on the WCST (p's < .001), although the difference was larger for the FAS group (Figures 5 and 6). The group x site interaction was also significant, F (1,156) = 37.6, p < .001, as were the main effects of group, F (1,162) = 37.5, p < .001, and site, F (1,162) = 25.4, p < .001. Follow-up pairwise LSD comparisons revealed that the SD-CON group differed from the MOS-CON group (p < .001) but the two FAS groups were similar. Because we were interested in whether WCST performance represented a relative strength in children with FAS and in light of the significant group x test interaction, we analyzed difference scores (WCST-FSIQ) in a 2 x 2 ANOVA similar to that described above (Figure 6). Results revealed a significant main effect of group, F (1,162) = 7.8, p = .006. No other main or interactive effects were significant. These data suggest that, consistent with our previous findings, scores on the WCST were significantly higher than FSIQ scores in all groups, which may be due to psychometric properties of the WCST. However, differences between the two tests were significantly larger in the FAS group, regardless of site. The convergence of these findings across two sites suggests, as we previously reported, that performance on the WCST represents a relative strength in this population. Importantly, having a low IQ score did not sufficiently explain this outcome. If that had been the case, both the FAS groups and the Moscow control group would have shown similar difference scores. In contrast, the magnitude of the difference was similar in both CON groups, regardless of IQ. Although it is unclear whether this relative strength can be generalized to other nonverbal problem-solving tests, it may provide at least some initial direction for defining a behavioral profile in individuals with FAS.

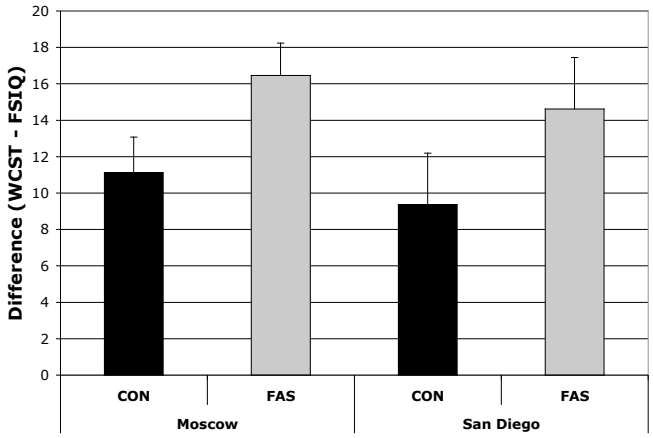

Figure 6. Difference scores (WCST – FSIQ)

One cautionary note is that the MOS-CON group was disproportionately affected by missing data. Ten controls had missing WCST data for this analysis, whereas none of the other groups had missing data. We are in the process of obtaining and scoring the remaining WCST protocols.

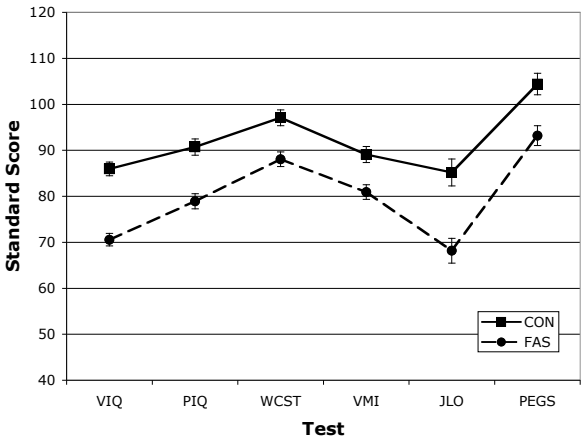

Figure 7. Profile of functioning

Finally, a repeated measure ANOVA was conducted on six of the neuropsychological test scores: VIQ, PIQ, WCST composite, VMI, JLO, and Pegs. This analysis revealed the following significant interactions: test x group, F (5,152) = 3.5, p = .005, test x site, F (5,152) = 17.7, p < .001, and group x site, F (1,156) = 37.6, p < .001. In addition, there were main effects of group, F (1,156) = 48.0, p < .001 and site, F (1,156) = 9.3, p = .003. Follow-up pairwise LSD comparisons revealed that for all tests, the FAS group scored lower than the CON group, but the differences were larger on VIQ and JLO. The group x site interaction was similar to that described above and the test x site interaction appeared to be due to site differences on the VIQ, WCST, JLO, and

Pegs. The group x site x test interaction was not significant, thus the data presented are collapsed across site (Figure 7).

Summary of San Diego-Moscow Comparisons and Goals for Current Proposal

Our current data support neurocognitive deficits in children with FAS, although the data from the Moscow sample suggests that overall IQ plays a large role in the functional profile of this population. Given the large number of children to be examined as part of the consortium, we will be in a better position to evaluate the relationship between general ability level and other test performances.

Other Neuropsychological Test Data from Moscow Sample

In addition to the tests described above, a few other measures have been collected from the Moscow sample. For example, we collected data concerning attention and hyperactivity ratings for the children in the FAS and CON groups. The rating scales used were adapted from DSM-IV ratings for attention deficit hyperactivity disorder (ADHD). For each child, the governess and teacher were asked to rate the symptoms of inattention and hyperactivity. As specified by the DSM-IV, a score of 6 or more symptoms for each domain was used to classify each child as meeting criteria for a particular domain (i.e., inattentive, hyperactive). For these data, we have a larger FAS sample size than above, with 87 children rated by a teacher and 90 children rated by a governess. Children with FAS were more likely than controls to be rated as inattentive by both the governess and the teacher, and these differences were significant. However, they were not rated as more hyperactive by either rater. These data are summarized in Table 2. Interestingly, these data are consistent with preliminary data obtained in San Diego that suggest that children with heavy prenatal alcohol exposure are more similar to controls than non-exposed children with ADHD on measures of kinetic activity.

Table 2. Behavior ratings for children with FAS and controls in the Moscow sample. Values represent the percentage of children in each group that met criteria in each domain.

Domain	CON (%)	FAS (%)	X^2 (df = 1)	OR	95% CI
Inattention					
Governess	41.5	70.0	9.66, p = .002	3.29	1.53-7.10
Teacher	40.4	67.8	9.41, p = .002	3.11	1.49-6.48
Hyperactivity					
Governess	36.6	53.3	3.17, p = .08	1.98	0.93-4.23
Teacher	40.4	49.4	0.99, p = .32	1.44	0.70-2.95

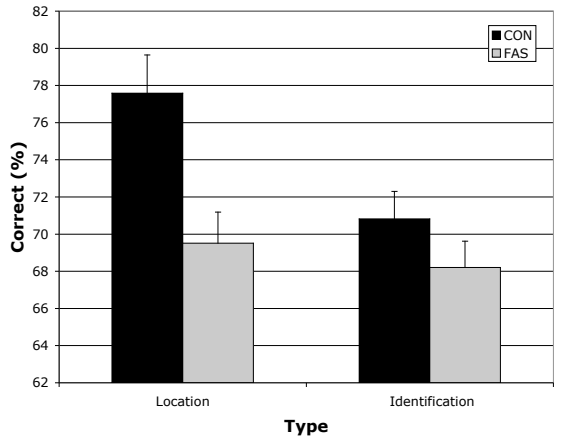

Figure 8. Memory for object location and object identity.

Data were also collected on a measure assessing immediate memory for object identification and object spatial location. In this test, which is similar to standardized measures given in the US, children were shown a series of 12 cards with pictures of objects. Each card was placed on a board and after all the cards were presented, the child was asked to recreate the array with the same cards (object location). Responses were scored for accuracy of location. Immediately following the spatial recall test, the children were asked to recall the names of the objects on the cards (object identification). Accuracy scores were analyzed by 2 x 2 repeated measures ANCOVA with group as the

between-subjects factor and the two recall scores as the within-subject repeated measure. Because IQ did not interact with group, FSIQ was included as a covariate in this analysis. Age was also included as a covariate. This analysis suggested that the FAS group had a relative weakness on the object *location* but not the object *identification*. This was supported by a significant group x test interaction, F (1,172) = 4.23, p <. 05 as well as a significant main effect of group, F (1,172) = 4.975, p = .027. These data are illustrated in Figure 8. Interestingly, these data support a previous study done in San Diego, in which we reported that children with heavy prenatal alcohol exposure were impaired on “where” but not “what” visuo-spatial processing [21].

Neuropsychological Assessment of FAS at the Center for Behavioral Teratology

Over the last decade we have developed a program of study aimed at understanding the brain and behavioral changes seen in FASD. In the interest of space, only those measures specifically relevant to the current proposal will be presented.

Test of Variables of Attention (TOVA)

In a recent study, we attempted to develop a predictive model for children with heavy prenatal alcohol exposure [22]. Deficits in attention are a hallmark of the effects of heavy prenatal alcohol exposure. However, as indicated, a functional profile that discriminates alcohol-exposed children from non-exposed controls is not well defined. We attempted to distinguish children with heavy prenatal alcohol exposure from non-exposed controls using four measures of attention functioning: the Freedom from Distractibility index from the Wechsler Intelligence Scale for Children-Third Edition (WISC-III), the Attention Problems scale from the Child Behavior Checklist (CBCL), and omission and commission error scores from the Test of Variables of Attention (TOVA). Data from two groups of children were analyzed: children with heavy prenatal alcohol exposure and non-exposed controls. Children in the alcohol-exposed group included both children with or without fetal alcohol syndrome. Groups were matched on age, sex, ethnicity, and social status. Data were analyzed using logistic regression. This technique is useful for predicting the presence or absence of a characteristic (e.g., prenatal alcohol exposure) based on a set of predictor variables. The final model included the Freedom from Distractibility index from the WISC-III and the Attention Problems scale from the CBCL. The TOVA variables were not retained in the final model. Classification accuracy was 91.7% overall. Specifically, 93.3% of the alcohol exposed children and 90% of the control children were accurately classified. Graphic representation of the model is presented in Figure 9. Probability of being alcohol-exposed is displayed on the Y-axis and performances on the two variables in the model are displayed on the X and Z-axes. These data indicate that children with heavy prenatal alcohol exposure can be distinguished from non-exposed controls with a high degree of accuracy using two common measures. The specificity of this model needs to be tested so that it may be used clinically to distinguish children with heavy prenatal alcohol exposure from other clinical groups, like children with ADHD or low IQ scores. We hope to test the model in the larger Moscow sample and using the data to be collected as part of the neurobehavioral core.

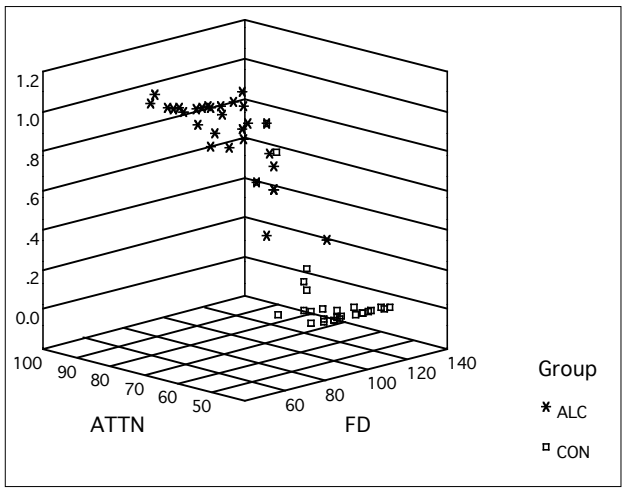

Figure 9. Classification of children with prenatal alcohol exposure and controls

While the TOVA was not retained in the model just described, we continue to believe it may be an important measure, as suggested by a second recent study [23]. In this study, we compared children

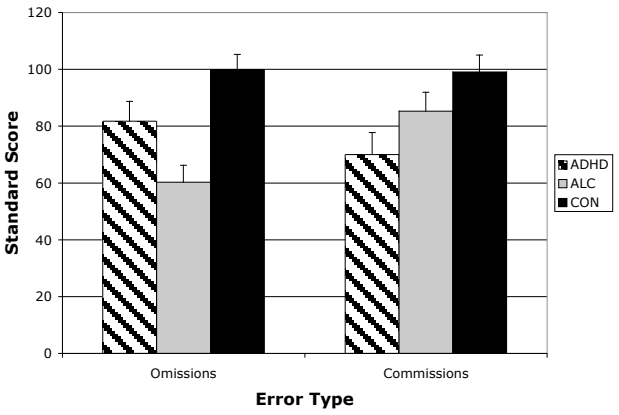

Figure 10. Continuous performance (TOVA) performance

with heavy prenatal alcohol exposure to non-exposed children with ADHD on a computerized test of attention to determine whether the groups could be distinguished based on their performance. The rationale for this study was to determine if the profile of attention deficits in children with heavy prenatal alcohol exposure was the same as the profile of non-exposed children with ADHD. Deficits in attention and hyperactivity are hallmarks of heavy prenatal exposure to alcohol, and children with such exposure are often diagnosed with ADHD, however, it remains unclear whether their functional profiles overlap. We compared children with ADHD with heavy prenatal alcohol exposure, non-exposed children with ADHD, and non-exposed controls on a test of sustained visual attention, the Test of Variables of Attention (TOVA). Diagnoses of ADHD were made using a structured psychiatric interview and groups were matched on age, sex, socioeconomic status (SES), and ethnicity. Omission and commission errors, suggesting inattention and impulsivity, respectively, were analyzed by repeated measures ANOVA. The three groups differed on both types of errors, but in different ways. Children with heavy prenatal alcohol exposure were different from children with ADHD (and similar to controls) on errors of commission but different from controls (and similar to children with ADHD) on errors of omission (Figure 10). These results suggest that while inattention is representative of children with ADHD with or without heavy prenatal alcohol exposure, impulsivity is more specific to non-exposed ADHD children. These types of errors may be used to distinguish children with heavy prenatal alcohol exposure from non-exposed children with ADHD. The TOVA is one of the measures proposed as part of the neurobehavioral core.

Auditory and Visual Focused Attention

In another study, children with heavy prenatal alcohol exposure and non-exposed controls were evaluated using a paradigm developed to test visual and auditory focused attention [24]. For both visual and auditory conditions, visual (blue or yellow squares) and auditory (high or low tones) stimuli were randomly presented via a computer at a rate of 450-1450msec and inter-target intervals (ITI) of 450-30000msec. Participants were required to respond manually to visual or auditory targets depending on the condition. For the visual condition, alcohol-exposed children responded with lower accuracy and slower reaction time (RT) for all ITIs. In contrast, for the auditory condition, alcohol-exposed children were less accurate but displayed slower RT only on the longest ITI (Figure 11). These data suggest that children with heavy prenatal alcohol exposure have deficits in attention that are not global in nature. Rather, deficits in visual attention were pervasive while auditory attention deficits occurred only when ITIs were long (>10sec). These results extend those of Coles et al. [8] which indicated deficits in visual but not auditory sustained attention. Although this specific test is not one of the proposed measures for the consortium, we hope that we will extend our findings by using the auditory and visual TOVA in a larger sample.

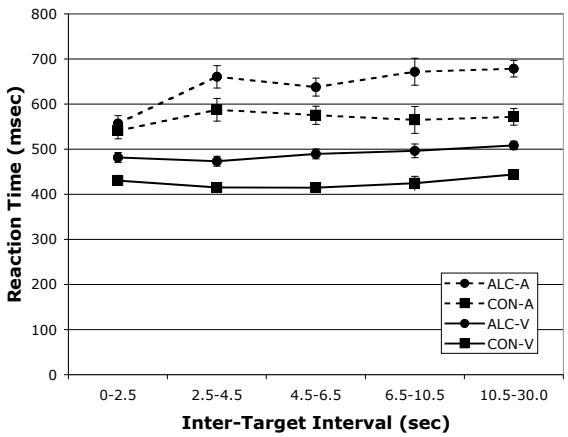

Figure 11. Auditory and visual attention performance

Tests of Executive Function

We have also examined executive function in two studies of children with FASD and non-exposed controls. In the first study [11], we utilized a battery of tests (the Delis-Kaplan Executive Function System) to assess four domains of executive function: planning ability, cognitive flexibility, selective inhibition, and concept formation and reasoning. The tasks consisted of primary executive function measures as well as measures of secondary component skills such as motor speed or basic naming skills. The children with FASD had deficits on all primary measures when compared with non-exposed controls and these deficits were especially apparent on tests involving planning and response inhibition. Furthermore, in most cases, children with and without the FAS diagnosis did not differ from one another. A critical finding was that the primary executive function deficits were not entirely explainable by concomitant deficits on component skills, meaning that basic deficits like motor speed slowing did not account for higher order deficits. In the second study, we examined verbal and nonverbal fluency in children with FASD and non-exposed controls [12]. Fluency was defined as the ability to generate multiple responses within both rule and time constraints. The verbal and nonverbal fluency measures each consisted of three conditions, including a set-shifting task. When compared to non-exposed controls, children with FASD displayed deficits in both fluency domains, demonstrating impaired verbal and nonverbal fluency. In addition, prenatal alcohol exposure predicted performance on the set-shifting design fluency task above and beyond performance on more traditional fluency tasks. Deficits were apparent in children with FASD even without a diagnosis of FAS. In addition, IQ was not related to traditional or set-shifting fluency, whereas diagnostic group (FASD or control) remained a significant predictor even when IQ was included in the model. These studies, taken together, suggest that children with FASD experience higher order deficits in executive function that cannot be accounted for by more basic tasks or by IQ and they occur in FASD children with or without FAS. Thus, executive function deficits may represent one of the core deficits in FASD.

Vineland Adaptive Behavior Scale (VABS)

Another domain to be addressed within the consortium is child behavior, including adaptive behavior. In a previous study [25], we assessed the relationship between social skills and verbal IQ score in children with FAS and controls. Parents of three groups of children were interviewed using the social skills domain from the Vineland Adaptive Behavior Scale (VABS). A group of children with FAS (N = 15) was compared to two control groups. The control groups included children matched on VIQ to the FAS group (the VIQ group, N = 15) and children with IQ scores in the average to above-average range (the CON group, N = 15). The children ranged in age from 5 years 7 months to 12 years 11 months at the time of assessment. All groups differed with regard to social ability, as measured by the VABS (CON > VIQ > FAS), even when the effects of SES were held constant. The three subdomains of the VABS social scale (interpersonal relationship skills, use of play and leisure time, and coping skills) were examined, and results showed that the children with FAS were most impaired on the subdomain that assessed interpersonal relationship skills. In addition, the difference between the age-equivalent score for the VABS social scale and the child's chronological age was calculated for each child. There was a significant correlation between this difference score and chronological age for children in the FAS group but not for children in the two control groups. Specifically, in older children with FAS, there was an increased discrepancy between their ages and their age-equivalent scores, a discrepancy that was not present in children in the control groups. These results suggest that social deficits in children with FAS are beyond what can be explained by low IQ scores and indicate that there may be arrested, and not simply delayed, development of social abilities in children with FAS. Importantly, using the Moscow sample, the relationship between IQ score and adaptive behavior can be addressed in a larger group of children.

Child Behavior Checklist (CBCL)

In a related study [9] to the one just described, we compared parent ratings of behavior in children with heavy alcohol exposure with and without FAS (the ALC group), and non-exposed controls (the CON group). Groups were matched on age, sex, SES, ethnicity, and verbal IQ score. We used the Child Behavior Checklist (CBCL), which is part of the neurobehavioral core assessment battery. Multivariate analyses of covariance revealed significant differences on the Competence, Problem, and Summary scales (p's < 0.05). In addition, when we compared children in the ALC group with or without FAS, there were no significant differences on any of the scales (*p*'s > 0.10). These results suggest that prenatal alcohol exposure results in significant and profound impairment of parent-rated behaviors, and that these deficits are not explained entirely by the presence or absence of facial dysmorphology, general intellectual functioning, or demographic factors.

Finger Localization

Another task that is included in the current proposal is finger localization. Performance on this task is related to the integrity of the corpus callosum, a structure known to be affected by heavy prenatal alcohol exposure. We recently reported [26] a study in which we used a finger localization task to measure the transfer of information across the corpus callosum in children and adolescents with histories of heavy prenatal alcohol exposure and age- and sex-matched controls. When compared with non-exposed controls, alcohol-exposed children made more errors on trials for which information had to cross the corpus callosum ("crossed" trials) than on trials for which it did not ("uncrossed" trials) (Figure 12), and they also made more errors as the task increased in complexity. Additionally, correlations with magnetic resonance imaging data in a subset of children revealed that impairment in interhemispheric transfer was related to reductions in the size of the corpus callosum. These correlations were independent of effects expected from the relationship between corpus callosum size and general intellectual functioning alone. Based on these results, we concluded that children with heavy prenatal alcohol exposure display subtle deficits in the interhemispheric transfer of information in the somatosensory domain. A larger study involving more children with brain image data will further strengthen this conclusion.

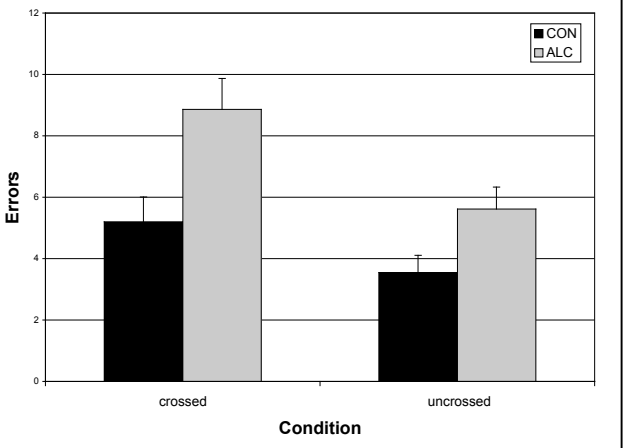

Figure 12. Finger localization results

Brain Imaging Studies

In addition to the test battery proposed by the neuropsychological core, we are proposing to include brain imaging studies using both the San Diego and Moscow samples. Since 1992 we have conducted several studies using brain magnetic resonance imaging (MRI) of children with FASD in San Diego. In the interest of space, the studies related to regions of interest and those that relate structure and function will be highlighted. A complete list of relevant publications is listed at the end of this section.

In our first clinical case study, we documented MRI findings from two children with FAS [27], including abnormalities of the corpus callosum including agenesis in one case, and volumetric reductions in the basal ganglia and thalamic structures. We followed this study with additional evidence for alterations in both the corpus callosum [28, 29] and the caudate nucleus [30-32]. Specifically, our studies of the corpus callosum have indicated that this structure appears to be especially vulnerable to heavy

prenatal alcohol exposure, and that there is an increase in the incidence of callosal agenesis in this population. Furthermore, in addition to callosal area reductions, most severe in the splenium, we have shown that the corpus callosum is significantly displaced in individuals exposed to alcohol prenatally. In comparison to controls, this structure was more anterior and inferior in posterior regions with relatively normal localization of anterior regions in the alcohol-exposed group (Figure 13).

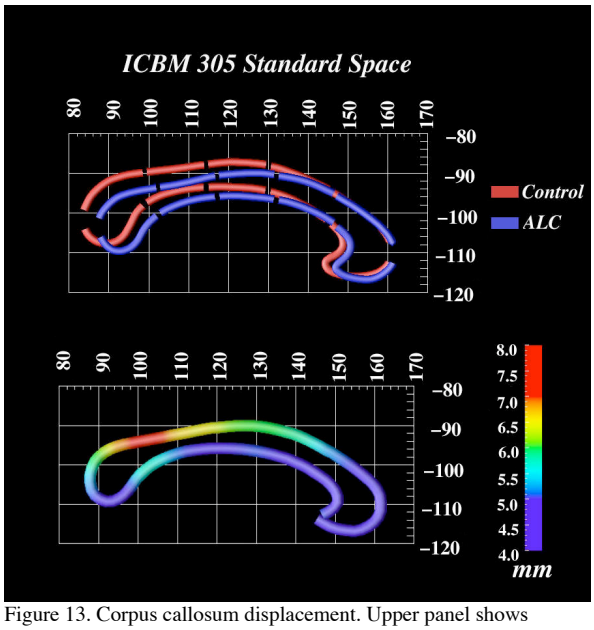

Figure 13. Corpus callosum displacement. Upper panel shows comparison between alcohol-exposed and control subjects. Note divergence in posterior (left) regions. Lower panel shows average displacement in millimeters between alcohol-exposed and control subjects.

In addition to our studies of the corpus callosum, we recently mapped the density of the gray and white matter in the brain using statistical parametric mapping. The results suggested abnormalities in the temporal-parietal regions of the brain, particularly in the left hemisphere. Increased gray matter and decreased white matter were apparent in individuals with FASD [33]. These results are consistent with those of Archibald et al. [32], which suggested decreased overall parietal volume and decreased white matter volume in this region. Thus, it appears that the parietal region of the brain may be an additional target of heavy prenatal alcohol exposure. We hope to replicate these findings in the larger sample and relate the changes seen in the parietal lobe to neuropsychological function.

Finally, we have also conducted three studies in which we correlated neuropsychological and neuroanatomical findings. In the first study, twenty-two neuropsychological variables and nine brain variables were chosen for analysis of brain-behavior relationships. First, simple correlations between brain and behavior variables revealed that the caudate volume was significantly ($p < .10$) related to the greatest number of variables, followed by the cerebellum and the parietal lobe. The relationship between the caudate and the neurobehavioral variables was examined further, using multiple regression analyses, statistically controlling for other predictive variables. Even after other variables were considered, the addition of caudate volume to the model significantly increased the amount of explained variance in four measures. These were measures of inhibition (WCST perseverative responses and CVLT-C false positives) and verbal learning and recall (CVLT-C A-total and LDF), which have been previously reported as measures sensitive to prenatal alcohol exposure. Importantly, caudate volume was significantly related to performance on these behavioral measures even after accounting for other brain measures, IQ, or diagnostic group (FAS vs. PEA).

In two separate studies we examined the relationship between corpus callosum abnormalities and cognitive functioning. In one study [26], correlations with magnetic resonance imaging data in a small group of children revealed that impairment in interhemispheric transfer (as described above) was related to reductions in the size of the corpus callosum. Importantly, these correlations were independent of effects expected from the relationship between corpus callosum size and general intellectual functioning alone. In the other study [29], we demonstrated that the amount of corpus callosum displacement, as mentioned above, is correlated with impairment in verbal learning ability and that callosal displacement is a better predictor of verbal learning than regional callosal area. This brain-behavior relationship was only significant within the alcohol-exposed group (and not controls), and the effect was not solely mediated by overall impaired verbal intellectual functioning.

Papers

Lee, K.T., Mattson, S.N., and Riley, E.P. (manuscript submitted, 2003). Classifying children with heavy prenatal alcohol exposure using measures of attention. Abstract published in Journal of the International Neuropsychological Society, 9 (2), 202.

Roebuck, T.R., Mattson, S.N., and Riley, E.P. (2002). Interhemispheric Transfer in Children with Heavy Prenatal Alcohol Exposure. Alcoholism: Clinical and Experimental Research, 26 (12), 1863-1871.

Sowell, E.R., Mattson, S.N., Thompson, P.M., Jernigan, T.L., Riley, E.P., and Toga, A.W. (2001). Mapping callosal morphology and cognitive correlates: Effects of heavy prenatal alcohol exposure. Neurology, 57 (2), 235-244.

Sowell, E.R., Thompson, P.M., Mattson, S.N., Tessner, K.D., Jernigan, T.L., Riley, E.P., and Toga, A.W. (2001). Voxel-based morphometric analyses of the brain in children and adolescents prenatally exposed to alcohol. Neuroreport, 12 (3), 515-523.

Archibald, S.L., Fennema-Notestine, C., Gamst, A., Riley, E.P., Mattson, S.N., and Jernigan, T.L. (2001). Brain dysmorphology in individuals with severe prenatal alcohol exposure. Developmental Medicine and Child Neurology, 43 (3), 148-154.

Schonfeld, A.M., Mattson, S.N., Lang, A.R., Delis, D.C., and Riley, E.P. (2001). Verbal and nonverbal fluency in children with heavy prenatal alcohol exposure. Journal of Studies on Alcohol, 62 (2), 239-246.

Mattson, S.N. and Riley, E.P. (2000). Parent ratings of behavior in children with heavy prenatal alcohol exposure and IQ-matched controls. Alcoholism: Clinical and Experimental Research, 24 (2), 226-231.

Mattson, S.N., Goodman, A.M., Caine, C., Delis, D.C., and Riley, E.P. (1999). Executive functioning in children with heavy prenatal alcohol exposure. Alcoholism: Clinical and Experimental Research, 23 (11), 1808-1815.

Thomas, S.E., Kelly, S.J., Mattson, S.N., and Riley, E.P. (1998). Comparison of social abilities of children with fetal alcohol syndrome to those of children with similar IQ scores and normal controls. Alcoholism: Clinical and Experimental Research, 22 (2), 528-533.

Mattson, S.N., Riley, E.P., Gramling, L., Delis, D.C., and Jones, K.L. (1998). Neuropsychological comparison of alcohol-exposed children with or without physical features of fetal alcohol syndrome. Neuropsychology, 12 (1), 146-153.

Mattson, S.N., Riley, E.P., Sowell, E.R., Jernigan, T.L., Sobel, D.F., and Jones, K.L. (1996). A decrease in the size of the basal ganglia in children with fetal alcohol syndrome. Alcoholism: Clinical and Experimental Research, 20 (6), 1088-1093.

Riley, E.P., Mattson, S.N., Sowell, E.R., Jernigan, T.L., Sobel, D.F., and Jones, K.L. (1995). Abnormalities of the corpus callosum in children prenatally exposed to alcohol. Alcoholism: Clinical and Experimental Research, 19 (5), 1198-1202.

Mattson, S.N., Riley, E.P., Jernigan, T.L., Garcia, A., Kaneko, W.M., Ehlers, C.L., and Jones, K.L. (1994). A decrease in the size of the basal ganglia following prenatal alcohol exposure: A preliminary report. Neurotoxicology and Teratology, 16 (3), 283-289.

Mattson, S.N., Riley, E.P., Jernigan, T.L., Ehlers, C.L., Delis, D.C., Jones, K.L., Stern, C., Johnson, K.A., Hesselink, J.R., and Bellugi, U. (1992). Fetal Alcohol Syndrome: A case report of neuropsychological, MRI, and EEG assessment of two children. Alcoholism: Clinical and Experimental Research, 16 (5): 1001-1003.

Related Abstracts

Calarco, K.E., Mattson, S.N., Robertson, B., and Riley, E.P. (2003). Heavy prenatal alcohol exposure or ADHD? Errors make the difference. Journal of the International Neuropsychological Society, 9 (2), 152.

Kane, A., Mattson, S.N., Klopp, R., Coles, C.D., Marintcheva, G., Riley, E.P. (2003). Relationship of IQ and WCST performance in children with fetal alcohol syndrome. Journal of the International Neuropsychological Society, 9 (2), 202.

Flury, L., Mattson, S.N., Kodituwakku, P.W., Adnams, C., Turner, G., Li, T.K., and Riley, E.P. (2002). Neuropsychological phenotypes for identifying children with fetal alcohol syndrome. Genetic Epidemiology 23, 281.

Mattson, S.N., Lang, A.R., and Calarco, K.E. (2002). Attentional focus and attentional shift in children with heavy prenatal alcohol exposure. Presented at International Neuropsychological Society meeting, Toronto, Ontario, Canada, February 2002. Journal of the International Neuropsychological Society, 8 (2), 295.

Marintcheva, G., Riley, E.P., Mattson, S.N., Coles, C.D., Konovalova, V., Matveeva, A. (2001). Neuropsychological test performance in Russian children with FAS compared to controls matched for age, sex, IQ, and living environment. Alcoholism: Clinical and Experimental Research, 25 (5), 123A.

Mattson, S.N., Riley, E.P., Archibald, S.A., & Jernigan, T.L. (2001). Caudate volume predicts CVLT-C and WCST performance of children with heavy prenatal alcohol exposure. Alcoholism: Clinical and Experimental Research, 25 (5), 74A.

Mattson, S.N., Roebuck, T.M. and Riley, E.P. (1996). Wisconsin card sorting performance in children prenatally exposed to alcohol. Alcoholism: Clinical and Experimental Research, 20 (2 Suppl.), 74A.

d. Research Design and Methods

Participants

Participants will be children, ages 7-18 years, with heavy prenatal alcohol exposure and non-exposed controls. These children will be compared to each other on all aspects of the proposed study. There will be two alcohol-exposed groups, comprised of children with FAS and FASD (without FAS), respectively. By including two groups we will both increase our sample size and have available a larger spectrum of effects. By definition, all children in the FAS/FASD groups will be heavily exposed (i.e., born to alcohol-abusing or alcohol-dependent women). Our previous research has shown qualitative similarities between alcohol-exposed children with or without FAS [9, 11, 13, 14]. Thus, we will compare the FAS and FASD groups to each other and if appropriate combine them into one group for comparison to controls.

San Diego Component. Alcohol-exposed and control participants will be selected from ongoing studies at the Center for Behavioral Teratology (CBT) at San Diego State University. The CBT is currently following over 100 children with heavy prenatal alcohol exposure and enrollment will continue during the course of this study (9/29/2003-9/28/2008). The majority of these children (58.3%) are referrals from Dr. Kenneth Lyons Jones, a dysmorphologist with extensive experience evaluating children with heavy prenatal alcohol exposure and co-author of the original reports describing FAS. Dr. Jones is PI of the dysmorphology core of this application. The remaining referrals

come from other professionals in the community (23.3%) and other forms of publicity including the Internet (18.4%). Both the PI and Dr. Jones routinely provide in-service training throughout the San Diego community, including agencies that target underserved populations. Dr. Jones will evaluate all alcohol-exposed children, as described below. We typically recruit 10 new alcohol-exposed children into our studies each year. However, we hope to be able to increase our community outreach and advertising, with the goal of increasing our sample sizes.

Moscow Component. Alcohol-exposed and control participants will be selected from ongoing studies at the Institute of Psychiatry in Moscow, Russia. The Institute of Psychiatry is responsible for psychological services for children living in boarding schools and special orphanages. Children in the special orphanages typically have below average intellectual functioning and either are orphans or have parents who have lost parental rights. Children in the boarding schools may still be in the legal custody of their parents, but for some reason are felt to better cared for in the special boarding schools and again they have below average intelligence or special needs. Thus, the special orphanages and boarding schools house children with below average intellectual function and these include a large number of children with FAS. As detailed in the preliminary data section, since 1999, teams of pediatricians trained by Dr. Kenneth Lyons Jones and Dr. Luther Robinson have evaluated 3805 children. Following preliminary examinations, diagnoses were confirmed by either Dr. Jones or Dr. Robinson. Although we have currently been targeting children who meet the criteria for FAS, there exist a large number of children with known alcohol exposure but who do not meet the criteria for FAS. They will also be included in this study. We currently have 69 children with histories of alcohol exposure but who do not meet criteria for FAS and 19 of these have been confirmed (as “not FAS”) by the experts. Thus, the Moscow FASD groups will consist of children with and without the diagnosis of FAS. Based on our current sample, we anticipate that approximately 100 new children with FAS/FASD will become available (i.e., by aging into the sample or placement in the institution) during the tenure of this study and thus, will increase our sample size.

Alcohol-Exposure Histories

In both samples, the levels of alcohol exposure in the FASD groups are not precisely known given the retrospective nature of the study. While determining a critical dose or critical period of exposure is highly desirable, it is not the aim of this study and is left to existing prospective studies.

San Diego Component. In the San Diego sample, consumption levels based on maternal report, social service records, or medical records indicate heavy alcohol consumption during pregnancy. Reports of alcohol consumption range from 3-4 glasses of wine a day to “drunk day and night.” Typical reports include drinking a fifth of vodka per day and drinking a case of beer per day. We are very conservative in our acceptance of hearsay and rumor of alcohol exposure and require more concrete evidence (e.g., direct report of the parent or a close relative, or medical records) of such exposure. Children with limited information on prenatal alcohol exposure are not eligible to participate. In addition, due to the retrospective nature of this study, the information on other drug exposure is sparse and is typically dichotomous in nature (e.g., the mother smoked or did not smoke). However, given the importance of other drug exposure, this factor will be included in statistical analysis if possible. In addition to a review of the medical and associated documents by the PI, the caretakers complete a questionnaire on prenatal alcohol exposure, medical, and demographic information at the time of testing. Data obtained include maternal age, medical status of child, psychiatric status of child and family, maternal and paternal occupation and education.

Although a prospective measure of alcohol consumption is extraordinarily valuable, this is a retrospective study and thus it is important to recognize the nature of the population followed by the CBT. Typically, children are referred because there is known or suspected prenatal alcohol exposure and parents are interested in determining if an alcohol-related diagnosis is appropriate for their child.

Some children are adopted at early ages and parents are interested in participating in research, and some parents have concerns about potential or existing behavior problems. This type of self/clinically-referred sample is different from a prospectively identified population of children, but the importance of our sample is that it provides the opportunity to study children with heavy exposure rather than the low to moderate levels of exposure typical of prospective studies. Further, we believe our sample is representative of the larger population of children with heavy prenatal alcohol exposure. These children are not typically identified prior to birth but rather often go unrecognized until school age. Thus, we feel the strengths and value of our sample outweigh any potential weaknesses.

Moscow Component. In Moscow, data concerning alcohol exposure is obtained through a review of medical and social records conducted by the nurse at the orphanage or boarding school. In addition to information on alcohol-exposure, records are reviewed for the following data: maternal age, prematurity, birth weight, maternal rejection, sibling status, whether there are any mentally retarded siblings, whether the mother is deceased and cause of death, whether parental rights are intact, whether the child was abandoned by the parent and why, maternal education and occupation.

As with the San Diego sample, this represents a valuable group, in spite of the lack of prospective ascertainment. Children in this sample are placed in “special” orphanages and boarding schools because of their general level of intellectual functioning. We have already demonstrated that a high rate of FAS exists among these children. However, of equal importance is the presence of a control group of a similar intellectual level and environmental background. By design, all children are living in the same institutions; they differ only in the presence or absence of prenatal alcohol exposure.

Dysmorphological Evaluation

All alcohol-exposed children from both sites will be examined by a dysmorphologist using standard criteria, as described in the Dysmorphology Core. Briefly, the dysmorphic exams include measures of height, weight, head circumference, palpebral fissure length, innercanthal distance, and philtrum length. Ratings are made on the thinness of the upper vermillion and the smoothness of the philtrum. All diagnoses are done blind to maternal alcohol consumption. The criteria for classification are based on IOM guidelines as well as previous work in South Africa and Moscow, and include: (1) Growth deficiency defined as prenatal or postnatal weight and/or height $\leq 10^{th}$ % for sex and age using National Center for Health Statistics current growth charts; (2) At least two of the following facial features: palpebral fissure length unilaterally or bilaterally $\leq 10^{th}$ % for age; philtrum smoothness using the Astley/Clarren Lipometer [34] valued at 4 or 5; thin smooth vermillion border of the upper lip using the Astley/Clarren Lipometer [34] valued at 4 or 5; maxillary hypoplasia; (3) Neurobehavioral/ Neurodevelopment problems consisting of microcephaly defined as OFC $\leq 10^{th}$ % adjusted for age and sex; obvious structural brain abnormalities and/or confirmed neurodevelopmental or neurobehavioral disorder in areas of: attention, memory, motor function, language, cognitive, and socio-economical development, with or without mental retardation.

San Diego Component. Regardless of referral source, Dr. Jones evaluates all children with histories of prenatal alcohol exposure. Of the children we are currently following, 48.1% meet criteria for FAS. The remaining 51.9% of children are considered structurally normal although they have histories of heavy prenatal alcohol exposure, as described above. Although Dr. Jones has evaluated our sample of children previously, we hope to have him re-evaluate all alcohol-exposed children in conjunction with this study, using methodology employed in the Moscow sample.

Moscow Component. As mentioned previously, children in the orphanages and boarding schools are seen by teams of pediatricians trained by Drs. Ken Jones and Luther Robinson. Diagnoses of FAS or Deferred, as described above, are confirmed by Dr. Jones or Dr. Robinson. Thus far, the pediatricians have seen over 3800 children and over 200 have received confirmed diagnoses of FAS.

Children with confirmed diagnoses of FAS as well as children with histories of alcohol exposure but who do not receive the FAS diagnosis (either "not FAS" or Deferred) will participate in this study.

Control Groups

Comparison groups will be included at both sites.

San Diego Component. In addition to the children with heavy prenatal alcohol exposure, a group of non-exposed control (CON) children will be included as participants. This group consists of normally developing children who have no history of exposure to alcohol during gestation. They are matched to the FAS/FASD group on the basis of age, sex, handedness, ethnicity and race, and SES (as determined by the Hollingshead Four Factor Index of Social Status). These children are recruited from the community by word of mouth and by advertising (e.g., flyers, advertising in parent magazines). Children are not included in the CON group if alcohol exposure is known or suspected. The CBT has enrolled nearly 100 children who meet criteria for the CON group and enrollment will continue during the duration of this study (9/29/2003-9/28/2008).

Moscow Component. In Moscow, controls will be residents of the same orphanages and boarding schools that house the children with FAS/FASD, and will be similar in general intelligence and living environment. Children in the control groups will only be included if alcohol exposure can be ruled out.

Sample Size

San Diego Component. Approximately 75-100 children will be tested for each component of the study. The total sample will be equally divided between the three groups (FAS, FASD, CON). As mentioned, the CBT has an active enrollment and follow-up process. We have been successful in maintaining contact with 85% of our participants (93% of alcohol-exposed participants). Thus, enrollment is adequate for the current study. Our previous studies have ranged in size from 10-50 children per group. Based on the types of studies proposed herein and our previous work, we feel that group sizes of approximately 25 will provide adequate power to detect statistical and meaningful differences between the groups should they exist. A sample size of 25 per group provides power of .80 (alpha = .05, beta = .20) to detect group differences of 0.80SD. This is equivalent to a standard score difference of 12 points. In addition, the inclusion of both dysmorphic and non-dysmorphic children in the FAS/FASD groups will allow a comparison both between these groups and between the FAS/FASD groups and the control group.

Moscow Component. Larger sample sizes are available in Moscow, as outlined above. However, given that one of the comparison groups will be similar in IQ to the FAS/FASD groups, larger sample sizes are necessary to detect group differences, if in fact they do exist. Our goal is to examine three groups (FAS, FASD, CON) of 75-100 children each. The CON group will be similar to the FAS/FASD groups in terms of general intellectual functioning and living environment. A sample size of 75 per group provides power of .80 (alpha = .05, beta = .20) to detect group differences of 0.46SD. This is equivalent to a standard score difference of approximately 7 points. In addition, the inclusion of both dysmorphic and non-dysmorphic children in the FAS/FASD groups will allow a comparison both between these groups and between the FAS/FASD groups and the control group.

Inclusion and Exclusion Criteria

Children will be invited to participate if they meet the following inclusion criteria:

1. Age between 7 and 18 years. In San Diego, we currently have approximately 130 children enrolled who will fall into this age range during the course of the study and approximately 50% are alcohol-exposed (25% have FAS). In Moscow, we have over 250 children who are within the age range, and approximately 70% have confirmed diagnoses of FAS.
2. Speak English or Russian as their primary language, depending on site.

Exclusionary criteria are as follows:

1. Significant head injury with loss of consciousness more than 30 minutes.
2. Significant physical (e.g., uncorrected visual impairment or hemiparesis) or psychiatric disability (e.g., psychosis) that would preclude participation.
3. Other known causes of mental deficiency (e.g., congenital hypothyroidism, neurofibromatosis, chromosomal abnormalities). Children will be excluded from the CON group if prenatal alcohol exposure is known or suspected or information is unavailable.

General Procedures

Children currently enrolled in the CBT research programs in San Diego and Moscow, as well as any new enrollees, will be invited to participate in these studies if they meet the inclusion criteria outlined above. Children or their parents/guardians are free to discontinue participation at any time. Following IRB-approved informed consent and assent procedures, children will be tested individually in a quiet and distraction-free room. In San Diego, testing will be conducted by a trained psychometrist, blind to group membership. In Moscow, testing will be conducted by a psychologist. Test sessions will be designed to last no more than three hours (depending on the age of the child) and to include breaks. Children will be eligible for all components as long as they continue to meet the eligibility criteria. New children will be invited to participate as they become available. In San Diego, parents will be asked not to give their children any stimulant medication (e.g., methylphenidate) on the day of testing, however, no child will be excluded from participation if their parent is unwilling to do this. However, for safety and ethical purposes, withdrawal from other non-stimulant drugs will not be requested. Medication is not an issue in Moscow, as children are not typically medicated. All children are provided with an incentive to participate (San Diego and Moscow) and parents are provided with funds for travel and child-care if needed (San Diego).

Measures

The measures selected for this protocol come from two sources, core and secondary tests from the neurobehavioral core and site-specific tests included for this proposal. All measures will be administered in a standardized fashion across site using methodology suggested by the test publisher or author as appropriate for the age of the child. Core test administration will also be standardized across site, as determined by the neurobehavioral core.

TESTS FROM NEUROBEHAVIORAL CORE

The primary and secondary tests from the neurobehavioral core are listed in Table 3. The details of these tests are available in the neurobehavioral core and in Appendix 1, thus only brief descriptions will be provide here.

Table 3. Core Test Battery (7-18 years)

Domain	Test	Subtest
General Intellectual Ability	Leiter-R*	
Arousal and Attention	TOVA	Visual and auditory
	Leiter-R*	Attention subtests
Executive Functioning	DKEFS	Trails/Design Fluency
	PPT	
	CANTAB*	DMS, IED, SOC
	Go/No-Go	Oddball paradigm

Table 3. Continued		
Visual-Motor Integration, Motor, and Spatial Skills	VMI	VMI, visual perception, visual-motor coordination
	Finger Localization	
	Road Map Test of Direction Sense	
	Grooved Pegboard*	
	Handedness* (Edinburgh)	
	CANTAB	MOT/BLC, SSP
Memory	Leiter-R*	Memory Subtests
	CANTAB*	SRM, PRM, PAL
Emotion/Behavior	Achenbach*	CBCL/TRF/YSF(11-18)
	Pelham DBD	
	Vineland	

*Designated as primary core measures. All others designated as secondary core measures.

The following core tests were selected for administration at the San Diego and Moscow sites. General intellectual functioning will be assessed using the **Leiter International Performance Scale-Revised**. This test provides an IQ equivalent score (correlated with the WISC-III, r = .85) as well as scales for visualization and reasoning and attention and memory. Most participants at both sites will hve previously been administered a Wechsler IQ test. Attention will also be tested using the visual and auditory versions of the **Test of Variables of Attention (TOVA)** [35]. As indicated in the Preliminary Data section, we have successfully used the visual TOVA in our San Diego sample. The addition of the auditory version of the TOVA will allow us to follow-up on the visual-auditory differences suggested by our studies [24] and those of Coles et al. [8]. Executive functioning will be tested using the **Progressive Planning Test (PPT)** [36] and the **Cambridge Neuropsychological Test Automated Battery (CANTAB)** [37, 38]. Executive function has been suggested as a potential core deficit in FASD. We have previously shown deficits in this area using a broad range of tests [11, 12] and have recently begun to use the CANTAB in our San Diego and Moscow samples. Visual-spatial functioning will be tested with the **Road-Map Test of Direction Sense** [39], the **Beery Developmental Test of Visual Motor Integration (VMI)** [40], and subtests of the **CANTAB**. Preliminary data suggest that visual-spatial deficits may also represent core deficits in FASD. Learning and memory will be tested using subtests of the **CANTAB**. We have shown, in several studies, that children with FASD have profound deficits in learning of verbal information and learning and retention of non-verbal information [14, 15, 17]. Finally, behavior will be assessed using the **Vineland Adaptive Behavior Scale (VABS)** [41], **Achenbach Scales** [42-44], and the **Parent/Teacher Disruptive Behavior Rating Scale** [45]. These measures will be especially important in documenting the behavioral difficulties in children with FASD.

We anticipate that this testing battery will take about 5 hours. In San Diego, we plan on completing this testing battery in two sessions on a single day, separated by a lunch break. We will request parents bring their children to the CBT at 9:00AM. However cooperation and child motivation is critical and thus testing may be broken up into two days of testing within 2 weeks time. During the morning testing, parents will complete questionnaires and the VABS interview. Both children and parents will be provided with subject incentive for their participation. In Moscow, testing will be conducted at the orphanage. Our experience has been that long testing sessions are impractical. However, all attempts will be made to administer testing in a standardized fashion and to complete the battery within a two-week period.

SUPPLEMENTAL SITE-SPECIFIC TESTS OF INTERHEMISPHERIC TRANSFER

Because we are especially interested in the integrity of the corpus callosum, we have included a small number of tests sensitive to interhemispheric interaction: Tactile Performance Test and the Bimanual Coordination Test. We have also included three additional tests from the core: Finger Localization, Grooved Pegboard, and the Handedness Inventory.

Finger Localization Task (core test)

The finger localization task [46] is one of the core tests but is described here with our other interhemispheric tests. This test involves an examiner lightly touching the tip of one or two fingers of the child with a sharpened pencil point. Children are asked to indicate which finger was touched by touching that finger with the thumb of the same hand (uncrossed condition) or by touching the corresponding finger with the thumb of the opposite hand (crossed condition). There are three conditions: 1) hands in view, one finger stimulated; 2) hands out of view, one finger stimulated; and 3) hands out of view, two fingers stimulated consecutively. Each of these three conditions consists of four 16-trial blocks, two uncrossed blocks followed by two crossed blocks. Starting hand is counterbalanced across subjects. Children's hands are placed in a vertical plane with palms facing each other, thus providing a mirror image of each other and minimizing directional confusion. Vision is excluded by blindfold. The two-finger condition is included to manipulate task complexity. For this condition children are asked to "touch the same fingers, in the same order" with the thumb of the same hand or to touch the corresponding fingers with the thumb of the opposite hand. For all conditions, children are told which hand was to be stimulated, how many fingers will be touched (1 or 2), and which hand they should use to respond. The examiner records responses and self-correction is allowed. No feedback is given concerning accuracy of performance on trials. We have previously used this measure in children with heavy prenatal alcohol exposure [26]. Administration time is approximately 15 min.

Grooved Pegboard Test (core test)

The Grooved Pegboard Test [47] consists of a pegboard with 25 grooved slots. The child is required to place a grooved peg into each of the slots, first with the right hand and then the left hand. The time to complete the task with each hand is recorded. Normative data are available for children ages five to 16. Administration time is approximately 8 minutes.

Edinburgh Handedness Inventory (core test)

Handedness is examined using the Edinburgh Handedness Inventory [48], in which each child is asked which hand they use for the following tasks: writing, drawing, throwing, using scissors, using a toothbrush, using a knife (without fork), using a spoon, using a broom (upper hand), striking a match, and opening a box (lid). Administration time is approximately 5 minutes.

Test of Transfer of Learning

The Tactile Performance Test (TPT) from the Halstead Reitan battery [49] is proposed to test whether alcohol-exposed children exhibit impairments in the interhemispheric transfer of newly learned material. The TPT is a measure of complex psychomotor ability that includes a significant problem-solving component, tactile form perception, spatial learning, and spatial recall. For this test, children are blindfolded and seated facing the table upon which the form-board is placed. The blocks are placed in a random sequence in front of the child, with the exception that blocks adjacent to each other on the form-board were not placed next to each other on the table. The child's hand is guided over the blocks and the form-board and then the child is asked to fit the blocks into their proper places. The examiner records time to complete the task using the dominant hand, then the non-dominant hand, and then the dominant hand again. The task is administered in the standardized manner according to the Halstead Reitan battery. Administration time is approximately 30 minutes.

Test of Bimanual Coordination

A computerized version of an Etch-a-Sketch task [50] is proposed to measure cooperation and coordination between the two hands. This task assesses speed and accuracy when both hands must coordinate to move a cursor between narrow guidelines presented on a computer screen. The Etch-a-Sketch device consists of a box with two knobs, the right controlling the vertical movement and the left horizontal movement. Children are instructed to draw a line within a demarcated path using the two knobs. Children are asked to navigate the cursor through a series of unimanual and bimanual angled paths (Figure 13). The unimanual-angled pathways consist of two trials for each hand, which test simple motor speed with the right and left hand individually. These unimanual pathways consist of a 90-degree pathway requiring only the right hand and a 0-degree pathway requiring only the left hand. The bimanual pathways consist of three right-to-left angled paths (22, 45, and 67 degrees) and three left-to-right angled paths (112, 135, and 157 degrees). To avoid practice effects, the presentation of the trials is randomized within the right and left angles. The unimanual trials are randomized separately from the bimanual trials and are presented first. Each of these angled paths is tested both with visual feedback and then without visual feedback for the last half of the target path. Time to complete each path and accuracy of path are measured. Accuracy is determined by the number of times the child leaves the demarcated path and by the length of the line drawn attempting to follow the path. Administration time is approximately 10 minutes.

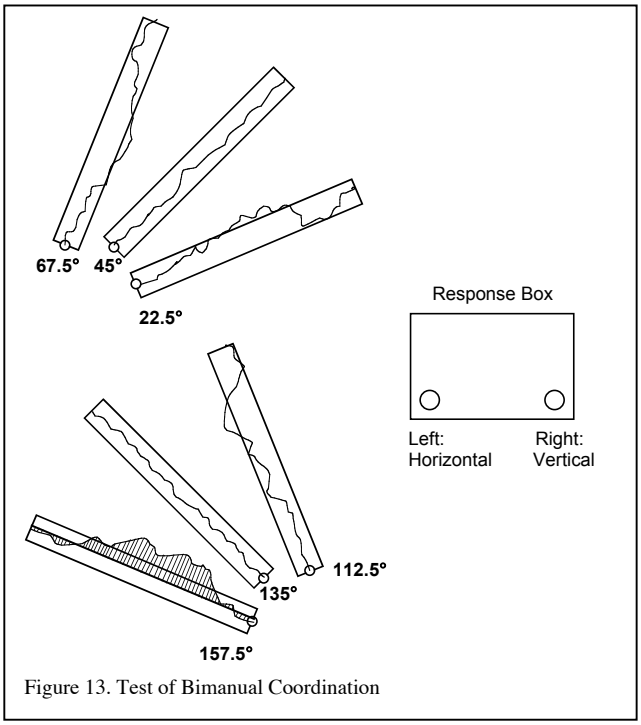

Figure 13. Test of Bimanual Coordination

We anticipate that this testing battery will take about 60-90 minutes, which will be completed in a single session. All testing will take place in a quiet distraction-free room. Children will be provided with subject incentive for their participation.

SUPPLEMENTAL SITE-SPECIFIC TESTS OF BRAIN STRUCTURE AND FUNCTION

Children involved in our project in the CBT will also undergo brain-imaging studies so that functional data from neuropsychological testing can be correlated with structural data from brain imaging. Both structural and functional magnetic resonance imaging data will be conducted in collaboration with the imaging core. Following calibration using mechanical and human phantoms (as described in the imaging core), we will acquire a high resolution T1-weighted 3 dimensional image data set. The image data will be collected with voxel dimensions of approximately 1 by 1 mm within the sagittal plane (plane of acquisition), with a TR of 24 ms, TE=5 ms, NEX=2, flip angle=45 degrees, field of view of 30 cm, 124 slices with section thickness of 1.2 mm, no gaps. This protocol takes approximately 19 minutes of imaging time at 1.5 Tesla. In Moscow, we may only acquire midsagittal sections from each participant due to the lower magnet strength at that site. The most global analysis proposed to be conducted by all imaging sites is measurement of the corpus callosum in the midline sagittal plane. A much shorter imaging time is required for a similar protocol with NEX = 1 (about 9 minutes), and will yield images comparable (though suboptimal) to the higher resolution data, adequate for automated corpus callosum measurement. However, if after consultation with the imaging core, a more detail acquisition protocol is possible, we will proceed as above. Primary areas of interest for analysis are the parietal and temporal lobes, the frontal-subcortical system, the

hippocampus, the cerebellum, and the corpus callosum. We have been studying these areas for a number of years and a summary of our findings is in the Preliminary Data section.

3-D FACIAL IMAGING

In collaboration with the Facial Imaging Core, we will ascertain 3-D facial images of alcohol-exposed and control participants. Previously, it has been demonstrated that a collection of anthropometric data can identify a subset of variables which can accurately distinguish individuals with FAS from those who were alcohol-exposed but do not manifest the full spectrum of clinical features, and those who were not alcohol-exposed [51]. Collection of such data can be relatively tedious and requires specialized training. The advent of new technology, such as three-dimensional (3-D) digitizing instruments, makes the collection of such data potentially easier and cost-effective. The utilization of images obtained from the 3-D laser camera will allow for new analytical approaches coupled with quantitative assessment of facial form that in turn should allow us to build on previous work to create a more efficient and broadly applicable approach to recognizing children of various ages and ethnicities who have been affected by prenatal exposure to alcohol. Greater understanding of the phenotypic correlates of prenatal alcohol exposure will allow for better understanding of the pathophysiology of alcohol exposure, especially when this information is combined with information collected on other systems affected by ethanol exposure such as neural and cognitive development. The integration of these research efforts will help to clarify the degree to which craniofacial variation reflects underlying disruptions in brain form and function. Details of the protocol to collect 3-D images can be obtained from the Facial Imaging Core.

SPECIFIC HYPOTHESES

In addition to the overall aims of the consortium, we have several specific hypotheses that we hope to test with the proposed studies. We plan on depending on both the neuroimaging and informatics cores to assist us with our analyses.

The specific aim of this proposal is to determine whether a phenotype exists in children with FASD. Children with FASD and controls with a broad range of ability will be examined at both sites, using neuropsychological and neuroanatomical measures. We will assess approximately 300-375 children, two-thirds of whom will have FASD. Using this large sample, the relationship between overall IQ and specific domains of function will be addressed. For example, there are three CANTAB subtests sensitive to executive function (DMS, IED, SOC). By comparing the performances of children with FASD to controls matched on general intellectual functioning, we can determine whether previously reported deficits in executive function are in fact, core deficits. If matching on IQ eliminates group differences it does not necessarily indicate that deficits do not exist. Rather, it would suggest that executive function deficits are not specific to this population but are explained by general levels of function. We predict that deficits in executive function, visual spatial function, object location identification (but not object recognition), learning (but not memory deficits), and attention (but not hyperactivity) will be supported as core deficits. Our general analysis strategy will be similar to that described in the preliminary data section and will involve standard analysis of variance techniques with group and site as factors. Our preliminary data, presented above, suggests that the children with FASD in Moscow are similar to those in San Diego but the two control groups are different. Thus, we anticipate main effects of site and possibly significant group x site interactions, reflecting the importance of environmental factors in neuropsychological outcome. In addition, we anticipate using descriminant function analyses but will consult closely with the informatics core on specific analysis strategies.

We anticipate that with the large number of children tested we will be able to test several specific hypotheses, in addition, to the overall aim of defining the phenotype. For example, we are interested in the relationship between neuroanatomical and neuropsychological test data and specifically, the

relationship between the mid-sagittal area of the corpus callosum, callosal displacement, and our measures of interhemispheric interaction. Correlation analysis will be used to address this specific aim.

We also anticipate examining the relationship between specific cortical areas and tests of neuropsychological function. For example, we hypothesize a relationship between parietal regions and measures of spatial location from the CANTAB and between temporal regions and CANTAB measures of object recognition. Again, these relationships will be addressed with correlation analysis and in conjunction with the neuroimaging core.

RELATIONSHIP TO CORES

By the nature of the consortium arrangement proposed in this project, we expect to utilize many of the functions of the supporting cores.

a. Imaging Core: we plan on examining approximately 75 children/year using MRI and will rely on the imaging core for analysis and guidance in methodology. These sample sizes are proposed given the lack of normative data and the possibility of lost scans due to technical or subject factors. Approximately 225-275 children will be examined in Moscow and 75-100 children will be examined in San Diego.
b. Dysmorphology Core: Dr. Jones and Dr. Robinson have already evaluated many of our potential participants, however we anticipate approximately 50 new participants each year will need examination. The dysmorphology core will validate diagnoses made by the pediatricians.
c. Neurobehavioral Core: We will rely on the neurobehavioral core for materials, equipment, translation of materials, and training for the neuropsychological tests proposed. Approximately 75 children/year will be examined (225-275 children in Moscow and 75-100 in San Diego).
d. Facial Imaging Core: While facial imaging is not a specific aim of this proposal, we will make available children from both sites for the Facial Imaging Core, as described above. We anticipate that approximately 75 children/year will be available (225-275 children in Moscow and 75-100 in San Diego).
e. Informatics Core: Data from the core consortium tests will be submitted to the informatics core for addition to the consortium database. We also anticipate utilizing the statistical support for our site-specific tests.

TIMELINE

Year 01: October-December, 2003: training, hiring, translation of materials; January-September, 2004 Data collection. We anticipate testing approximately 75-100 children each year. Travel to Moscow, Attend consortium meeting at RSA annual meeting.

Year 02-04 (October-September): Continue testing children at a rate of approximately 75-100 children/year. Travel to Moscow, attend consortium meetings at RSA annual meetings.

Year 05: October, 2007-June, 2008 Continue testing children to reach final sample sizes; July-September, 2008 collect any remaining data, confirm diagnoses of all children. Travel to Moscow, attend consortium meeting at RSA annual meeting.

e. Human Subjects Research

Protection of Human Subjects

1. RISKS TO SUBJECTS

A. Human Subjects Involvement and Characteristics: Participants for this proposed study are children with FASD and non-exposed controls. Children will range in age from 7-18 years of age and approximately 100-125 children in each group (FAS, FASD and controls) will be

assessed. Groups will be similar in terms of age, sex, ethnicity and race, and SES. Other than having prenatal alcohol exposure, all participants will be healthy. In addition to age, the other inclusion criterion is that English or Russian is the primary language spoken (depending on site). The exclusion criteria are as follows: significant head injury with loss of consciousness more than 30 minutes, significant physical (e.g., uncorrected visual impairment or hemiparesis) or psychiatric disability (e.g., psychosis) that would preclude participation, and other known causes of mental deficiency (e.g., congenital hypothyroidism, neurofibromatosis, chromosomal abnormalities). In addition, children will be excluded from the control group if prenatal alcohol exposure is known or suspected, or information is unavailable. Children are the main focus of this research project because fetal alcohol syndrome is considered a developmental disorder. In addition, the fact that many of the alcohol-exposed children will have IQ scores below the average range may qualify them as a special class of subject. Intellectual disability is common in the majority of children with FAS and heavy prenatal alcohol exposure, thus their inclusion is necessary.

B. Source of Materials: Data collected for the proposed studies will be in the form of test results, questionnaires, and interviews. All data will be obtained specifically for research purposes. The only existing records that may be used are medical records, obtained by permission, to document prenatal alcohol exposure, other medical conditions, or medication usage.

C. Potential Risks: There are no potential physical, social, economic, or legal risks to the subjects and only minimal psychological risks. It is possible that the subjects will experience frustration because of poor performance on the neuropsychological tests. This risk will be managed by utilizing reasonable criteria for discontinuation for all tasks. On those tasks that are administered via computer, there is a small risk of eyestrain or headache from staring at the computer screen. This risk will be managed by limiting the amount of time on any one task wherever possible. In addition, the child's comfort level will be monitored throughout the testing, and testing will be discontinued if necessary.

2. ADEQUACY OF PROTECTION AGAINST RISKS

A. Recruitment and Informed Consent: Children with heavy prenatal alcohol exposure, ranging in age from 7-18 years, will be recruited for this research. Many of these children are current participants in research studies at the Center for Behavioral Teratology (CBT) at San Diego State University. The CBT is currently following over 100 children with heavy prenatal alcohol exposure and enrollment will continue during the course of this study (9/29/03-9/28/08). The majority of these children (58.3%) are referrals from Dr. Kenneth Lyons Jones. The remaining referrals come from other professionals in the community (23.3%) and other forms of publicity including the Internet (18.4%). Both the PI and Dr. Jones routinely provide in-service training throughout the San Diego community, including agencies that target underserved populations. The control children are recruited from the community by word of mouth and by advertising (e.g., flyers, advertising in parent magazines). The CBT has enrolled nearly 100 children who meet criteria for the control group and enrollment will continue during the duration of this study. In Moscow, the sample will be recruited from orphanages and boarding schools, through the Institute of Psychiatry. We have been conducting a pilot study and are already aware of over 200 children with FAS and nearly 70 with FASD. Teams of pediatricians trained by Dr. Jones and Dr. Luther Robinson evaluate all children.

Informed consent will be obtained from parents or legal guardians of all participants. Following IRB approval, the PI or CBT personnel will review an informed consent document with each parent and any questions will be answered. Informed consent will also be obtained from participants who are 18 years of age, or their legal guardian. The informed consent document

will include a description of the study and any potential risks (as described above) or benefits. In addition, assent will be obtained from children, age 7-17 years by the psychometrist or research assistant.

B. Protection Against Risk: The minimal psychological risk of frustration will be managed by utilizing reasonable criteria for discontinuation for all tasks. The risk of eyestrain will be managed by limiting the amount of time on any one task wherever possible. In addition, the child's comfort level will be monitored throughout the testing, and testing will be discontinued if necessary.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

The minimal risks involved in this study are outweighed by the greater potential for benefit to this population of children. Although the participants themselves may not directly benefit from the testing, the knowledge that will be gained may be utilized in assisting other children who are similar to them. Upon request, and if possible given the nature of the testing, a summary of test results will be provided to the parent/guardian. In addition, upon request, and only with written permission of the legal guardian, test results will be provided to health care providers or teachers in order to improve care of the child.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

The knowledge to be gained from the proposed research centers on improving our understanding of the effects of heavy prenatal alcohol exposure on brain function in children. Although the individual participant may not benefit directly, the knowledge gained from this research may help to identify a profile of strengths and weaknesses in children with heavy prenatal alcohol exposure, and subsequently improve treatments available for this population. Thus the importance of the research far outweighs the minimal risk it involves.

Inclusion of Women

Participants in the proposed series of studies will be both male and females. Currently, of the participants included in the San Diego study, 50% are female. In the Moscow sample, approximately 40% are female.

Inclusion of Minorities

No racial or ethnic group will be excluded form the sample. In our San Diego sample, approximately 38% are minorities. In Moscow, the sample is exclusively Caucasian. Specific details of minority enrollment for the originally funded study are found on the Inclusion Enrollment Report (page 46).

Inclusion of Children

All participants in the proposed series of studies will be children between the ages of 7-18 years. Thus, 100% of participants will be children.

Data and Safety Monitoring Plan

Not applicable

f. Vertebrate Animals: Not applicable

g. Literature Cited

1. Stratton, K., C. Howe, and F. Battaglia, *Fetal alcohol syndrome: Diagnosis, epidemiology, prevention, and treatment*, ed. Institute of Medicine. 1996, Washington, DC: National Academy Press. 213 pp.

2. Sampson, P.D., et al., *Incidence of fetal alcohol syndrome and prevalence of alcohol-related neurodevelopmental disorder.* Teratology, 1997. **56**(5): p. 317-326.
3. Mattson, S.N. and E.P. Riley, *A review of the neurobehavioral deficits in children with fetal alcohol syndrome or prenatal exposure to alcohol.* Alcoholism: Clinical and Experimental Research, 1998. **22**(2): p. 279-294.
4. Streissguth, A.P., et al., *Final Report: Understanding the occurrence of secondary disabilities in clients with fetal alcohol syndrome (FAS) and fetal alcohol effects (FAE)*. 1996, Seattle, WA: University of Washington Publication Services. 71 pp.
5. Miller, G.A. and J.P. Chapman, *Misunderstanding analysis of covariance.* Journal of Abnormal Psychology, 2001. **110**(1): p. 40-48.
6. Adams, K.M., G.G. Brown, and I. Grant, *Analysis of covariance as a remedy for demographic mismatch of research subject groups: Some sobering simulations.* Journal of Clinical and Experimental Neuropsychology, 1985. **7**(4): p. 445-462.
7. Connor, P.D., et al., *Individual differences in auditory and visual attention among fetal alcohol-affected adults.* Alcoholism: Clinical and Experimental Research, 1999. **23**(8): p. 1395-1402.
8. Coles, C.D., et al., *Auditory and visual sustained attention in adolescents prenatally exposed to alcohol.* Alcoholism: Clinical and Experimental Research, 2002. **26**(2): p. 263-271.
9. Mattson, S.N. and E.P. Riley, *Parent ratings of behavior in children with heavy prenatal alcohol exposure and IQ-matched controls.* Alcoholism: Clinical and Experimental Research, 2000. **24**(2): p. 226-231.
10. Barnes, M.A. and M. Dennis, *Discourse after early-onset hydrocephalus: core deficits in children of average intelligence.* Brain and Language, 1998. **61**(3): p. 309-334.
11. Mattson, S.N., et al., *Executive functioning in children with heavy prenatal alcohol exposure.* Alcoholism: Clinical and Experimental Research, 1999. **23**(11): p. 1808-1815.
12. Schonfeld, A.M., et al., *Verbal and nonverbal fluency in children with heavy prenatal alcohol exposure.* Journal of Studies on Alcohol, 2001. **62**(2): p. 239-246.
13. Mattson, S.N., et al., *Heavy prenatal alcohol exposure with or without physical features of fetal alcohol syndrome leads to IQ deficits.* Journal of Pediatrics, 1997. **131**(5): p. 718-721.
14. Mattson, S.N., et al., *Neuropsychological comparison of alcohol-exposed children with or without physical features of fetal alcohol syndrome.* Neuropsychology, 1998. **12**(1): p. 146-153.
15. Mattson, S.N., et al., *Verbal learning and memory in children with fetal alcohol syndrome.* Alcoholism: Clinical and Experimental Research, 1996. **20**(5): p. 810-816.
16. Mattson, S.N. and E.P. Riley, *Implicit and explicit memory functioning in children with heavy prenatal alcohol exposure.* Journal of the International Neuropsychological Society, 1999. **5**(5): p. 462-471.
17. Mattson, S.N. and T.M. Roebuck, *Acquisition and retention of verbal and nonverbal information in children with heavy prenatal alcohol exposure.* Alcoholism: Clinical and Experimental Research, 2002. **26**(6): p. 875-882.
18. Flury, L., et al., *Neuropsychological phenotypes for identifying children with fetal alcohol syndrome. Presented at the International Genetics of Epidemiology Society meeting, New Orleans. November 15-16, 2002.* Genetic Epidemiology, 2003. **23**: p. 281.
19. Mattson, S.N., T.M. Roebuck, and E.P. Riley, *Wisconsin card sorting performance in children prenatally exposed to alcohol.* Alcoholism: Clinical and Experimental Research, 1996. **20**(2 (Suppl.)): p. 74A.
20. Connor, P.D., et al., *Direct and indirect effects of prenatal alcohol damage on executive function.* Developmental Neuropsychology, 2000. **18**(3): p. 331-354.

21. Mattson, S.N. and K.E. Calarco, *"What" and "Where" visuospatial processing in children with heavy prenatal alcohol exposure.* Journal of the International Neuropsychological Society, 2002. **8**(4): p. 513.
22. Lee, K.T., S.N. Mattson, and E.P. Riley, *Classifying children with heavy prenatal alcohol exposure with attention measures.* Journal of the International Neuropsychological Society, 2003. **9**(2).
23. Calarco, K.E., et al., *Heavy prenatal alcohol exposure or ADHD? Errors make the difference.* Journal of the International Neuropsychological Society, 2003. **9**(2).
24. Mattson, S.N., A.R. Lang, and K.E. Calarco, *Attentional focus and attentional shift in children with heavy prenatal alcohol exposure.* Journal of the International Neuropsychological Society, 2002. **8**(2): p. 295.
25. Thomas, S.E., et al., *Comparison of social abilities of children with fetal alcohol syndrome to those of children with similar IQ scores and normal controls.* Alcoholism: Clinical and Experimental Research, 1998. **22**(2): p. 528-533.
26. Roebuck, T.M., S.N. Mattson, and E.P. Riley, *Interhemispheric transfer in children with heavy prenatal alcohol exposure.* Alcoholism: Clinical and Experimental Research, 2002. **26**(12): p. 1863-1871.
27. Mattson, S.N., et al., *Fetal alcohol syndrome: A case report of neuropsychological, MRI and EEG assessment of two children.* Alcoholism: Clinical and Experimental Research, 1992. **16**(5): p. 1001-1003.
28. Riley, E.P., et al., *Abnormalities of the corpus callosum in children prenatally exposed to alcohol.* Alcoholism: Clinical and Experimental Research, 1995. **19**(5): p. 1198-1202.
29. Sowell, E.R., et al., *Mapping callosal morphology and cognitive correlates: Effects of heavy prenatal alcohol exposure.* Neurology, 2001. **57**(2): p. 235-244.
30. Mattson, S.N., et al., *A decrease in the size of the basal ganglia following prenatal alcohol exposure: A preliminary report.* Neurotoxicology and Teratology, 1994. **16**(3): p. 283-289.
31. Mattson, S.N., et al., *A decrease in the size of the basal ganglia in children with fetal alcohol syndrome.* Alcoholism: Clinical and Experimental Research, 1996. **20**(6): p. 1088-1093.
32. Archibald, S.L., et al., *Brain dysmorphology in individuals with severe prenatal alcohol exposure.* Developmental Medicine and Child Neurology, 2001. **43**(3): p. 148-154.
33. Sowell, E.R., et al., *Voxel-based morphometric analyses of the brain in children and adolescents prenatally exposed to alcohol.* NeuroReport, 2001. **12**(3): p. 515-523.
34. Astley, S.J. and S.K. Clarren, *A case definition and photographic screening tool for the facial phenotype of fetal alcohol syndrone.* Journal of Pediatrics, 1996. **129**(1): p. 33-41.
35. Leark, R.A., et al., *T.O.V.A. Test of Variables of Attention: Professional Guide*. 1999, Los Alamitos: Universal Attention Disorders, Inc. 105.
36. Kodituwakku, P.W., et al., *Specific impairments in self-regulation in children exposed to alcohol prenatally.* Alcoholism: Clinical and Experimental Research, 1995. **19**(6): p. 1558-1564.
37. Robbins, T.W., et al., *Cambridge Neuropsychological Test Automated Battery (CANTAB): A factor analytic study of a large sample of normal elderly volunteers.* Dementia, 1994. **5**(5): p. 266-281.
38. Robbins, T.W., et al., *A study of performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: Implications for theories of executive functioning and cognitive aging.* Journal of the International Neuropsychological Society, 1998. **4**(5): p. 474-490.

39. Lezak, M.D., *Neuropsychological Assessment*. 3rd ed. 1995, New York: Oxford University Press. 1026.
40. Beery, K.E., *Manual for the Developmental Test of Visual-Motor Integration*. 1989, Cleveland: Modern Curriculum Press. 112.
41. Sparrow, S.S., D.A. Bella, and D.V. Cicchetti, *A Manual for the Vineland*. 1984, Circle Pines, MN: American Guidance Services.
42. Achenbach, T.M., *Integrative Guide for the 1991 CBCL/4-18, YSR, and TRF Profiles*. 1991, Burlington, VT: University of Vermont Department of Psychiatry. 211.
43. Achenbach, T.M., *Manual for the Teacher's Report Form and 1991 Profile*. 1991, Burlington: University of Vermont.
44. Achenbach, T.M., *Manual for the Child Behavior Checklist/4-18 and 1991 Profile*. 1991, Burlington, VT: University of Vermont Department of Psychiatry. 288.
45. Pelham, W.E., Jr., et al., *Teacher ratings of DSM-III-R symptoms for the disruptive behavior disorders.* Journal of the American Academy of Child and Adolescent Psychiatry, 1992. **31**(2): p. 210-218.
46. Galin, D., R. Diamond, and J. Herron, *Development of crossed and uncrossed tactile localization on the fingers.* Brain and Language, 1977. **4**(4): p. 588-590.
47. Spreen, O. and E. Strauss, eds. *A compendium of neuropsychological tests: Administration, norms, and commentary (2nd ed.)*. 2nd ed. 1998, Oxford University Press, New York, NY, USA. xvi, 736.
48. Oldfield, R.C., *The assessment and analysis of handedness: The Edinburgh Inventory.* Neuropsychologia, 1971. **9**(1): p. 97-113.
49. Reitan, R.M. and D. Wolfson, *Neuropsychological Evaluation of older Children*. 1992, South Tucson, Arizona: Neuropsychology Press. 894.
50. Steese-Seda, D., W.S. Brown, and C. Caetano, *Development of visuomotor coordination in school-age children: The Bimanual Coordination Test.* Developmental Neuropsychology, 1995. **11**(2): p. 181-199.
51. Moore, E.S., et al., *New perspectives on the face in fetal alcohol syndrome: what anthropometry tells us.* American Journal of Medical Genetics, 2002. **109**(4): p. 249-260.

h. Consortium/Contractual Arrangements N/A

i. Consultants N/A

APPENDIX MATERIALS

APPENDIX 1: Detailed descriptions of the tests from the Neurobehavioral Core (see page 35)

APPENDIX 2: Published Articles

APPENDIX 1: Detailed descriptions of the tests from the Neurobehavioral Core (see page 35)

Leiter International Performance Scale-Revised

This measure (Stoelting, 2001) can be used with individuals ages 2-20 years. It provides an assessment of global ability through its Visualization and Reasoning (VR) Domain battery. In the recent revision, an Attention and Memory Battery (AM) was added as well. The complete battery ranges from 10 to 20 subtests, depending on age. The VR Battery requires about 40 minutes to administer and the AM Battery, about 35 minutes.

There is a screening IQ assessment that can be administered in 25 minutes. The Leiter-R is correlated with other frequently used measures of ability, including the WISC-III (.85). It also includes "growth" scores that can be used to assess progress in children with developmental disability and to chart relatively small differences in cognitive performance over time or between groups.

The Leiter-R has several characteristics that make it appropriate for this collaborative cross-cultural study. It is completely nonverbal and does not require a spoken word from either examiner or child. The child is not required to read or write any material. For this reason, the same form can be used in different countries and in different cultural groups. In fact, the Leiter-R is widely used in Europe. Although the manual has been translated into other languages, translation to Russian will be required. The norms are based on a United States population but included Native American, Hispanic, Asian-American and Hispanic groups as well as Caucasian. The test manual notes that Leiter-R standard scores in these groups were less disparate from those of the majority culture than were scores on the WISC-III.

TOVA (Test of Variables of Attention)

The TOVA is a computerized continuous performance test that assesses processing abilities in both the visual and auditory modalities [34]. For the visual task, the stimuli are colored squares with smaller black embedded squares either at the top of the colored square (target) or the bottom (distracter). The auditory TOVA task presents the subject with either a target tone ("Middle G") or a non-target tone ("Middle C") through external computer speakers. For both conditions, stimulus length is 100msec and inter-trial interval is 2sec. The goal of each task is to correctly respond to each target by pressing a button as quickly as possible. During the first half of the test (stimulus-infrequent condition), the target is presented 22.5% of the time. During the second half of the test (stimulus-frequent condition), the target is presented 77.5% of the time. The function of the different conditions serves to examine the effects of differing demands on attention and inhibition. Each condition involves a practice session and time required is about 25 minutes per condition. Four variables are produced: (1) errors of omission (missed targets) which measures inattention, (2) errors of commission (non-target response) which measures impulsivity or disinhibition, (3) response time which measures processing time for a correct response to the target, and (4) variability which measures inconsistency in response times. The software automatically records the subject's responses and calculates standard scores and *z*-scores for each variable, based on normative data.

Progressive Planning Test (Kodituwakku, 1993)

The Progressive Planning Test is an experimental measure of planning and problem solving and is thus, sensitive to deficits in executive function [36]. Participants are required to move 3 to 5 colored beads that are arranged in a specific order in an initial position on one of three stakes to create a series of prespecified new arrangements on another stake (goal positions). The moves are subject to two rules: (1) only one bead can be moved at a time, and (2) once removed from its initial position, a bead must not be returned to that position. These rules constrain the path to the goal, increasing the working memory load in some problems. Psychometric properties of the test are desirable (split-half

reliability= .84). Unpublished developmental norms are available for ages 5-8. Administration time is approximately 15 min.

Road-Map Test of Direction Sense (Money, 1976)

In this test, the examiner traces a dotted pathway with 32 turns and the subject is required to tell the direction (left or right) taken at each turn. Some of the turns on the test are un-rotated (in the direction the subject is facing) and the other turns are rotated. Developmental norms are available for ages 5 through 18 [39]. Administration time is approximately 5 min.

Cambridge Neuropsychological Test Automated Battery

The Cambridge Neuropsychological Test Automated Battery (CANTAB) was selected as an instrument to assess visual attention due to its ability to reliably assess cognitive functioning and underlying neurological mechanisms. The subtests of the CANTAB were designed to assess frontostriatal circuitry involved in tasks involving executive functions such as planning, set-shifting and spatial memory. The CANTAB was originally developed to assess cognitive function in elderly and demented patients, however, a number of studies have since demonstrated its applicability to children's cognitive functioning in normal [46] and clinical populations [47-50]. The required equipment and the selected subtests are described below. Administration time is approximately 45 min.

Equipment

The CANTAB utilizes touch screen technology to record responses, which allows testing with limited verbal requirements and provides accurate measurement of reaction time (RT). Testing will be conducted on an Advantech PPC 120 computer with a 12-inch touch-sensitive screen. As suggested in the CANTAB administration manual, all participants will be seated 60 cm away from the screen to discourage resting a hand on the computer and will be administered the same subtests in the same order. CANTAB testing takes 30-45 minutes.

Subtests

Motor Screening (MOT). This test is primarily used as a screening task and is administered at the beginning of all CANTAB batteries to ensure that the subject can identify and touch the targets presented on the screen. In this task, crosses are displayed on the screen and the subject is directed to touch the cross with the forefinger of the dominant hand. This test provides a baseline measure of response latency (msec) that can be used to compare with same-subject performance on subsequent CANTAB tests.

Big-Little Circle (BLC). This test is designed to assess the subject's ability to follow an explicit rule, and then reverse the rule. In this task, the subject is presented with two boxes on the screen: one containing a big circle and the other containing a little circle. The subject is instructed to touch the little circle. After 20 pairs, the rule is changed, and the subject is instructed to touch the big circle. Dependent variables are the percent correct and mean latency (msec) for correct and incorrect responses.

Pattern Recognition Memory (PRM). This is a test of visual, or *what* memory, and involves the ability to discriminate between a previously displayed pattern and one that has not been displayed. In this task 12 different patterns appear in a box on the screen, followed by two boxes, one that displays a pattern from the earlier phase while the other box displays a novel pattern. The participant is instructed to touch the box containing the pattern that was previously seen. There are two sets of 12 trials (24 total trials). Dependent measures are accuracy (% correct patterns selected) and mean RT for correct and incorrect responses.

Spatial Recognition Memory (SRM). This is a test of spatial, or *where* memory, and taps parietal function. In the learning stage of this task, five squares (targets) are presented one at a time in different locations on the computer screen. During the choice stage, one target is presented along with a distracter in a novel location. The participant is asked to indicate the target location by touching that square. This repeats for the remaining four boxes in the stimulus set. There are four trials of 5 boxes. Dependent measures are accuracy (% correct locations selected) and mean RT for correct and incorrect responses.

Delayed Matching to Sample (DMS). This test assesses the ability to remember a stimulus and then match it to the same stimulus among distracters. Thus, it involves a type of *what* visuospatial processing and taps temporal lobe function. The target is a complex visual stimulus that varies in color and shape. The target stimulus is presented briefly, followed by four choices, one of which is the correct response. The three distracters vary along the dimensions of color and shape. There is a variable delay between target and response choices of either 0, 4, or 12 seconds. In addition, there are “simultaneous” trials in which the target and the response choices appear concurrently. There are three practice trials followed by 40 test trials (10 each of the simultaneous, 0, 4, and 12 second conditions). The dependent measure is the percent correct for each condition.

Paired Associates Learning (PAL). This test comprises eight trials in which the subject is required to remember both *what* the target pattern was and *where* it was presented in a series of squares on the screen. First, the patterns are revealed one at a time to the participant during the learning phase; during the test phase the participant is shown the same patterns and asked to touch the appropriate squares. If the participant responds correctly, a new learning phase begins. If the response is incorrect, then the previous learning phase repeats until the correct response is made. There are two trials of one, two, and three patterns, then one trial each of six and eight patterns. If a participant does not meet criteria for moving to the next trial after ten presentations, the test is automatically terminated. Two dependent measures will be used from this task: the number of trials completed and the number of errors.

Spatial Span (SSP). This task is a measure of visual memory, similar to the Corsi block test, requiring the subject to remember the sequence in which squares on the screen change color. Thus it represents a measure of visual *where* memory, and taps parietal function. Trials begin with two squares changing color, one at a time and the participant is instructed to touch the same squares in the same order. There are three trials at each span length and span lengths increase by one until all three trials at a given length are failed or until the maximum span of nine is reached. There are two dependent measures: spatial span (maximum sequence correctly remembered), and an error score indicating the mean number of incorrect boxes selected per trial.

Intra-Extra Dimensional Shift (IED). This subtest is a measure of the subject’s ability to attend to a specific perceptual feature of a stimulus, and then shift attention to the previously irrelevant dimension. Utilizing feedback from the computer, subjects are required to determine which of two dimensions (e.g., shape or a line) is relevant, and maintain that focus with different examples (intra-dimensional shift). After six successive correct responses are made, the relevant stimulus changes, requiring the subject to shift attention to the previously irrelevant dimension (extra-dimensional shift). Dependent variables are stage achieved (out of 9 possible stages), trials to criterion, and mean latency (msec) for each stage.

Stockings of Cambridge (SOC). This is a test of spatial planning, similar to the Tower of London test. In this task the subject sees two displays of three stacked colored balls. The object is to make the balls in the lower display match those of the upper display. Balls are moved one at a time by touching and dragging to a new location. This task begins simply (1 move) and increases in complexity up to 5 moves. Time to completion and number of moves required are recorded. This task also includes a

control for motor performance. The upper display moves balls one at a time and the subject follows the pattern on the lower display. This allows for a comparison between the amount of time expended on motor activation (motor control task) and that required for planning (test task).

Vineland Adaptive Behavior Scales – Revised

The Vineland Adaptive Behavior Scales – Revised (VABS-R) measures adaptive behavior in 3 domains: Communication, Socialization, and Daily Living [41]. The VABS-R assesses the child's independent functioning in their environment through a non-directive parent interview. Three variables representing each domain score and the composite score will be analyzed. This interview takes approximately 30-60 minutes.

Achenbach Scales

There are three Achenbach scales that make up a comprehensive evaluation of childhood behavioral functioning, the Child Behavior Checklist completed by the parent or caregiver, the Teacher Report Form completed by the teacher, and the Youth Self Report, completed by the child (ages 11-18).

Child Behavior Checklist. The Child Behavior Checklist (CBCL) is a 113-item questionnaire that measures a child's competence and problem areas as perceived by the parent or caregiver [44]. There are three responses (not true, somewhat or sometimes true, very true or often true) and eight syndrome scales (Withdrawn, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior, and Aggressive Behavior). In addition, for children age 6 and older, three competence scales measure the child's perceived competence in activities, social, and school settings. The eight syndrome scales are summarized in three scales: Internalizing (Withdrawn, Somatic Complaints, and Anxious/Depressed), Externalizing (Aggressive Behavior, Delinquent Behavior), and Total problem scales. The dependent measures are the Summary scales (Internalizing, Externalizing, Total) and the eight problem scales.

Teacher Report Form. The Child Behavior Checklist-Teacher Report Form (CBCL-TRF) is a companion measure to the CBCL and is completed by the child's teacher [43]. The same scales as the parent version are obtained. The dependent measures are the same as for the CBCL.

Youth Self Report. The Youth Self Report (YSR) is the child version of the CBCL and is completed by children aged 11-18 years. It requires a 5th grade reading level or can be administered orally. It has competence and problem scales parallel to the CBCL and uses the same 3-point scale as the other versions. The dependent measures are similar to the other forms and include two competence scales (Activities and Social), eight problem scales, and three summary (Internalizing, Externalizing, and Total) scores.

The Parent/Teacher Disruptive Behavior Rating Scale

The Parent/Teacher Disruptive Behavior Rating Scale [45] is a parent/teacher-rated questionnaire that consists of 45 items, which are scored on a 4-point scale (Not at all, Just a little, Pretty much, and Very much). Pretty much and Very much responses to problem behaviors provide the requisite information for making DSM-IV diagnoses of attention deficit hyperactivity disorder, conduct disorder, or oppositional defiant disorder. The test can be scored either by counting endorsed symptoms for each disorder or by comparing the target child's factor scores.

Beery Developmental Test of Visual Motor Integration (4th edition)

The Beery Developmental Test of Visual Motor Integration (VMI) assesses visual-motor integration by requiring the child to copy 24 geometric figures [40]. This test is constructed to measure the level of visual-motor development from the age of three. Each design is harder than the last and testing is continued until three consecutive figures are failed. There are two supplemental tests: the VMI Visual Perception and the VMI Motor Coordination tests. These tests use the same stimulus forms and thus

are comparable to the main test. Normative data are available for all ages and administration time is approximately 10 minutes.