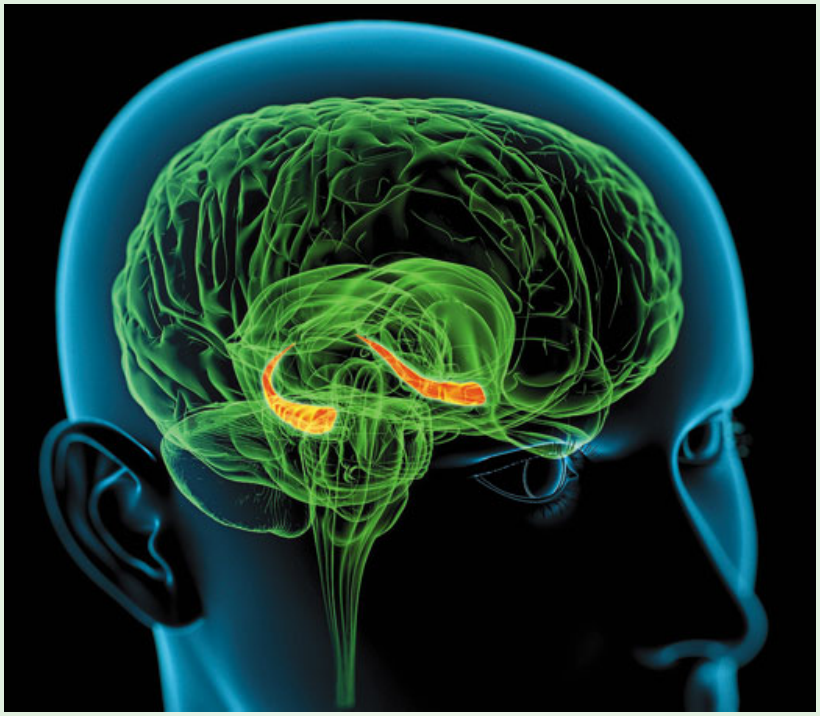
JOINT BLOOD TRIBE, LAKELAND, AND LETHBRIDGE FASD PROJECT



Final Report submitted to the Alberta Centre for Children, Family, and Community Research

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Key features of the Joint Blood Tribe, Lakeland, and Lethbridge Project on Effective FASD Prevention.

The Canadian Centre of Behavioural Neuroscience of the University of Lethbridge in partnership with the Blood Tribe Department Health Inc., the First Steps for Healthy Babies Program, Chinook Health Region First Steps and Lakeland Centre for FASD agreed to work together in an interdisciplinary research project on Fetal Alcohol Spectrum Disorder.

1. OBJECTIVES

The research project had two primary objectives and various secondary objectives. The primary objectives were:

1. To establish the level of effectiveness over a one-year interval of an interventionist prevention model for Fetal Alcohol Spectrum Disorders (FASD), involving high-risk women recently implemented in two communities, the Blood Reserve and the City of Lethbridge, interacting with the two First Steps for Healthy Babies programmes in those communities.

2. To establish the level of functional deficits in the areas of psychological and neuropsychological functioning in high-risk women that may be a consequence of FASD and contribute to lack of effectiveness of traditional education and service interventions.

ADDITIONAL BENEFITS

In addition to the primary research outcomes, the program should provide five benefits:

1. Both projects would entail further developing relationships and partnerships among colleagues of the Blood Tribe, in Lethbridge service agencies, Lakeland Centre for FASD, and the social science and health science researchers at the University.

2. A legacy effect—the research would lay the foundation for more complete longitudinal studies of benefits of prevention programmes, exposing service providers to research activities and practices and exposing several more basic researchers to the practicalities and circumstances of research in this kind of service context.

3. We will provide training to First Nations research assistants enabling development of research competence to implement their own research projects.

4. If we find clear evidence that the programmes are effective primary prevention of FASD, that is if we can demonstrate a decrease in number or probability of FASD births caused by participation in the programmes then there are strong implications for policy decisions. For example, it will be possible to calculate an approximate cost-benefit analysis, factoring in the anticipated number of FASD births prevented, the life-time extra costs of providing services to an FASD individual, and the costs of the prevention programmes per prevented FASD birth. A demonstration of effectiveness in reducing FASD incidence

should positively influence policy decisions across Alberta and, more generally, Canada.

5. There is a significant service component to this project. Three advocates/mentors will be added, with additional training opportunities: one to each of the primary prevention programmes in Standoff, Lethbridge, and Lakeland.

2. INITIATION PROCESS

STEP 1: The project originated through a consultation meeting on Fetal Alcohol Spectrum Disorder among representatives of community groups, social service agencies, criminal justice, the Canadian Centre for Behavioural Neuroscience, the Blood Tribe Department of Health, and the Chinook Health Region. All of these individuals were drawn from the southern Alberta region and had an interest in FASD. There was strong interest expressed by the Blood Tribe representatives and the Families First, First Steps Program of the Chinook Health Region in collaborating on a project involving prevention. A request was made from each interested party to identify ways that a research project could enhance the efficacy of their activities. From the list received, a set of objectives was created and circulated to representatives of the groups for feedback.

STEP 2: As a result of that consultation process a draft research proposal was developed and sent to the Ministry of Childrens' Services for input. We were advised to expand the scope of the work to include a collaborative interaction with Lakeland Centre for FASD.

STEP 3: Incorporating input from the Ministry of Children's Services, a draft research proposal was submitted to the Alberta Centre for Child, Family, and Community Research. Advice and recommendations were received from the Scientific Director, prior to a positive funding decision being made.

REFLECTIONS ON THE INITIATION PROCESS

The community consultation process was extremely useful in bringing together diverse interest groups with a focus on FASD. This event and

subsequent efforts to establish the joint project, not only directed the selection of project objectives, but welded together a working relationship between the Blood Tribe Dept of Health and CCBN and strengthened ties between workers at the Blood Tribe Dept of Health and the First Steps program in the Chinook Health Region.

An unusually diverse set of goals was identified through the first three steps. In particular there was a strong push to make progress on an extraordinarily wide range of fronts, to enhance service delivery, train service providers in research methods, conduct neuropsychological experiments, provide neuropsychological assessments, create a set of measures of FASD prevention success, create and deliver customized software for tracking characteristics of FASD prevention clients, and to hire and train mentors/research assistants for 3 project performance sites. The divergence in aims was a continuing challenge.

A second challenge arose in respect to pressure to maintain 3 performance sites. This came not only from political interests but from the partners on the ground as well. From the perspective of key research deliverables it would have been far better to focus on a single performance site (Lethbridge First Steps) and offer indirect assistance to the Blood Tribe's nascent efforts around FASD prevention. Perhaps a meeting involving the key stakeholders, including the Ministry, in the project together with a representative of the ACCFCR prior to a funding decision could have identified a smaller, realistic set of objectives and sites.

A third challenge was based upon the nature of the principal investigator's training and background skills. He is first and foremost a

biomedical researcher with little training or experience in community research or social service activities. As a result, more time should have been taken at the outset to identify key project collaborators with strengths in the areas of his relative weakness. A trio of co-investigators could have been more effective in such a wide-ranging project.

3. IMPLEMENTATION

3.1 SERVICE/PREVENTION PROGRAMME

A survey tool was created that contained a large number of items collected by mentors/research assistants in the Lethbridge First Steps (primarily), Blood Tribe, and Lakeland FASD Prevention programmes the measures included a wide range of information about children, family status, criminal-justice interactions, length of time in programme, contraceptive use, social network, addictive behaviour, specific health concerns, diet, and others (see APPENDIX A and B). The data were entered into a database implemented in Microsoft's ACCESS program. A mentor/research assistant was hired at the Blood Tribe and at the Lakeland program for this period of one year. In addition a database software expert was hired to prepare the instrument and a database coordinator was hired to train mentors/research assistants at each performance site.

All of the raw data have been provided to ACCFCR and data analyses are still on-going. In particular, the Lethbridge performance site retains the database and they continue to add information to it that will serve for evaluation in the future. One feature of the data is that no FASD children were born to any of the at-risk women in the program.

3.1.1 Database

Currently there are 19 sections within the FASD assessment/survey (Appendix A & B) from general background to addiction information gathered. The ASI assessment has key indicators predictive of risk of producing an FASD child. The FASD assessment/survey has greatly been modified from the ASI version to accommodate other assessments with clear overlap. In total the FASD assessment has 140 pages and takes 4

hours to conduct. These items were selected based upon discussions with members of the Advisory Board and a review of the published, peer-reviewed literature on prevention programme assessments. Care was taken to adopt items that had been validly used with Central North American Native groups.

1. Addiction Severity Index (ASI)
2. Addiction Severity Index (ASI) North Dakota/Native American Version (ND/NAV)
3. Family APGAR
4. Center for Epidemological Studies (CES-D) Major Depressive Disorder Scale
5. CEBU Longitudinal Health and Nutrition Study

By mid-2005 we had prepared and had received approval for our Partnership Agreements with the Blood Tribe Dept of Health Inc, Lakeland Centre, and Chinook Health Region (Appendix C) and our Consent Forms. This enabled us to obtain ethics approval from the Human Subjects Research Committee of the University of Lethbridge.

Special mention should be made about the interaction between our project and the Blood Tribe Department of Health Inc. At the initiation of the collaborative arrangement we encountered several challenges, all of which led to solid resolutions. Questions such as: Who owns the data? Or Why are you doing this? created very significant negotiation sessions. Our final agreement was signed by the Chief Executive Officer of the Blood Tribe Dept of Health Inc, the organization that created the FASD programme on the Blood Reserve. We note the following concerning the Blood Tribe Dept of Health Inc.:

Original leadership & representation:

1. Chief Executive Officer – Charlie Weasel Head

2. CORE Committee – members-at-large
3. Project Coordinator - Rebecca Many Grey Horses

Leadership & Representation #2:

1. Acting Chief Executive Officer – Clark Bruised Head
2. CORE Committee – members-at-large
3. Director of Kainai Wellness Center – Sandi Many Chief
4. Project Coordinator – Wendy Mistaken Chief

Leadership & Representation #3:

1. Acting Chief Executive Officer – Lillian Crop Ear Wolf
2. Finance – Clark Bruised Head
3. Director of Kainai Wellness Center – Sandi Many Chief
4. Acting Coordinator – Vanessa Buckskin

Leadership & Representation #4:

1. Chief Executive Officer – Chris Shade (November 2006)
2. Director of Kainai Wellness Center – Sandi Many Chief
3. Coordinator – Vanessa Buckskin
4. Representative – Dr. Esther Tail Feathers

During the relatively short life of the affiliation of this project with the Blood Tribe we interacted with 4 different leadership boards. Our principal advocate on the ground there, Project Coordinator, left to join Lethbridge First Steps within one month of our starting. Our research coordinator, Ruth Provost is a Blood Tribe member and was primarily responsible for the continuing affiliation. Each time a new Chief Executive Officer took office, we had to restart our process. There did not appear to be continuity of institutional approval and commitment. This was our major challenge.

As a result of the continuing negotiations around this issue, we have created an organization (Kainai Medical Services, Limited Partnership) that includes Chris Shade, Dr. Esther Tailfeathers, a small number of other Blood Tribe professional and clinicians from Southern Alberta, and the Blood Tribe DoH. This is a mixed non profit/for profit group whose goal is to explicitly provide continuity in development of health services and access to data for research purposes. This group has successfully implemented a much needed pulmonary assessment laboratory with full time technician, created a weekly children's neurobehavioural assessment clinic, and has the only functioning FASD Assessment team in our region.

3.1.2 Outcomes and Deliverables

1. Hired and trained 3 prevention programme mentors/researchers in data collection;
2. Created database of items related to FASD prevention that is still in use at the Lethbridge FASD Prevention programme and will be subjected to analyses this summer. Data on approximately 70 women is complete;
3. Provided computerized CANTAB Neuropsychological Test Battery to Lakeland Centre and Blood Tribe Dept of Health.
4. Provided training in data collection and database use to all members of the Lethbridge First Steps team.
5. Provided neuropsychological assessments for 31 clients of Lethbridge First Steps. Many of these assisted clients in accessing social services.
6. Provided MRI scans for all Neuro component participants.

7. One legacy is the continuing relationship between CCBN and the Blood Tribe, especially around child assessment and FASD. One example is the children's clinic, but we have also facilitated the approval in principle to site an externally funded Blood Tribe Centre of Health Excellence Building on the University of Lethbridge campus. A formal memorandum of agreement has been signed by both the University and the Blood Tribe Chief and Council. The PI was a key liaison in this process.
8. The research coordinator for the project went on to successfully complete a Masters degree.
9. One neuroscience PhD candidate elected to complete her dissertation using her interaction with the neuropsychological and neurophysiological aims of the project.
10. In the neuroscience arms of this project we did discover significant effects. We conducted an initial screening of visual abilities and visual evoked potentials in women from the Lethbridge First Steps programme and discovered no evidence for visual perceptual difficulties in those women with FASD (Section 7 below). Components of visual spatial information processing were deficient in women in the programme with FASD relative women in the programme without FASD. There was also a clear trend for the former group to exhibit less neural coupling between frontal cortical regions and posterior parietal regions during task performance (Section 6 below) and temporal lobe activation during spatial working memory revealed significant difference among groups (Section 8 below). In contrast, the memory performance of both groups was similar in our virtual navigation task and in our spatial

working memory task. This may reflect other conditions in our non FASD control group that disrupt these processes or our FASD group may have found compensatory strategies as they reached full maturity. Both of the in-programme groups performed significantly worse than an age-matched group composed of undergraduate women enrolled at the University of Lethbridge.

11. Publications:

1. Sorensen, PL; Zeman, PM; Sutherland, RJ (2006). Impaired patterns of synchronous cortical activity in individuals with fetal alcohol spectrum disorders during a virtual spatial navigation task. Psychophysiology, 43, suppl.1, S94.
2. Sorensen, PL; Zeman, PM; Sutherland, RJ (2006). Differing patterns of synchronous cortical activity during a virtual spatial navigation task. International Journal of Psychophysiology, 61(3), S1, 377.
3. Sorensen, PL; Prenatal ethanol effects on event-related potentials and cognition in young adults. Dissertation in preparation. Dept of Neuroscience, Univ of Lethbridge.
4. Sorensen, PL; Saucier, DM; Sutherland, RJ Patterns of cortical activation during virtual navigation are affected by prenatal alcohol exposure. Manuscript in preparation.
5. Sorensen, PL; Saucier, DM; Sutherland, RJ Patterns of cortical activation during spatial working memory are affected by prenatal alcohol exposure. Manuscript in preparation.

12. Presentations:

1. Sorensen, PL; Zeman, PM; Sutherland, RJ Impaired cortical activity in adults with prenatal alcohol exposure. Annual Meeting, Canadian Society for Brain Behaviour and Cognitive Science, Victoria 2007.
2. Sorensen, PL Impaired cortical activity in adults with prenatal alcohol exposure. Hotchkiss Brain Institute Seminar, 2007
3. Sutherland, RJ Levels of FASD prevention, FASD Teleconference for Rural Education, U of Calgary, May 2007.
4. Sutherland, RJ, Prenatal Alcohol Exposure: Interpreting basic and applied research approaches. FASD Conference, Lethbridge College, May 2007.

4. NEUROPSYCHOLOGY & NEUROPHYSIOLOGY

General Methodology

Participants

The home visitation program of the Chinook Health Region referred 13 adult right-handed females (aged 19 to 32) with fetal alcohol spectrum disorder (FASD) and 17 female controls (aged 20 to 32). The FASD control participants were matched to the FASD participants with respect to age, educational background, socioeconomic status, health, history of abuse, past and current drug usage and current alcohol usage. A worker from the home visitation program accompanied the participants to the university for the sessions. Twenty female, right-handed students (aged 18 to 28) from the University of Lethbridge also participated in this study. They received an additional 1% or 2% to their final grade in an

undergraduate psychology class as compensation. Informed consent was obtained from each subject. Approval for this study was granted by the ethics committee of the University of Lethbridge, Alberta, Canada.

The number of subjects who completed the neuropsychological testing, spatial navigation EEG task (virtual Morris Water task) and the spatial working memory EEG task varied. Thirteen of the individuals from the FASD group and 17 from the matched controls completed at least some of the neuropsychological testing. Nine individuals from the FASD group, 10 from the matched control group and 11 from the university group completed the virtual Morris water task (vMWT). Eight individuals from the FASD group, 12 from the matched control group and 6 from the university group completed the spatial working memory task. Four individuals were subsequently dropped from the study due to diagnoses received partway through the study or concerns regarding English as a second language (ESL). Other participants only completed part of the process. In some cases, the individual began testing but refused to finish the task. Others attended one or two of the sessions but would not attend the remaining session(s). One individual formally dropped out of the study while two could not be located partway through the program. Some participants' data for one of the EEG tasks was removed from the study: one individual adjusted the EEG net partway through the test session while seven other individuals did not have enough "clean" EEG segments to process. University students completed only the vMWT or the spatial working memory task, not both.

Behavioural testing

Neuropsychological Battery.

The FASD and matched control groups completed a neuropsychological evaluation given by a provincially certified psychologist at either the University of Lethbridge or at the office of Alberta Neuropsychological Services. The test battery was chosen to evaluate general intellectual functioning as well as cognitive skills that prior research has indicated are impaired by prenatal ethanol exposure: spatial skills, memory, and executive functioning. The evaluation consisted of the following tests:

Wechsler Adult Intelligence Scale (3rd Edition)- WAIS-III

Wechsler Memory Scale (3rd Edition)- WMS-III

Rey-Osterrieth Complex Figure Test

Chicago Word Fluency Test

Newcome Verbal Fluency Test

Semmes Body Placing Test

Right/Left Differentiation Test

Dichotic Listening Task

And from the CANTAB Eclipse Battery:

Motor Screening (MOT)	Screens for visual, movement and comprehension difficulties
Affective Go/No-go (AGN)	information processing biases for positive and negative stimuli
Big/Little Circle (BLC)	comprehension, learning and reversal
Delayed Matching to Sample (DMS)	immediate and delayed perceptual matching
Intra-Extra DimensionalSet Shifting (IED)	rule acquisition and attentional set shifting
Matching to Sample Visual Search (MTS)	ability to match visual samples and reaction and movement time

Paired Associates Learning (PAL)	episodic memory and learning
Pattern Recognition Memory (PRM)	recognition memory for patterns
Reaction Time (RTI)	speed of response
Rapid Visual Information Processing (RVP)	sustained visual attention
Stockings of Cambridge (SOC)	spatial planning and motor control
Spatial Recognition Memory (SRM)	recognition memory for spatial locations
Spatial Span (SSP)	working memory capacity
Spatial Working Memory (SWM)	working memory and strategy use
Verbal Recognition Memory (VRM)	immediate free recall, and immediate and delayed recognition memory

The testing was typically conducted over two sessions. Neuropsychological testing was not completed with the university control group participants due to financial costs involved.

Virtual Morris Water Task.

Stimulus.

The participants were presented with a visible platform version of the virtual Morris water task (vMWT). Briefly, the participants were required to remember the location of a platform in a computer generated, virtual pool by orienting themselves to either the color of the platform (nonspatial cue condition) or to the location of the platform relative to pictures on the walls of the virtual pool room (spatial place condition).

Participants were seated comfortably approximately 180 cm from a Dell Trinitron 40 cm CRT computer screen with a refresh rate of 75 Hz.

Before the commencement of each trial, the participants viewed a blank screen with a cross ("+") reference point centered in the screen for 2000 ms. The virtual environment consisted of a round pool situated in a square room. A different image, framed as a picture, was placed on each of the four walls. Two visible square platforms were placed in different quadrants of the pool (Figure 1). To navigate in the virtual pool, the subject pressed the left or right arrow key on a keyboard. Constant forward motion was controlled by the computer program. For each trial, the subject began in a random starting location facing the pool wall. Each block consisted of four trials during which the platform locations and distal cues on the walls remained constant. When the subject reached the incorrect platform, forward motion would continue and the subject would appear to "swim through the platform". When the subject reached the correct platform, forward motion would stop and the phrase "Platform Found" was presented on the screen. As the correct platform was found by chance in trial one, data from trial one was omitted from the analyses.

Accuracy.

The total number of correct responses (from trials two to four) for the cue and place conditions was calculated. Correct responses were defined as "swimming" to the correct platform first within 60 seconds.

Latency.

The latency from trial onset to correct platform was calculated for trials two through four of each set. The mean latency was calculated for place and cue trials separately.

Spatial Working Memory.

The spatial working memory n-back test was modified for use with individuals with fetal alcohol spectrum disorders. The n-back task, first and foremost, needed to be designed to avoid penalizing participants whose working memory was intact but processing or response times were slower. It also needed to identify memory processes uncontaminated by interference from prior trials. At a practical level, the participants need short, discrete trials to maintain attention and motivation and could be stopped at any point in the session; in addition, the trials needed to be structured to avoid non-responding by the participants. (Several participants displayed tendencies to not respond when frustrated or when they felt they couldn't answer correctly during a prior spatial task. Non-responding has also been reported as a problem with this population in other studies.)

Stimulus presentation was managed using E-prime. Five symbols were taken randomly from the keyboard ("*", "&", "#", "@" and "$"). The same symbol was used throughout each trial. Five locations on the screen were identified: the left upper corner, left lower corner, right upper corner, right lower corner and center. Trials for 1-back, 2-back and 3-back were pseudo randomly distributed throughout the blocks. For the one-back trials, a symbol was presented on the screen in one of the five locations. A question mark was then presented in the center of the screen. This indicated to the participant that the subsequent symbol would be the test symbol. If the location of the symbol matched the location of the symbol presented in the trial period, the participant was to push the "1" key on the computer keyboard. If it did not match, the participant was to push

the “0” key. For the two-back trials, a symbol was presented on the screen in one of the five locations. The symbol was then presented in a second location. This was followed by the question mark and then the symbol in the test location. If the test location matched the location of the first symbol, the participant was to push “1”. If the test location matched the location of the second symbol, the participant was to push “2”. And if the test location did not match either of the trial locations, the subject was to push “0”. For the three-back trials, a symbol was again presented on the screen in one of the five locations. The symbol was then presented in a second location and then in a third location. Following the question mark, the symbol was then presented in the test location. Again, if the test location matched the location of the first symbol, the participant was to push “1”. If the test location matched the location of the second symbol, the participant was to push “2” whereas if the test location matched the location of the third symbol, the participant was to push “3”. Finally, if the test location did not match either of the trial locations, the participant was to push “0”.

Accuracy.

The number of correct responses was calculated for the one-back, two-back and three-back responses.

Latency.

The latency from onset of the test symbol to first button push was recorded and averaged for the one-back, two-back and three-back responses.

Structural Imaging

Individuals from the FASD and matched control groups completed an MRI scan. (University control participants were not scanned due to the financial cost involved.) The two groups were scanned using a Philips (Koninklijke Philips Electronics N.V.) scanner operating at 3.0 Tesla at the Diagnostic Imaging department of the Lethbridge Regional Hospital, Chinook Health Region. Three scans were performed. A 22-slice T2-weighted Grase scan was initially performed followed by T1-weighted sagittal and coronal scans. The parameters for the T1-weighted protocol included: overcontinguous slices, 124; slice thickness, 1.20 mm; echo time, 4.60 ms; flip angle, 20° (sagittal) and 25° (coronal); field of view, 220 mm; and acquisition time, 5 min 30 s (sagittal) and 5 min 52 s (coronal). The scans were downloaded onto DVDs and provided to the author. The scans, as per the agreement with the Chinook Health Region, were not viewed by a radiologist.

The BrainVISA 3.1.6 (http://brainvisa.info) software program was used to segment the T1-weighted MR images to quantify volumes. The results of each stage of analysis were visualized using the associated software, Anatomist (http://brainvisa.info). The T1-weighted MR images were first loaded into BrainVISA and the images were oriented and virtually normalized by manually marking the anterior and posterior commissures for each subject. The images were preprocessed to remove extracortical tissue and then classified as gray matter, white matter or cerebral spinal fluid. Brain volumes were then graphed and analyzed.

EEG Data acquisition

Data was collected using a 128-channel Geodesics dense-array sensor net and Net Station acquisition software (Electrical Geodesics, Inc., Eugene, Oregon). The Locator program from EMSE (Source Signal Imaging, Inc., San Diego, CA) was used in conjunction with Polhemus (Polhemus, Colchester, VT) to record the relative spatial location of each electrode for each subject.

EEG data was recorded at 500 Hz with a high pass filter of 0.1 Hz and a low pass filter of 200 Hz. Using NetStation acquisition software, data epochs were extracted that began 1000 ms before and terminated 2500 ms after the onset of the trial. The epochs and EEG channels were manually inspected to discard those contaminated with non-stereotyped artifacts (e.g., muscle movement). (Trials containing stereotyped, repetitive movements, such as eye blinks, were not eliminated due to the limited number of trials available for analyses.)

Pre-Analyses Formatting

The data files for each condition for each subject were concatenated (see Figure 1). The data were down-sampled to 250 Hz to reduce memory demands during analyses and were then digitally filtered (low pass filter at 45 Hz) to minimize line noise artifacts and drifts using a zero-phase linear filter. Finally, the data were re-referenced to an average reference. Data epochs were selected to encompass both a pre-trial onset interval and an interval encompassing the early part of navigation. The data were segmented into epochs from –1000 ms to 2500 ms (with 0 ms being the moment of task commencement).

For the vMWT, trial one from each block was omitted from data analysis as the participants found the correct platform by chance. Twenty-nine non-artifact trials per participant for each of the 2 conditions were included for analysis.

For each participant, the segmented EEG data collected were 'cleaned' using an ICA-based artifact removal procedure. Briefly, the datasets were concatenated for ICA decomposition. It was then separated into components using the runica (Makeig et al., 1997) EEGLab 4.515 (Delorme and Makeig, 2004) function. Electrode artifact components were identified by visual inspection of scalp topographies. The separated data were then re-assembled, omitting those components (twelve) identified as electrode artifacts. The files were then formatted for Matlab (Matlab 7.0.1, The Mathworks, Inc., Natick, MA).

Concatenation

In order to compare across participants and groups, the data of all participants for the EEG task being analyzed was concatenated to provide a single, large dataset (Dataset 'A'). This provided a set of components that represented patterns of activity common across participants or across groups and not components that related to individual subject differences. Combining datasets also improves the ratio of artifact (random) to cortical activity, thus emphasizing brain activity. Concatenating all datasets is not without drawbacks. Participants with unique scalp topographies or temporal patterns, participants for whom the electrode array was distorted or participants with a poor signal to noise ratio in their data may not display group components (a problem also facing traditional ERP analysis). Or, alternatively, a separate

component might be created for that subject. The most serious drawback is the potential inability to discover components that are unique to only the FASD group. These potential components may be averaged out of the data. Concatenating the files may only reveal how FASD individuals differ from average and not how they may be compensating using differing regions of the brain. However, without first determining typical components associated with the task, relevant differences cannot be determined.

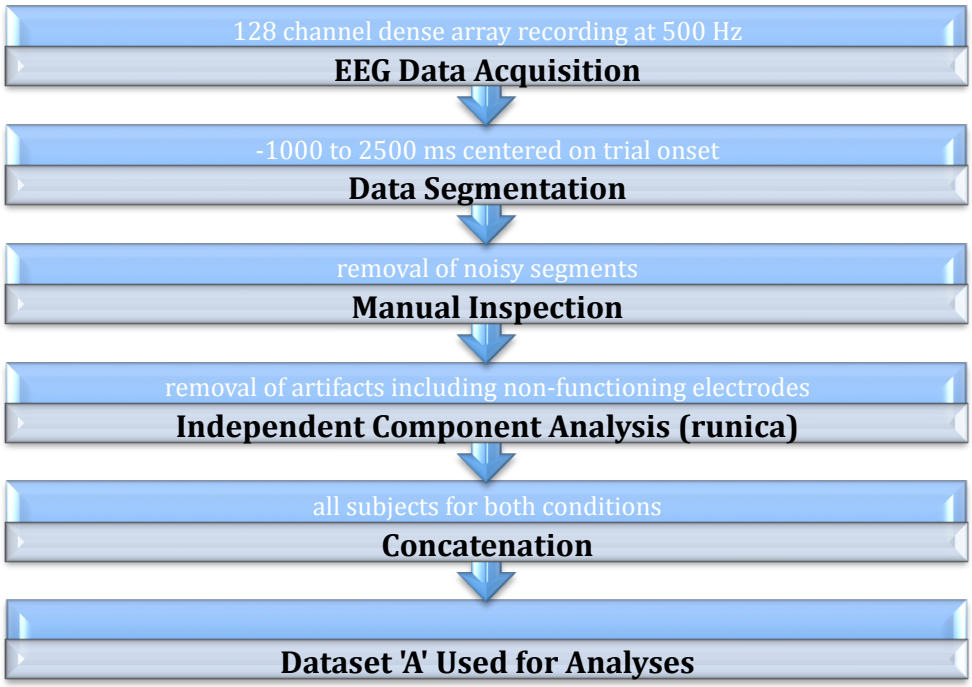

Figure 1. Steps for Preprocessing of EEG Data

Data Mining

Independent Component Analysis.

Event-Related Potentials.

Event-related potentials (ERPs), waveforms reflecting cortical voltage changes over time, represent neurophysiological patterns of cognitive functioning. These patterns are altered in response to experimental

variables. The alterations may reflect changes in morphology (pattern) of the waveforms, in the latency, duration or amplitude of one or more of the peaks, or in the scalp distribution of the waveform pattern. ERPs are typically calculated by averaging electrophysiological voltage changes within a specified time window synchronized to the onset of a stimuli or response.

Extensive use of ERPs in research analyses has yielded a catalogue of major ERP components and their hypothesized functional equivalents. For example, auditory and visual evoked potentials consist of an "N1", a negative-going deflection around 100 ms post-onset of the visual or auditory stimuli and a "P2", a positive deflection around 200 ms post-onset. These two peaks reflect the activity generated in the visual and auditory primary cortices. Perhaps the most extensively reported ERP is the P300, a group of positive deflections appearing at approximately 250 ms post-onset. The P300 includes the P3a, a positive deflection seen in the frontal scalp region subsequent to unexpected novelty, the P3b, a positive deflection associated with categorization, and the positive slow wave, associated with contextual updating.

The calculation and interpretation of ERPs rest upon several assumptions. First, the timing (latency) and strength (amplitude) of the voltage deflection constituting the ERP and the shape of the resulting peak are assumed to be consistent across trials, across subjects and across treatment groups. ERPs, therefore, would be most effective when analyzing data tightly synchronized to a presentation trigger, sensory input or individually identifiable stimuli (for example, a response to a

specific word or a button push). Second, the latency and amplitude of the ERP (and the underlying cognitive processes involved in the task) are assumed to remain constant from the first through to the last trial. This assumes that the waveform does not change in response to repeated presentations, practice or improved performance over time. Violation of the latency assumption would appear in analyses of peak onset and offset. If the latency variability was greater in the disabled population than for the matched controls, the peak onset and offset latencies would be adversely and disproportionately affected in the disabled group results. Third, the cognitive processes involved are predominantly expressed in the voltage deflection only during stimulus/response presentation. Changes in background activity constitute "noise" or artifacts unrelated to the cognitive processes necessary to complete the experimental task.

Other assumptions inherent to ERPs create ambiguous interpretations of research results. Perhaps the most damaging assumption is that each electrode represents isolated electrical activity underlying that electrode. Token acknowledgement is typically given in the form of labels such as "scalp" topography. However, electrode selection, analyses and interpretations are regularly completed as though the electrodes represent not just the scalp, but also the cortical topography. EEG data recorded at individual electrodes depict the sum (or more accurately, the weighted linear mixture) of multiple underlying cortical sources. Examination of correlated activity across regions is also hampered by volume conduction. This spatial smearing of multiple EEG source signals results in strong correlations among nearby electrodes. Research reporting correlation among electrodes ignores the probability that

adjacent electrodes do not record correlated activity, rather they record differing strengths of the same activity from the same source (Onton et al., 2006).

The assumptions underlying ERPs have been challenged by current research. For example, component latency may not remain constant. Ridderinkhof and colleagues (2004) and Debener and colleagues (2005) observed that response latencies increased over trials subsequent to error feedback. Debener and colleagues (2005) hypothesized that this reflected an increasingly more cautious approach to each trial. Makeig and colleagues (Jung et al., 2001) noted variable latencies when the data was analyzed with respect to the onset of the trial. They found that the variable latencies were correlated to variable response times. Tanaka and colleagues (2006) initially reported no differences in the P300 peak amplitude measures from trials of one's own face versus a trained face. However, when they (Zeman et al., 2007) re-calculated the peak amplitude measures within individualized windows around each peak, rather than using a standardized time frame (relative to trial onset), the mean amplitude was significantly greater for the trained face than for the subject's own face.

Research re-interpreting standard event-related potential peaks, such as the N100, as the sum of multiple source waveforms from different frequency bands has emerged (Contreras & Kerick, 2004; Delorme & Makeig, 2005; Jung et al., 2001; Makeig et al., 2004; Onton, Delorme & Makeig, 2005). These results contradict the ERP assumption that cognitive activity results from synchronized alterations within a wide

broadband of frequencies (as a single “entity”) or, that if narrow frequency bands comprise the ERP, frequencies alter in tandem in the same direction.

One limitation of a more practical nature has significant impact on the analyses of ERPs. ERPs require large number of trials to improve the signal-to-noise ratio sufficiently to detect the ERP of interest. Individuals with disabilities, such as fetal alcohol spectrum disorders, are frequently unable to complete the large numbers of trials required to obtain clear ERPs. This problem is compounded when trials are eliminated due to excessive “noise” or artifacts such as eye blinks. In addition, experimental tasks that are more open-ended or “open field” are not conducive to ERP analysis as each trial typically requires more time to complete, hence fewer trials can be completed. Moreover, the cognitive process(es) under investigation in an open-ended activity may not be consistently time-locked to a stimulus or response. The fluctuating ERPs could reflect a variety of different cognitive processes or overlap of processes.

Independent Component Analysis (ICA).

With the advent of high-density electrode arrays and higher sampling frequencies (for example, 256 Hz or 500 Hz), extracting relevant information from the EEG signals becomes more difficult. An alternative approach to ERP, blind source separation (BSS), uses only the recorded time course information and is “blind” to the models, theories or hypotheses related to the experiment. This class of methods includes both principal component analysis (PCA) and independent component analysis (ICA). Principal component analysis is now included in well-known

commercial packages (such as BESA); however, independent component analysis provides some key advantages over PCA.

Although both ICA and PCA are blind source separation methods involving linear decompositions of the data, the mathematical objectives, and therefore the interpretations of the results, are diametrical. The goal of PCA is to find temporally orthogonal components that "explains as much of the remaining variance as possible." (Makeig et al., 2004). Consequently, individual principle components are comprised of activity from an unknown number of independent sources. In contrast, ICA utilizes information-based signal processing (Onton et al., 2006) to separate data into underlying components that have the least possible mutual information (hence, the term "statistically independent").

As with ERP, ICA has its own underlying assumptions that are satisfied to varying degrees by EEG data. Several assumptions are shared with ERP such as the linear summation of electrical activity at scalp electrodes. The crux of independent component analysis rests on the assumption that EEG signals originate from different cortical sources that are temporally statistically independent and non-Gaussian. In addition, this temporal independence is sufficient to isolate individual signals from the mixed signals recorded from both physically distant and adjacent cortical regions at each electrode.

Mathematically, a signal mixture is expressed as:

$x = As$

where x denotes the set of signal mixtures, A denotes the mixing process and s denotes the independent source signals. To interpret this within an EEG framework, x would denote the electrophysiological activity recorded at each electrode. This recording would be a mixture of signals obtained from a variety of cortical sources. "s" denotes the electrophysiological signals produced by the cortical regions within recording vicinity of the electrode. A represents the interaction between the strengths of the different source signals, in addition to noise and artifacts. EEG data is arranged in a matrix of n electrodes (rows) by t time points (columns).

Independent component analysis "unmixes" these linearly mixed signals using only the statistics of the recorded time course information:

$$U = Wx$$

where the "unmixing" matrix, W, denotes a set of weight vectors that yields the matrix, U, of independent component time courses when multiplied by the original data, x (Onton et al., 2006). The unmixing matrix extracts the different sources by determining the relative projection weight at each electrode of a single component source and then multiplying that by the recorded EEG data (x) to yield the independent components. Data from N electrodes can be reconstructed as the sum of the N independent components (Makeig et al., 1997).

The fundamental criterion of maximal statistical independence is its' most contentious. The definition of "maximal statistical independence" conveys that "the value of one signal provides no information regarding the value of other signals" (Makeig et al, 2004). Although two components may display coherent activity over short time periods (in milliseconds), when

deriving components using data from the entire epoch, the algorithms will determine the components that are “maximally” independent from each other.

ICA versus ERP.

ICA components' relationship to ERP waveforms is increasingly being recognized (Jung et al., 2001; Makeig et al., 2004; Olbrich et al., 2005). For example, Makeig and colleagues (1997) found ICA components that accounted for 96.8% of the standard auditory response peaks, P2, N2 and P3, for undetected and detected auditory targets. In subsequent work, these researchers concluded:

After removing clear ocular and muscle artifact components from the raw data,... nine identified EEG component clusters together accounted for over 90% of the grand mean ERP variance (over all channels) as well as almost 60% of variance in the whole EEG. By contrast, the ERP data themselves accounted for only 6% of poststimulus EEG variance, supporting our claim that this analysis presents a more complete model of the event-related EEG dynamics occurring in these data than the averaged ERP (Makeig et al., 2004, p. 755).

Debener and colleagues (2005) detected two independent component clusters that accounted for portions of the novelty P3 and P3b response features, respectively. The frontal-parietal component cluster displayed the features of the P3b in response to novel environmental sounds, whereas the posterior-parietal component cluster reflected the latency and scalp topography of the classical P300, a deflection elicited by rare, typically task-relevant stimuli. The authors

concluded that ICA was able to accurately analyze spatiotemporally overlapping ERP processes.

ICA versus PCA.

As mentioned previously, ICA and PCA are both blind source separation algorithms. PCA is more familiar in statistical data analysis, feature extraction and data reduction. ICA was derived to recover signals or "sources" from observed linear mixtures that were independent, a stronger statistical standard than PCA's "uncorrelated" standard. Conceptually, ICA provides a better "fit" to EEG data than PCA. It is difficult, though, to objectively compare PCA directly with ICA due, not only to the differences in the aims of these two algorithms but also due to the large number of variations of the algorithm used (for example, Varimax and Promax PCA and Infomax, Fast, extended and log spectral ICA). In addition, ICA and PCA are frequently combined, not only with each other, but also with a wide variety of associated procedures such as wavelet analysis and clustering. However, Makeig and colleagues reported that ICA was more effective at removing artifacts from EEG signals recorded form normal and autistic participants than either PCA or regression (Jung et al., 2000). Bugli and Lambert (2007) also compared PCA with ICA, while analyzing the P300 complex. With ICA, they found two independent components that summarized the P3a and P3b in the frontal and parietal areas respectively. In contrast, when using PCA, they found only one component to correspond with the P300 peak; however, this component did not "separate the P3a and P3b phenomena" (p. 326).

ICA Source Localization and fMRI.

Indirect support for ICA in analyzing EEG data is provided when dipole modelling of ICA sources matches results found through fMRI studies.

Such studies must be interpreted cautiously, however, as the efficacy and accuracy of the dipole modelling program used (i.e., dipfit, BESA, LORETA, Beamform) will be reflected in the results. In addition, EEG and fMRI do not necessarily record the same cognitive processes.

Debener and colleagues (2005) described significant correlations between independent components derived from 32-channel EEG data with simultaneously obtained fMRI results during a performance monitoring task. They reported that when the location of the independent component for the ERN (error related negativity) was seeded in the region showing activation during the fMRI analysis, it accounted for 90.2% of the variance of the ERN. They also found significant correlation between single-trial EEG amplitude and fMRI BOLD response in the posterior frontomedial cortex (rostral cingulate zone, RCZ).

Other researchers have presented independent components with modelled locations in regions reported in fMRI or surgical studies. For example, Ossadtchi and colleagues (2004) decomposed MEG data into independent components. They subsequently clustered components depicting "spike-like characteristics". The modelled source locations for statistically significant component clusters were within the resectioned area for the three participants for whom surgical resection was later performed.

Matsumoto and colleagues (2005) reported significant correlations between reduced cortical activation, the BOLD repetition suppression effect, and the independent component N400 (reduced amplitude in related compared to unrelated word conditions) in the left superior

temporal gyrus. This corresponds to superior temporal lobe activation patterns reported in MEG, fMRI and PET studies (Helenius et al., 1998, 2002; Rissman et al., 2003; Sekiguchi et al., 2001).

Use of ICA.

The analysis of EEG data has evolved and expanded beyond the tradition ERP parameters of peaks, amplitude, latency and duration. The advent of advanced computer resources allows the data to be decomposed using blind source separation algorithms. PCA, and later ICA, allowed researchers to circumvent difficulties associated with ERP analysis such as volume conduction, noise contamination, variable response latencies and variable inter-trial phase-locking. ICA was introduced as both an adjunct and alternative to PCA. ICA counteracts difficulties associated with PCA such as the requirement that principal components be orthogonal, the less than optimal performance of PCA with components with spatial overlap, and the unknown number of sources comprised within a single principal component. The effectiveness of using ICA for data analysis of scalp-recorded EEG data has been demonstrated repeatedly (e.g., Debener et al., 2005; Gilley et al., 2006; Jung et al., 2000, 2005; Lee et al, 2006; Makeig et al., 1997, 1999, 2000, 2001, 2004; Piccione et al., 2006; Serby et al., 2005; Zeman et al., 2007).

As with all methodologies, ICA has limitations. Source signals that are highly temporally correlated may be inappropriately combined into a single component. As a result, bilateral activation may be modelled as a single, midline source. In contrast, when there are fewer sources than

electrodes, ICA will divide the single source across more than one component.

Despite the limitations, the advantages afforded by ICA make it the optimal methodology for analyzing the EEG data collected for this dissertation. Given the nature of the cognitive spatial tasks, and the limited attentional capabilities of some of the participants in the study, only a limited number of trials were available for analysis. ICA allowed the retention of trials that included eye blinks and other artifacts. These trials would have been discarded for ERP analysis. In addition, given research delineating neural damage caused by prenatal exposure to alcohol and the lack of documentation with respect to the amount and pattern of alcohol ingestion by the mothers of the participants in the study, the assumptions of waveform consistency (latency, amplitude, stimulus-locking and shape) across participants or trials were not viable. ICA, though, would allow analysis despite variations in waveform parameters. ICA also permits analyses by frequency bands. This provides an opportunity to compare the results obtained from the FASD human participants with results obtained for similar cognitive tasks completed with primates and rodents.

Multiple Origin Spatio-Temporal Modelling for Electroencephalography (MOST-EEG)

Mathematically, time and frequency are orthogonal (Buszaki, 2006) and cannot be analyzed concurrently. To analyze on a temporal dimension only however, risks eliminating information known to vary with cognitive tasks and skills, namely frequency bandwidth power. To analyze on a

frequency dimension only though, eliminates the temporal information thereby negating the rationale for EEG itself. Therefore, multiple origin spatio-temporal modeling for EEG (MOST-EEG), a novel combination of temporal and frequency analyses developed by Philip Zeman at the University of Victoria (Zeman et al., 2007, 2008; Figure 2), was employed to analyze the data. The analysis process allowed temporal analysis within specified frequency bands using volume estimations to verify the components selected for analysis.

Band-selective ICA and spectral shaping filter.

The runica algorithm (Delorme & Makeig, 2004) is a common ICA standard for decomposition of EEG data. Band-selective ICA (BSICA) (Zhang and Chan, 2006) adaptively estimates frequencies that provide for greater independence between sources. The characteristics of BSICA are complementary to those of runica. To spectrally shape the EEG data, then, the runica and BSICA First, runica is used to calculate a weight matrix W and a sphering matrix P from the cleaned EEG data, Dataset A (figure 2). Next, using these weights and sphering matrices, the BSICA algorithm is used to calculate filter coefficients, h, that reduce the statistical dependence of estimated sources. These coefficients emphasize those frequencies of statistical independence and in doing so, attenuate those frequencies of dependence. The filter coefficients, h, shape the spectra of the original cleaned EEG data, Dataset A, thereby creating a filtered dataset Ah. Next, using runica on the now filtered dataset Ah, creates a new sphering matrix Ph and weight matrix Wh (and the spectrally shaped source output sh, which is discarded). The new sphering matrix Ph and weight matrix Wh are applied to the original

unshaped EEG dataset A to identify the independent components and their scalp topographies (figure 2).

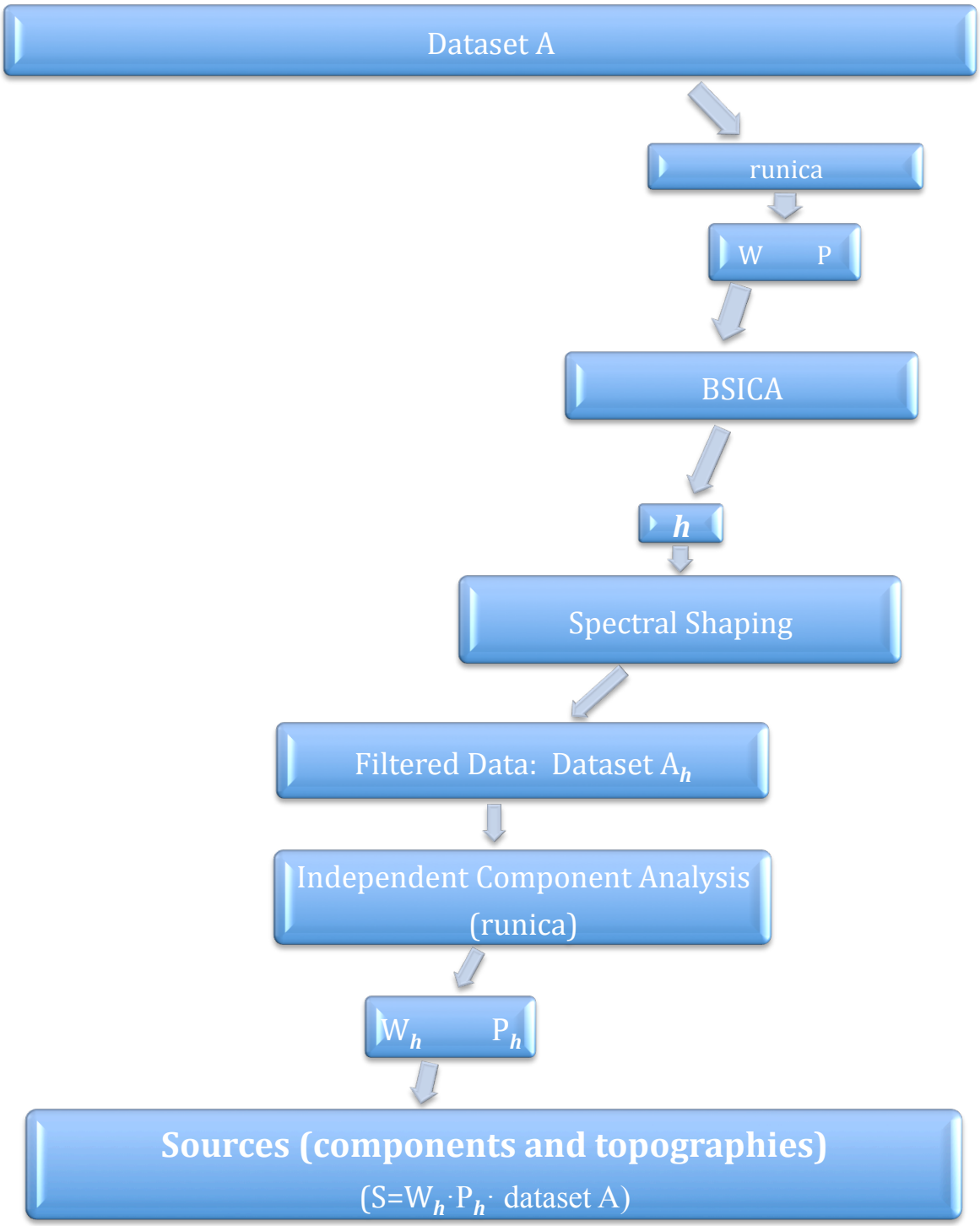

Figure 2. Steps for Independent Component Analysis

Identification and verification of relevant components

ICA-derived topographies were projected to a head volume domain using a modified LCMV Beamform algorithm proposed by Zeman and colleagues (2007). "Goodness" of each component was evaluated with three independent measures: volume representation ('peak of spectral volume', PSV), volume uniqueness ('measure of volume overlap', MVO), and quality of convergence ('total distance travelled' by the projected volume on each iteration of the runica algorithm, DT) (Zeman et al., 2007d) (figure 3). This provides objective, data-driven ranking using meaningful measures of how well sources can be represented as volumes (PSV) and how unique each source is by measures of volume overlap (MVO). The convergence of source center (DT) provides a confidence in the stability of a result.

The peak spectral values (PSV) were recorded for each component at the completion of each iteration. The PSV represents how well the set of electrode weights comprising the corresponding scalp topography project variance to a single voxel within the head model. Hence, it is the voxel-specificity of the volume domain projection of the topography. The topographies of components were plotted according to PSV. Those components with a PSV below the specified threshold (Figure 3) were thus classified as poor quality and were not examined further. The PSV threshold was determined by identifying the "knee" of the curve of ranked PSV scores. Those topographies with PSV scores above the threshold are displayed in Figure 4.

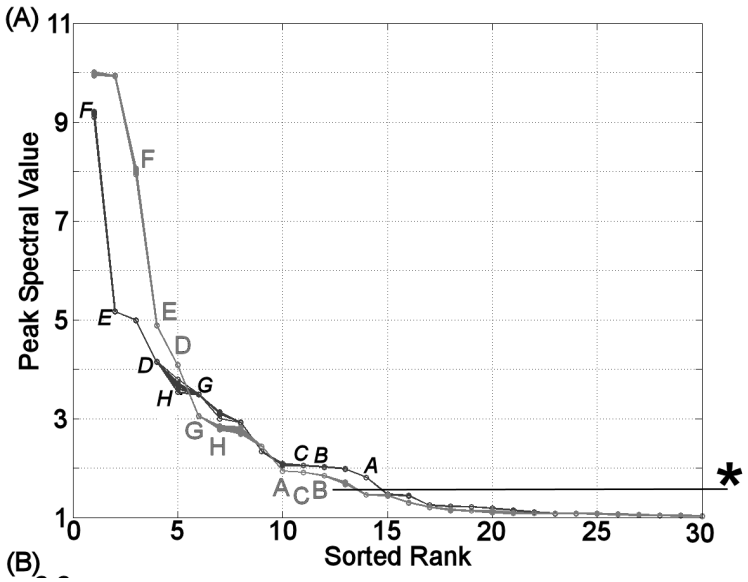

Figure 3. Non-shaped results (runica results without applying the shaping filter) are plotted in black. The shaped components (runica results after applying the shaping filter) are plotted in gray. The components from the vMWT dataset are sorted according to the calculated PSV. The (*) indicates the cut-off used to isolate useful components.

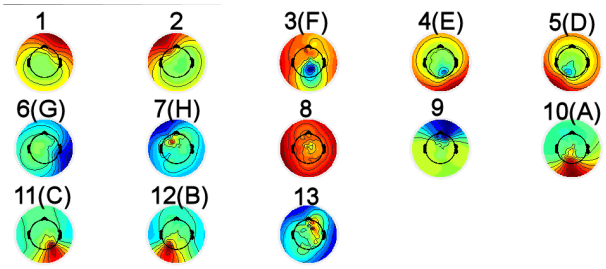

Figure 4. The scalp topographies of the 15 components with the largest PSV scores from the vMWT dataset. The letters correspond with the data points in Figure 3.

The MVO provides an indication of how modular the volume is with respect to a noise-floor defined by the median of overlaps of all other components. For the convergence measures, the XYZ location of the peak for each component was calculated for each iteration of runica. The

distance travelled (DT) for each iteration was calculated as the distance travelled between the current and the previous iteration (Zeman et al., 2007). For the first iteration, the distance travelled is zero. The results were then plotted for each component. Finally, the top components were projected into three dimensional space using a modified LCMV Beamform algorithm (Zeman et al., 2007). Calculations of power and phase of the EEG signal were then completed for those components that corresponded to anatomically relevant locations (Figure 5).

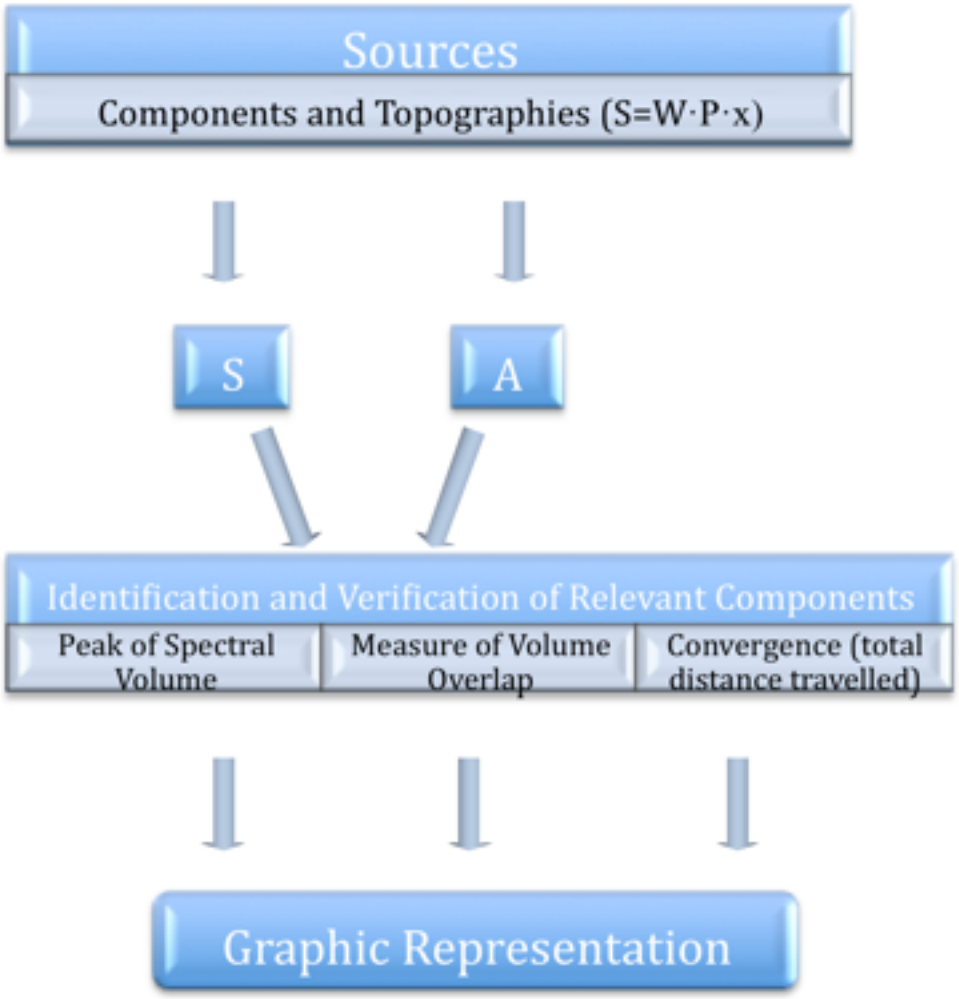

Figure 5. Determination of components of interest.

Power and Phase measurements

The root mean square (RMS) values for 2500 ms epochs across four frequency bands were plotted for each group and condition. Visual inspection of the waveforms dictated the final selection of components and the epoch lengths chosen for the pre- and post-trial intervals The pre-trial onset epoch ranged from –250 ms to 0 ms while the post-trial

epoch ranged from 0 ms to 250 ms. RMS values were calculated for the theta bandwidth (4 to 7 Hz), lower alpha bandwidth (7.5 to 9.5 Hz), upper alpha bandwidth (9.5 to 12 Hz), and gamma bandwidth (36 to 44 Hz). The phase was determined by calculating the phase in radians (0 to 2pi; 2 pi [2π] radians = 360 degrees) at trial onset.

Statistical Analysis

The neuropsychological battery results and behavioural results were analyzed using stepwise linear regression (Statistical Package for the Social Sciences; SPSS, Inc., Chicago, IL) with group as the outcome (dependent) variable and the test results as predictor (independent) variables. The stepwise linear regression permitted evaluation of the predictive value of neuropsychological and behavioural variables to classify individuals with FASD.

Repeated measures ANOVAs for RMS and phase values were calculated using SPSS. For the vMWT, the ANOVA evaluated a between-subjects factor of GROUP and within-subject factors of timing (pre-onset and post-onset epochs), components, frequencies (theta, lower alpha, upper alpha and gamma) and condition (place and cue). For the spatial working memory task, the ANOVA consisted of a between-subjects factor of GROUP and within-subject factors of components and memory load (1-back, 2-back and 3-back). Univariate results were adjusted using the Huynh-Feldt Epsilon (H-F) correction factor.

5. *NEUROPSYCHOLOGY PROJECT*

The cognitive and behavioural impairments resulting from prenatal alcohol exposure are significant and extensive (for reviews, see Mattson and Riley, 1998; Mattson et al., 2001; Roebuck et al., 1998). In addition to impaired academic skills (such as reading and mathematics, fetal alcohol exposure is associated with behavioural concerns (including impulsivity, perseveration and hyperactivity), social interaction difficulties and poor "executive functioning". Difficulty with learning and memory, as displayed by poor verbal skills, impaired working memory and poor spatial memory are consistently reported (Coles, 2001; Hamilton et al., 2003; Kelly et al., 2000, Kodituwakku et al, 2001; Streissguth et al., 1991, 1994, 1998). Equivalent cognitive and behavioural impairments were reported in individuals with a history of chronic prenatal alcohol exposure but without the physical features of FAS (Mattson et al., 1997).

Cognitive and behavioural deficits have surfaced in studies evaluating the effects of moderate or social drinking during pregnancy, although the effects were typically not as deleterious as those associated with higher levels of maternal alcohol consumption (Gusella & Fried, 1984; Streissguth, Barr & Sampson, 1990). In contrast to studies focusing on individuals with FAS or heavy, chronic prenatal alcohol exposure, children exposed to low or moderate amounts of alcohol prenatally had formal intelligence scores within the normal range (Carmichael Olson, Morse & Huffine, 1998). However, these children displayed impaired interpersonal interactions, impaired social skills and behaviour problems, concerns not evaluated with formal IQ tests. This range of expression from mild disabilities to severe, incapacitating disabilities represents a continuum of

alcohol's behavioral teratogenicity (Mattson & Riley, 1998). Prenatal alcohol exposure may not compromise the basic language and cognitive functions needed to perform appropriately in highly structured contexts. As a result, these individuals may score within the normal range on formal tests. However, prenatal alcohol exposure may result in an inability to function in daily social situations where the individual must cope with implicit and fluctuating demands within an unstructured setting.

Hypothesis

Women were recruited from the Home Visitation program of the Chinook Health Region. To qualify for this program, individuals must require assistance to function independently in the community. These individuals had difficulty with daily living skills, financial management, obtaining and maintaining employment and providing safe and healthy home environments for their children. Given Carmichael and colleagues (1998) results and research from animal studies suggesting that low to moderate levels of fetal alcohol exposure result in specific disabilities within the executive functioning and spatial realms, I hypothesized that the participants would score within average on formal tests of intelligence but have difficulty with tests designed to evaluate executive functioning and memory skills.

Methodology

Participants

The home visitation program of the Chinook Health Region referred 13 adult females with fetal alcohol spectrum disorder (FASD) and 17 female controls. The control participants were matched to the FASD participants with respect to age, educational background, socioeconomic

status, history of verbal and physical abuse, past and current history of drug use and current alcohol usage. A worker from the home visitation program accompanied the participants to the research sessions. Informed consent was obtained from each subject. Approval for this study was granted by the ethics committee of the University of Lethbridge, Alberta, Canada.

Nineteen of the participants completed all of the tests within the neuropsychological battery. Eleven participants refused to start or finish a subtest during the test session, did not return for the second day of testing, could not be located partway through the research project or withdrew from the project.

Neuropsychological Battery

The FASD and matched control groups completed a neuropsychological evaluation given by a provincially certified psychologist. The neuropsychological battery is described above.

The tests were chosen to assess general intelligence and areas known to be impaired in individuals with prenatal alcohol exposure: spatial skills, memory and executive functioning. The testing was typically conducted over two sessions that lasted approximately one to 1 1/2 hours each. A worker from the Home Visitation program brought the participants to either the EEG lab at the University of Lethbridge or to the psychologist's office at Alberta Neuropsychological Services for testing.

Statistical analysis

Using SPSS 16.0 (SPSS Inc., Chicago, IL), a stepwise linear regression was completed with GROUP as the outcome (dependent) variable and the Neuropsychological Tests as the predictor (independent) variables. Missing values were excluded in a pairwise fashion.

Results

The full scale intelligence quotients obtained (Figure 1)on the Wechsler Adult Intelligence Scale (WAIS-III) were within 2 SD of the published mean (X = 100, SD = 15) for the participants in the FASD group (n = 12; M = 95.25, range = 79 – 119, SD = 13.81) and the matched control (MC) group (n = 14; M = 106.43, range = 91 – 118, SD = 9.52). Similar results were obtained for the performance intelligence quotient (FASD group M = 97.33, range = 78 – 119, SD = 12.51; MC group M = 112.64, range = 94 – 130, SD = 10.51) and the verbal intelligence quotient (FASD group M = 94.33, range = 74 – 116, SD = 14.98; MC group M = 102.36, range = 88 – 117, SD = 9.58).

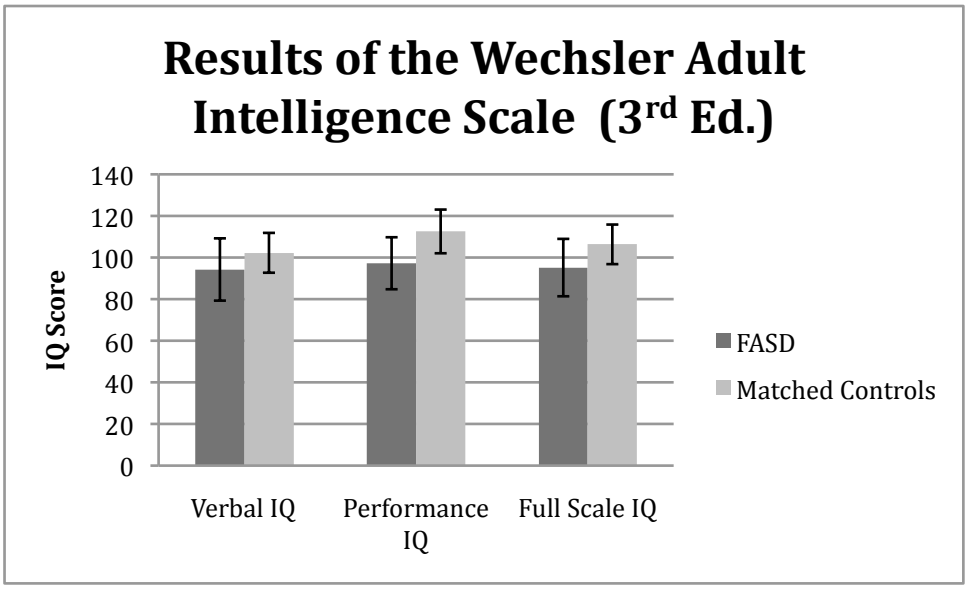

Figure 1. Scores on the verbal (verbal IQ), performance (performance IQ) and full scale (full scale IQ) intelligence quotients of the Wechsler Adult Intelligence Scale (3rd Edition).

The general memory index (Figure 2)obtained from the Wechsler Memory Scale-III (WMS-III) was within two standard deviations of the published mean (X = 100, SD = 15) for the participants in the FASD group (n = 12; M = 103.50, range = 92 – 125, SD = 9.36) and the matched controls (n = 16; M = 107.50, range = 91 – 124, SD = 9.44). Lower scores were obtained on the working memory index than the general memory index (FASD group M = 97.50, range = 74 – 118, SD = 13.21; MC group M = 99.13, range = 83 – 115, SD = 8.71), although the scores still fell within two standard deviations of the published test mean.

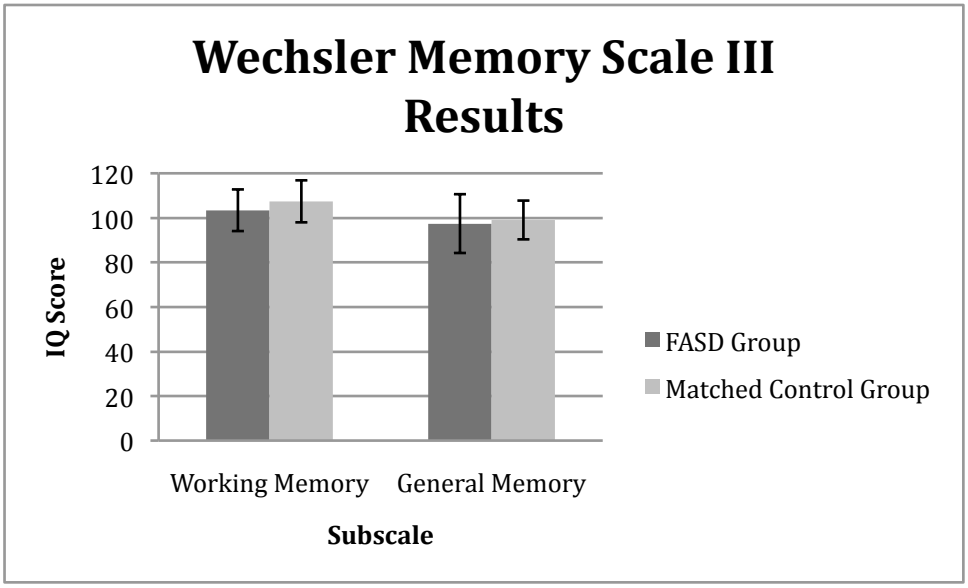

Figure 2. Scores for the general memory and working memory indices of the Wechsler Memory Scale.

		Rey-Osterrieth Complex Figure				Mooney Face Test	Chicago Verbal Fluency	Newcombe Verbal Fluency			Wisconsin Card Sorting Task	Dichotic Listening
		Copy	Recall	Right/left	Semmes			objects	animals	alternating		
FASD Group	Mean	32.50	13.42	44.08	33.58	22.25	46.00	20.42	17.75	15.42	5.88	44.30
	Number[a]	12	12	12	12	12	12	12	12	12	12	10
	Std. Deviation	4.15	7.49	6.75	1.51	1.66	16.34	3.99	3.49	3.03	0.43	10.17
	Minimum	23	3	32	30	18	13	15	13	11	5	29
	Maximum	36	25	53	35	24	78	25	26	21	6	61
Matched Control Group	Mean	34.73	19.67	49.14	35.15	23.13	58.67	24.21	21.36	16.00	5.87	47.46
	Number[a]	15	15	14	13	15	15	14	14	14	15	13
	Std. Deviation	2.74	5.94	6.16	5.84	1.51	14.69	7.15	4.13	2.18	0.52	6.04
	Minimum	26	9	34	30	20	29	10	15	13	4	40
	Maximum	36	28	57	54	25	84	35	30	21	6	61

Table 1. Raw scores for neuropsychological task.

a. Number of participants in group

Even though both groups scored within two standard deviations of the test mean, the WAIS performance intelligence quotient (WAISPIQ)

Wechsler Memory Scale III

		Primary Subtest Scaled Scores										
		logical I	verbal pr I	faces I	family I	logical II	verbal II	aud delay	faces II	family II	let-num	spatial
FASD Group	Mean	7.17	10.75	9.42	9.50	9.75	10.92	11.50	10.67	9.92	9.75	9.92
	Number[a]	12	12	12	12	12	12	12	12	12	12	12
	Std. Deviation	3.95	2.26	2.50	3.06	2.18	2.35	2.78	2.39	3.12	3.44	2.43
	Minimum	2	7	4	6	6	6	6	6	5	5	5
	Maximum	13	13	13	14	14	13	16	14	16	15	13
Matched Control Group	Mean	8.94	10.19	10.75	11.38	10.50	11.19	11.50	11.00	11.56	10.00	9.88
	Number[a]	16	16	16	16	16	16	16	16	16	16	16
	Std. Deviation	2.57	2.23	3.00	2.13	1.71	2.59	2.16	3.20	1.93	1.67	2.39
	Minimum	4	6	6	8	7	6	8	4	8	8	5
	Maximum	12	15	16	15	13	18	16	17	15	14	14

		Primary index Scores							
		Aud Imm	Vis Imm	Immed	Aud Del	Vis Del	Aud Rec D	General	Working
FASD Group	Mean	94.08	96.33	94.17	101.58	99.58	107.50	103.50	97.50
	Number[a]	12	12	12	12	12	12	12	12
	Std. Deviation	11.12	11.38	9.54	10.14	13.19	13.90	9.36	13.21
	Minimum	77	75	82	83	81	80	92	74
	Maximum	117	115	114	117	122	130	125	118
Matched Control Group	Mean	97.06	106.44	102.06	103.31	108.00	107.50	107.50	99.13
	Number[a]	16	16	16	16	16	16	16	16
	Std. Deviation	9.81	13.23	11.57	8.84	12.01	10.80	9.44	8.71
	Minimum	80	91	84	83	88	90	91	83
	Maximum	114	134	130	114	136	130	124	115

significantly predicted group membership, R^2 = .324, F(1,18) = 8.64, p = .009. The WMS Working memory index approached significance (p = .057). All other results were non-significant.

Wechsler Adult Intelligence Scale - III

		Verbal Scales					
		Vocab	Sim	Arith	Digit Span	Info	Comp
FASD Group	Mean	9.67	10.25	7.08	9.17	8.17	10.08
	Number[a]	12	12	12	12	12	12
	Std. Deviation	2.46	3.89	3.15	3.33	2.44	2.43
	Minimum	5	3	3	5	5	6
	Maximum	14	16	13	15	11	14
Matched Control Group	Mean	10.19	12.13	9.13	8.63	9.67	11.73
	Number[a]	16	16	15	16	15	15
	Std. Deviation	2.20	2.94	2.20	2.13	2.16	2.09
	Minimum	6	8	6	5	7	7
	Maximum	14	19	13	13	14	14

		Performance Scale					***Intelligence Quotients***		
		Pic Com	Coding	block	matrix	picture arrangement	Verbal	Performance	Full Scale
FASD Group	Mean	11.33	8.50	8.83	9.67	10.08	94.33	97.33	95.25
	Number[a]	12	12	12	12	12	12	12	12
	Std. Deviation	2.87	2.84	3.01	2.27	2.35	14.98	12.51	13.80
	Minimum	8	4	6	6	7	74	78	79
	Maximum	18	14	13	13	16	116	119	119
Matched Control Group	Mean	13.80	9.80	11.13	12.14	12.50	102.36	112.64	106.43
	Number[a]	15	15	15	14	12	14	14	14
	Std. Deviation	2.27	2.78	2.72	2.38	1.93	9.58	10.51	9.52
	Minimum	11	7	8	6	10	88	94	91
	Maximum	18	17	17	15	15	117	130	118

Table 3. Wechsler Adult Intelligence Scale – III results.

Discussion

Several research groups have reported scores on formal tests of intelligence within the normal range. Kerns, Don, Mateer and Streissguth (1997) reported that half of the adolescents and young adults, aged 16 to 27, diagnosed with FAS in their study scored within average on the WAIS or Wechsler Intelligence Test for Children (WISC). These individuals achieved a mean full scale score of 97.13 (range: 90 to 118). Korkman, Kettunen and Autti-Ramo (2003) found that the 12 to 14 year old participants who had been exposed to alcohol only during the first trimester scored an average of 98.2 on the WISC-III full scale IQ while those exposed during the first and second trimester scored an average of 93.3. (Those participants exposed prenatally to alcohol for all three trimesters dropped to an average full scale IQ score of 77.1.) The scores obtained by the participants in these two studies are similar to the scores achieved by the FASD participants in this study (FASD group $M = 95.25$).

The FASD group in the Kerns et al. (1997) study and the FASD group in this study both showed higher performance IQ scores than verbal IQ scores. This pattern though is not consistently reported in the literature. For example, Korkman and colleagues (2003) found that their FASD participants scored higher on the verbal IQ score than the performance IQ score.

Difficulty with executive functioning has been considered a hallmark trait of individuals with FASD. A common test of executive, frontal lobe functioning has been the Wisconsin Card Sorting Test (WCST). However, not all research groups have found that individuals with FASD have

difficulty with this specific task. While evaluating children with FASD and attention deficit/hyperactivity disorder, Vaurio, Riley and Mattson (2008) found that children with FASD scored significantly higher on the WCST than expected based on IQ scores. Our results were similar. Only one participant (from the FASD group) did not complete all six category shifts during the allotted number of trials.

Several research groups have reported within average scores on formal general intelligence tests but difficulty with cognitive skills such as attention and higher level cognitive skills (Aronson et al., 1997; Brown et al., 1991; Connor et al., 2001; Steinhausen, Willms & Spohr, 1994). Kerns et al. (1997) described difficulties on measures of complex sustained and alternating attentional tasks in addition to difficulties with attention when distracters were presented. Kodituwakku et al. (1995) reported that individuals with prenatal alcohol exposure performed as well as controls on rule learning and verbal knowledge but were significantly more impaired on tasks measuring fluid intelligence. Streissguth (2007) indicated that prenatal alcohol exposure was correlated with more cognitively challenging tasks such as reasoning, manipulation of information, learning of sequential information, inhibition and vigilance performance. She reasoned that individuals with prenatal alcohol exposure would have greater difficulty with more complex tasks as opposed to simple recall measures such as digit span.

The particular battery of tests that were administered to the participants in this study may not therefore have been strenuous enough to detect impairments in cognitive functioning or to distinguish between less severe expressions of FASD and non-FASD individuals. However, a

distinctive FASD cognitive profile may also be unrealistic given the differing profiles of neurophysiological damage associated with different patterns, amounts and timing of alcohol consumption during pregnancy. Carmichael Olson and colleagues (1998), in their study of nine, "nonretarded" teenagers with FAS, concluded that "no one neuropsychological profile characterized all patients and not all tests revealed problems" (p. 1998). The results of this study also indicated that individuals had difficulty with subtests of the WAIS-III and WMS-III (even in the presence of within average overall scores), in addition to difficulty with some of the additional tests administered, but no consistent pattern of deficits emerged across participants.

In contrast to most research that evaluate cognitive skills in individuals with FASD, the FASD participants in this study were compared to a control group that was matched on more factors than the typical criteria of age, gender and socioeconomic level. The lack of significant results for the majority of the neuropsychological test battery does not necessarily imply a lack of impairment but rather the lack of a distinctive FASD profile that can distinguish individuals with FASD from non-FASD matched controls. Or, the lack of significant results may potentially reflect a common pattern of specific learning disabilities seen within both groups. This in turn may mask any differences that could be attributed prenatal alcohol exposure.

Although all but one of the individuals in this study scored within two standard deviations of the mean on the WAIS-III and WMS-III, all were enrolled in a program due to difficulty with daily living skills, money management, household management, child care and obtaining and

maintaining employment. All individuals had a support worker to ensure that they attended the appointments. For individuals on the mild to moderate end of the FASD spectrum, the disability may not be in the cognitive domain per se, but rather in impaired interpersonal interactions, poor social skills, behavioural problems, and difficulty adapting to changing demands and situations encountered in daily life - skills not evaluated by formal IQ tests.

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6. *NEUROPHYSIOLOGY PROJECT: SIMPLE INDEPENDENT COMPONENTS ANALYSIS*

Participants:

11 female university students

13 female participants with a diagnosis of fetal alcohol spectrum disorder (FASD)

14 female participants enrolled in the same support program as the individuals with FASD but without a diagnosis of FASD

29 correct trials per participant for each condition were used for data analysis. We then concatenated the FASD and FASD-matched control groups (unaveraged data). This allowed us to work with a limited set of "noisy" trials and extract components that were well-represented in the groups.

2. Principal component analysis reduced the number of potential components from 128 to 40, retaining approximately 99% of the variance.

3. Independent component analysis (ICA) was used to extract maximally statistically independent time-domain sources and corresponding scalp topographies.

4. Time-domain correlation between sources was estimated using a sliding window with 50% overlap. Correlations were first calculated on individual trials for each subject. Individual trial correlations were then ensemble averaged to form an estimate of the correlation at unit intervals in time per subject.

5. An unconstrained Beamformer was used to localize ICA sources.

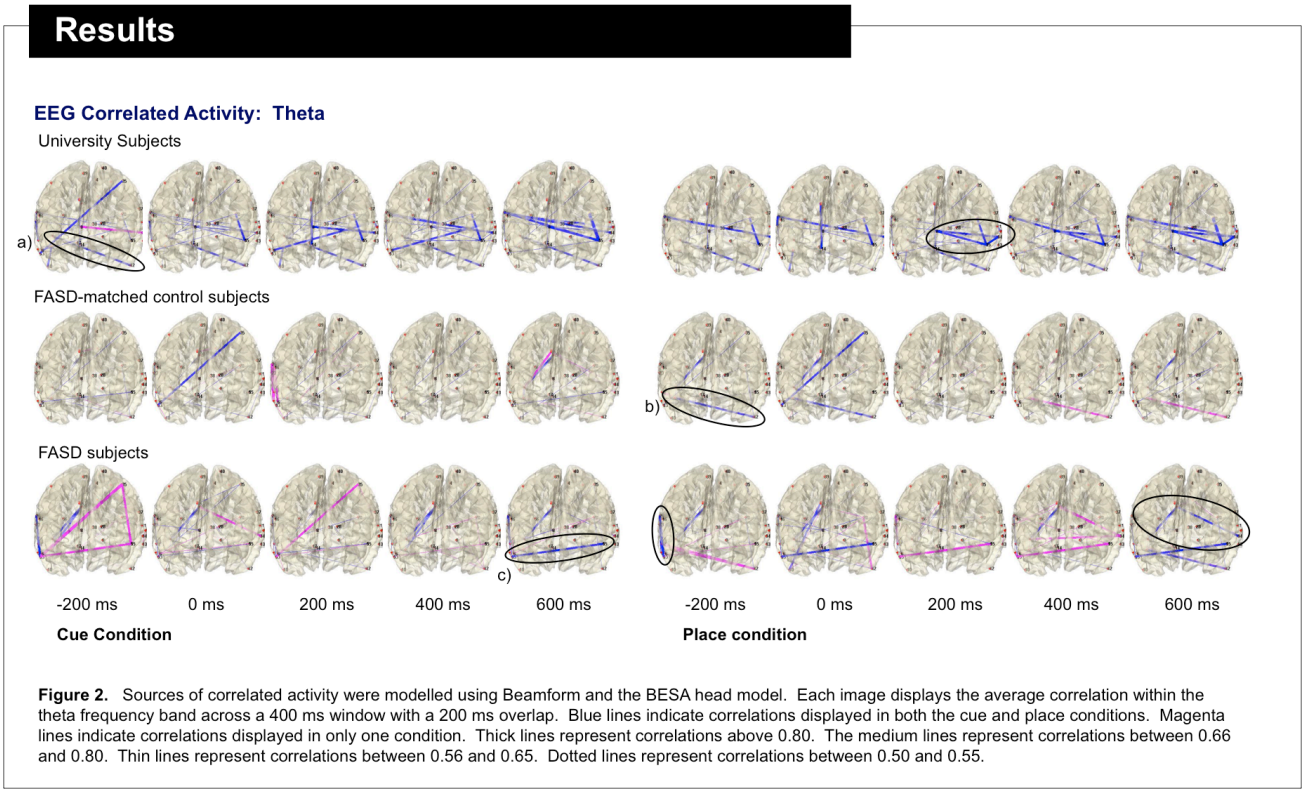

Figure 2. Sources of correlated activity were modelled using Beamform and the BESA head model. Each image displays the average correlation within the theta frequency band across a 400 ms window with a 200 ms overlap. Blue lines indicate correlations displayed in both the cue and place conditions. Magenta lines indicate correlations displayed in only one condition. Thick lines represent correlations above 0.80. The medium lines represent correlations between 0.66 and 0.80. Thin lines represent correlations between 0.56 and 0.65. Dotted lines represent correlations between 0.50 and 0.55.

EEG Correlated Activity in the theta bandwidth:

The university females displayed several patterns that began prior to trial onset and continued throughout the trial. In addition, the same components and correlated activities were displayed in both conditions. This indicates that the university students completed the two tasks using the same cognitive strategies. The place trials may not have been appreciably more difficult for these women. The university females also demonstrate greater connectivity throughout both trials than either of the other two subject groups. In addition, the university group displays intrahemisphere anterior-posterior connections in the left hemisphere, a pattern not seen in the FASD and FASD-matched control groups.

Correlated activity, between modelled components in the left, inferior temporal lobe and right, posterior inferior temporal lobe, was exhibited by

all three subject groups. It was the most consistent and predominate pattern for the FASD-matched control and the FASD subjects. These two groups demonstrated this correlation only in the place trials whereas the university subjects demonstrated this correlation in both place and cue trials.

The FASD group presented several patterns of correlated activation that were unique to that group. This indicates that these subjects are arriving at the correct answers using a different neural network than either of the other groups. They displayed interhemisphere modelled connections between the right and left temporal lobes suggesting that they are processing contextual information. However, this information does not appear to then interact with frontal regions. It does correlate with modelled motor regions.

Hippocampal volumes for the FASD subjects and the FASD-matched control subjects were not significantly different. The source localizations may not accurately represent FASD and FASD-matched control subjects IF their hippocampal volumes differ significantly from normative samples. We are currently investigating this.

The findings were not a result of impaired cognitive performance (as measured by the WAIS). The mean verbal, performance and full scale scores did not differ significantly between the FASD and the FASD-matched control groups. In addition, the means for both groups fell within the average range.

Although the FASD-matched control subjects performed similarly to the FASD subjects on most tests given, the deviations from the mean were greater. This suggests that the FASD-matched control group was a more

heterogeneous group. When scores from these control subjects were combined, the scores may have been negated.

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7. *VISUAL PROCESSING IN FASD*

Optometric anomalies are well-documented in the FASD literature. Most notably, physical anomalies such as the characteristic malformations of the external eye, epicanthus, short palpebral fissures and microphthalmia help confirm a diagnosis of FAS. Other predominant malformations include optic nerve hypoplasia and increased tortuosity of the retinal vessels (Miller et al., 1984; Chan et al., 1991; Hinzpeter et al., 1992; Hug et al., 2000) with 48% to 91% of the individuals with FAS demonstrating hypoplasia (Stromland, 1985; Stromland & Hellstrom, 1986; Hug et al., 2000) and up to 49% with increased tortuosity of, primarily arterial, vessels (Stromland, 1985). Associated with these physical anomalies is impaired visual acuity (Strömland, 1987; Hug et al., 2000; Carter et al., 2005).

Eye movement deficits have also been recorded. Green, Munoz, Nikkel and Reynolds (2007) instructed 8 to 12 year old subjects with FASD to look toward or away from a stimulus presented in the peripheral visual field. They reported that individuals with FASD displayed lengthened saccadic reaction times in addition to excessive directional errors.

Abnormal occipital functioning has also been reported. Medina, Ramoa and colleagues (Medina, Krahe, Coppola & Ramoa, 2003; Medina & Ramoa, 2005; Medina, Krahe & Ramoa, 2005, 2006) evaluated cortical plasticity using a ferret model of FAS. They described reduced neuronal orientation selectivity and reduced ocular dominance plasticity in ferrets exposed prenatally to alcohol. Fryer and colleagues (2009) evaluated white matter integrity in 15 adolescents with heavy prenatal alcohol

exposure using diffusion tensor imaging. They reported low fractional anisotropy in white matter innervating the occipital lobes bilaterally.

The scarcity of research on cortical processing of visual information, such as visual evoked potentials (VEPs), in the FASD population is striking given the available documented optometric and occipital anomalies. Olegard and colleagues (1979) reported abnormal responses to flash evoked and photic VEPs in 38% of infants of alcoholic mothers and questionable responses in 57%. Scher and colleagues (1998) described an interaction between trimester of prenatal alcohol exposure and latency of the N1 and P1 components of the VEP in FAS infants from birth to 18 months of age. These authors concluded that prenatal alcohol exposure led to delayed maturation of the visual system.

The effect on the visual system of mild to moderate prenatal alcohol exposure in humans has not been evaluated. Minimal information can be gleaned from animal research. Sprague Dawley rats exposed to 5% ethanol prenatally (the equivalent to mild to moderate exposure) achieved the same spatial frequencies as the controls in a visual discrimination task indicating normal visual acuity (Sorensen et al., 2004, unpublished data). This would imply that the magnocellular inputs to the striate cortex are not impaired in the mild to moderate exposed population.

Previous research discussing electroencephalographic (EEG) alterations in children and adults exposed prenatally to alcohol have not accommodated the potential interaction between abnormal visual (occipital) processing within the first 150 ms with later (impaired) waveforms representing cognitive functioning (such as the P300). As

such, attributing the source, both cognitively and physiologically, of later impaired waveforms may be premature when sensory processing abilities are unknown.

This study evaluates whether individuals with FASD demonstrate abnormal processing within the occipital regions following visual stimulus onset. This will verify whether visual processing is unaffected in individuals with mild-to-moderate FASD and therefore allow more accurate interpretation of the EEG results obtained during spatial tasks completed as part of a larger research project. Although all individuals in the study had normal or corrected-to-normal vision, normal visual acuity does not guarantee intact visual processing or integration of visual input. Given the within average scores on visual processing and integration tasks on the Wechsler Adult Intelligence Scale, and neuropsychological tests such as the Mooney Face Test (Sorensen, 2009), I predicted no significant difference in visual processing for the FASD group compared to the matched control and university control groups.

Materials and methods

Participants

The home visitation program of Chinook Health Region referred 13 adult females with a diagnosis of FASD and 17 female controls. The FASD control subjects were matched to the FASD subjects with respect to age, educational background, socioeconomic status, history of abuse and past and present drug and alcohol usage. A worker from the home visitation program drove the subjects to the university for testing. Ten female, right-handed university students from the University of Lethbridge also participated in this study. They received an additional 1% for their final grade in an undergraduate psychology class. Informed consent was

obtained from each subject. Approval for this study was granted by the ethics committee of the University of Lethbridge, Alberta, Canada.

Stimuli

The data analyzed was collected as part of a larger study evaluating the effect of prenatal alcohol exposure on cognitive functioning in adults. For this portion of the study, the subjects were presented with a visible platform version of the virtual Morris water task (vMWT). Briefly, the subjects were required to remember the location of a platform in a computer generated, virtual pool by orienting themselves to either the color of the platform (nonspatial cue condition) or to the location of the platform relative to pictures on the walls of the virtual pool room (spatial place condition).

Subjects were seated comfortably approximately 180 cm from a Dell Trinitron 40 cm CRT computer screen with a refresh rate of 75 Hz. The virtual environment consisted of a round pool placed in a square room. A different image, framed as a picture, was placed on each of the four walls. Two visible square platforms were placed in different quadrants of the pool (Figure 1). To navigate in the virtual pool, the subject pressed the left or right arrow key on a keyboard; forward motion was held constant by the computer program. For each trial, the subject began in a random starting location against the pool wall. Before the commencement of each trial, the subjects viewed a blank screen with a "+" reference point on the center of the screen for 2000 ms. Each block consisted of four trials during which the platform locations and distal cues remained constant. When the subject reached the incorrect platform, forward

motion would continue and the subject would appear to “swim through the platform”. When the subject reached the correct platform, forward motion would stop and the phrase “Platform Found” was presented on the screen.

Data acquisition

Data was collected using a 128-channel Geodesics dense-array sensor net and Net Station acquisition software (Electrical Geodesics, Inc., Eugene, Oregon). EEG data was recorded at 500 Hz with a high pass filter of 0.1 Hz and a low pass filter of 200 Hz. The Locator program from EMSI (Source Signal Imaging, Inc., San Diego, CA) was used in conjunction with Polhemus (Polhemus, Colchester, VT)to record the relative spatial location of each electrode for each subject.

Pre-Analysis Processes

The data files for each condition for each subject were concatenated. The data were down-sampled to 250 Hz to reduce memory demands during analyses and were then digitally filtered (low pass filter at 45 Hz) to minimize line noise artifacts and drifts using a zero-phase linear filter. Finally, the data were re-referenced to an average reference. Extracted data epochs were centered around the trial onset, when the subjects were presented with a first-person, color view of the pool situated in the virtual room. The epoch began 1000 ms prior to trial onset (when the subjects were viewing a blank, black screen) and terminated 2500 ms after the onset of the trial. The epochs and EEG channels were manually inspected using NetStation Acquisition software to discard those contaminated with non-stereotyped artifacts (e.g.,

muscle movement). (Trials containing stereotyped, repetitive movements, such as eye blinks, were not eliminated due to the limited number of trials available for analyses.) The files were then formatted for Matlab (Matlab 7.0.1, The Mathworks Inc., Natick, MA).

Data Analyses

The data for all subjects for both conditions was concatenated to create a single, large dataset. This provided a set of components that represented patterns of activity common across subjects or across groups. The dataset was then analyzed using Multiple Origin Spatio-Temporal Modelling for Electroencephalography (MOST-EEG, Zeman et al., 2007; Zeman, 2008). This software decomposed the dataset into components, using independent component analysis, projected the components onto a three dimensional volume using a modified LCVM Beamform algorithm and ranked the components along three dimensions: volume representation (voxel specificity of the volume domain), volume uniqueness (a measure of volume overlap) and quality of convergence (a measure of volume stability). Scalp topographies and volume representations of the top ranking components were visually inspected to determine which components were anatomically realistic. Three components were chosen for further analysis. Power measures (root mean square, RMS, values) for the pre-onset (-250 ms to 0 ms) and post-onset (0 to 250 ms) epochs were calculated across four frequency bands: theta (4 to 7 Hz); lower alpha (7.5 to 9.5 Hz), upper alpha (10 to 12 Hz) and gamma (36 to 44 Hz). Phase values were calculated at trial onset for each frequency bandwidth.

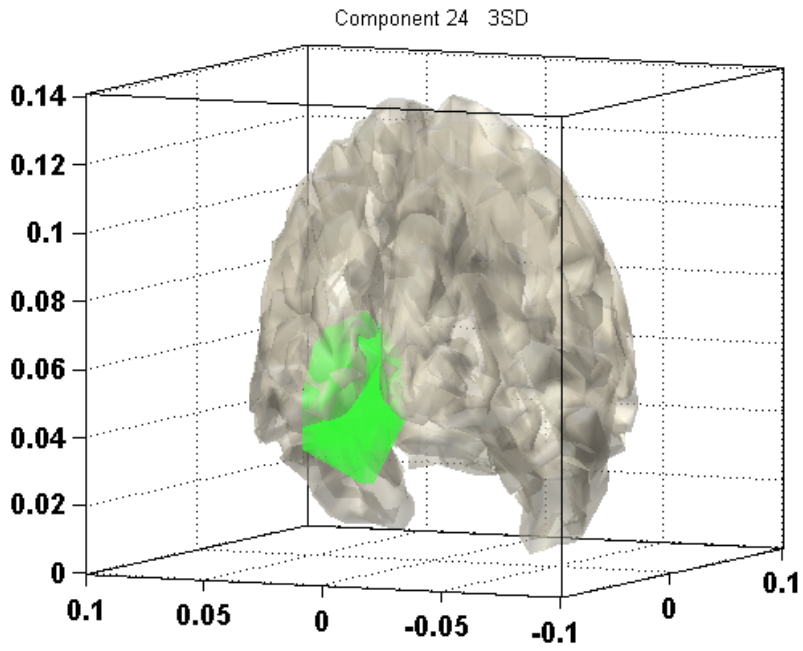
Statistical Analysis

Repeated measures ANOVAs were calculated using SPSS 16.0 ((SPSS, Inc., Chicago, Il.). "Group" was designated as the between-subjects factor while frequency (theta, lower alpha, upper alpha and gamma), components (three components), timing (pre-onset and post-onset epochs), and condition (place and cue) comprised the within-subject factors. Results were adjusted using the Huynh-Feldt Epsilon (H-F) correction factor.

RESULTS

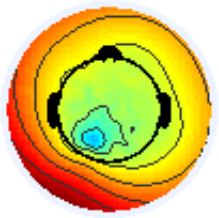
Figure 1 shows the topographical maps and volume projection of the three independent components. Component 24 and Component 52 localized to area V1 while Component 56 projected more laterally to the right hemisphere extra-striate cortex.

A

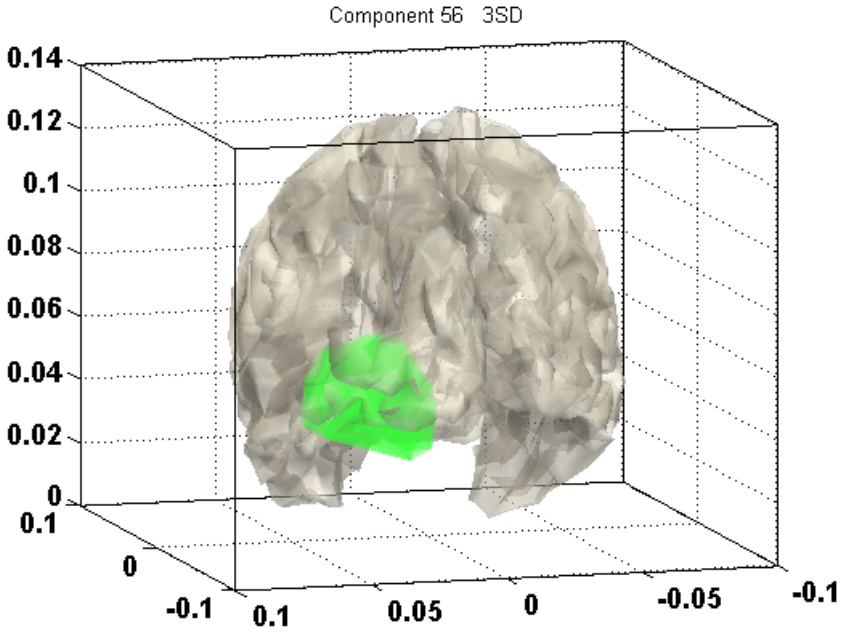


Component 24

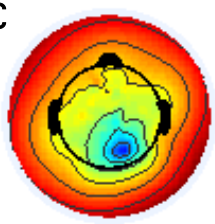
B



Component 56



C



Component 52

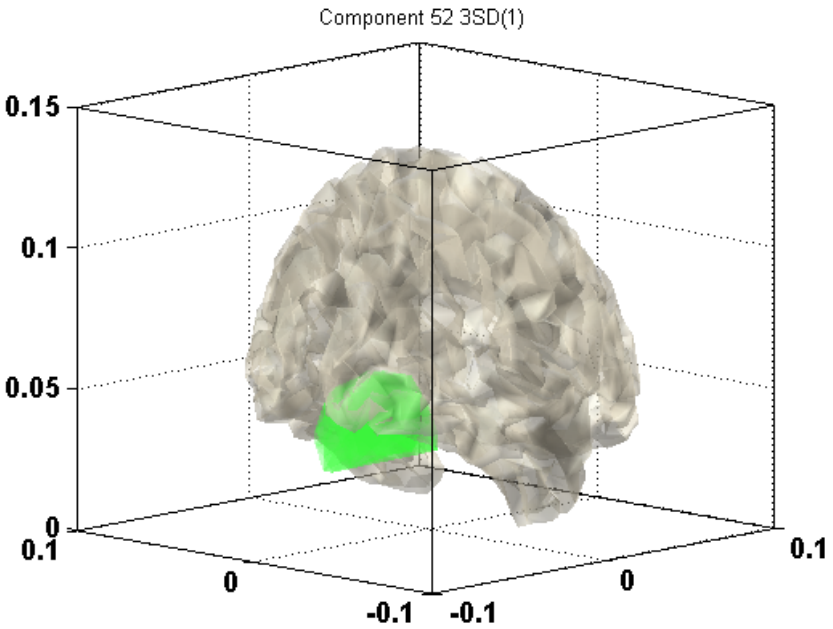


Figure 1. Scalp topographies and volume projection of three components. (A) Component 24 projected to area V1. (B) Component

56 projected to left occipital region. (C) Component 52 projected to right occipital region.

There was no significant between-subject effect of GROUP, $F_{(2, 27)}$ = 2.226, p = 0.127. There was a significant main effect, though, for Frequency, $F_{(1.870, 50.479)}$ = 7.730, p = .001 but not for Component or Timing. There was also no main effect of condition. This result was expected as the computer generated images for the place and cue trials were identical except for the colors of the platforms. (In cue trials, the platforms were different whereas in place trials, the platforms were identical.)

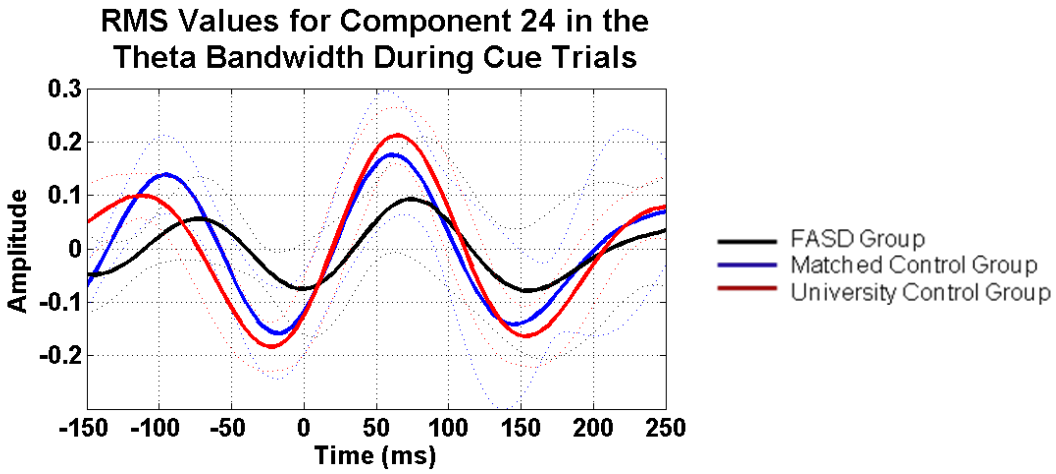
There were only two significant interactions among the within-subject factors, both which involved Frequency. A significant interaction was seen for Frequency X Component, $F_{(3.973, 107.282)}$ = 9.837, p = 0.000 and for Frequency X Condition, $F_{(2.820, 76.148)}$ = 4.232, p = 0.009. Figure 2 shows the waveforms of RMS values in the theta bandwidth for the place and cue trials.

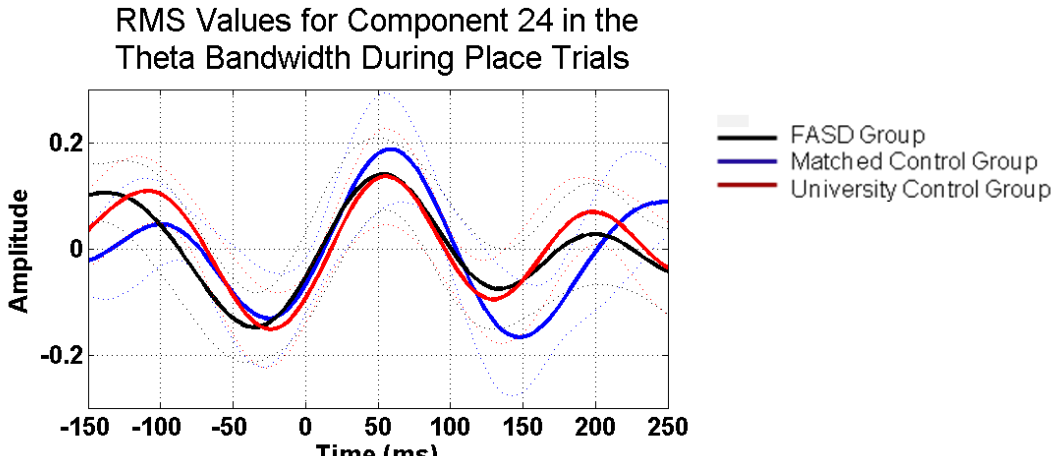
Mean RMS values for theta (M = 0.509, SE = 0.033) were significantly greater [$F_{(3.000, 25.000)}$ = 14.121, p = .000, Wilks' lambda] than mean values for the lower alpha, (M = 0.376, SE = 0.034), upper alpha (M = 0.365, SE = 0.039) and gamma (M = 0.366, SE = 0.039) frequency bands. The largest RMS values were recorded by Component 24, the primary visual sensory cortex, in the theta (M = 0.609, SE = 0.041), lower alpha (M = 0.434, SE = 0.045) and upper alpha (M = 0.398, SE = 0.038) frequencies. Component 52 displayed the largest RMS values in

the gamma (*M* = 0.407, *SE* = 0.045) but the lowest RMS values in the lower alpha (*M* = 0.332, *SE* = 0.029) and upper alpha (*M* = 0.326, *SE* = 0.032) frequency bands.

Pre-onset versus post-onset values displayed small differences. Pre-onset RMS values were slightly less than post-onset values in the theta (pre-onset *M* = 0.504, *SE* = 0.033; post-onset *M* = 0.515, *SE* = 0.034) and lower alpha frequencies (pre-onset *M* = 0.372, *SE* = 0.034; post-onset *M* = 0.380, *SE* = 0.034) but not in the upper alpha frequency band (pre-onset *M* = 0.373, *SE* = 0.041; post-onset *M* = 0.356, *SE* = 0.037). Pre- and post-onset RMS values for gamma were similar (pre-onset *M* = 0.369, *SE* = 0.040; post-onset *M* = 0.364, *SE* = 0.039).

A





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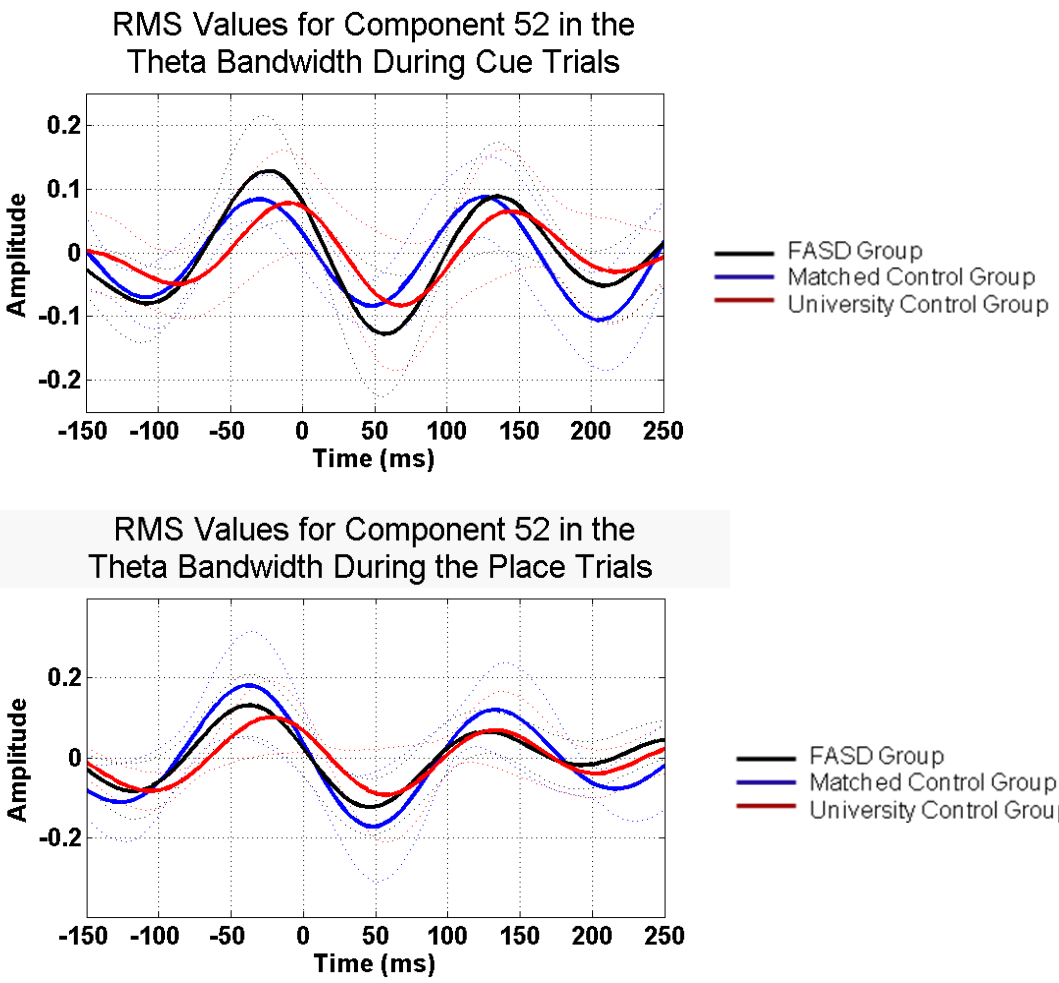
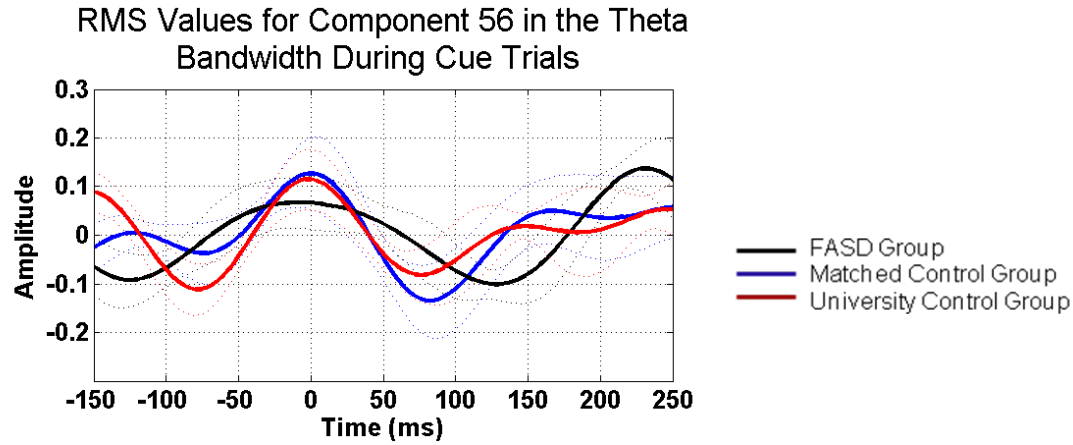

RMS Values for Component 52 in the Theta Bandwidth During Cue Trials
Amplitude
0.2
0.1
0
-0.1
-0.2
-150 -100 -50 0 50 100 150 200 250
Time (ms)
FASD Group
Matched Control Group
University Control Group
RMS Values for Component 52 in the Theta Bandwidth During the Place Trials
Amplitude
0.2
0
-0.2
-150 -100 -50 0 50 100 150 200 250
Time (ms)
FASD Group
Matched Control Group
University Control Group

C


RMS Values for Component 56 in the Theta Bandwidth During Cue Trials
Amplitude
0.3
0.2
0.1
0
-0.1
-0.2
-150 -100 -50 0 50 100 150 200 250
Time (ms)
FASD Group
Matched Control Group
University Control Group

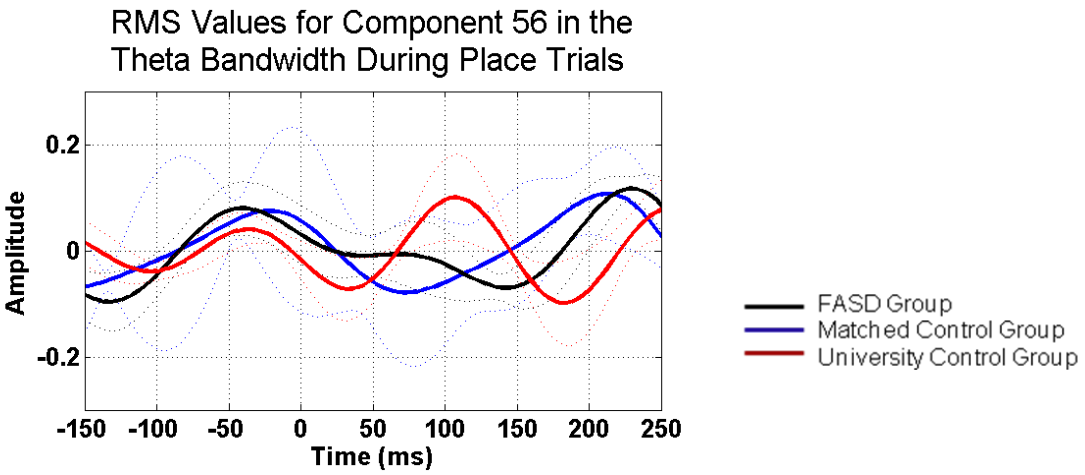


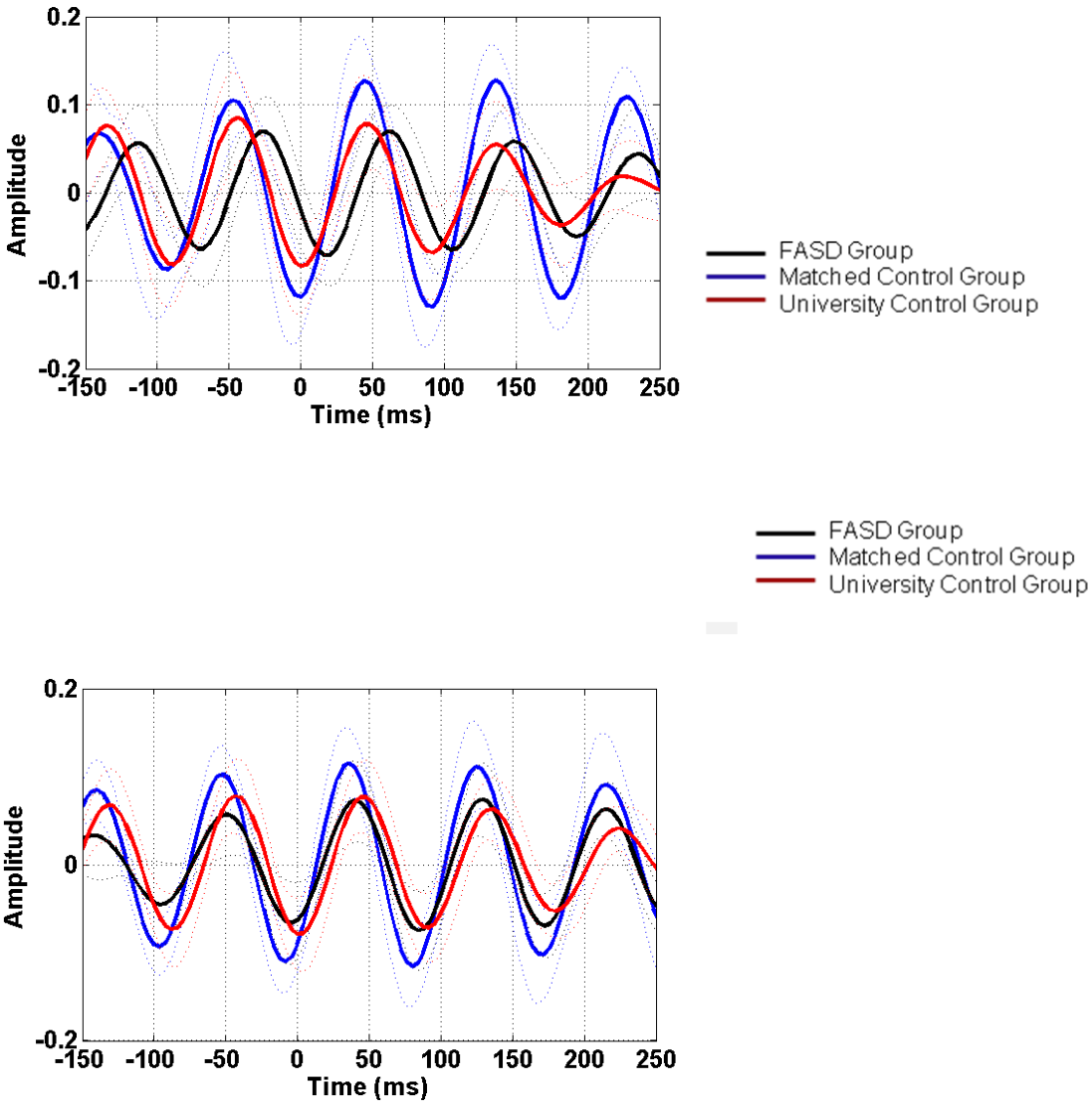
Figure 2. Comparison of theta RMS values for the three components projected to the occipital cortex. X-axis: time in ms centered at trial onset (0 ms). Y-axis: RMS values in μV. (a) RMS values for the cue and place trials for the three participant groups for Component 24. (b) RMS values for the cue and place trials for the three participant groups for Component 52. (c) RMS values for the cue and place trials for the three participant groups for Component 56.

Phase

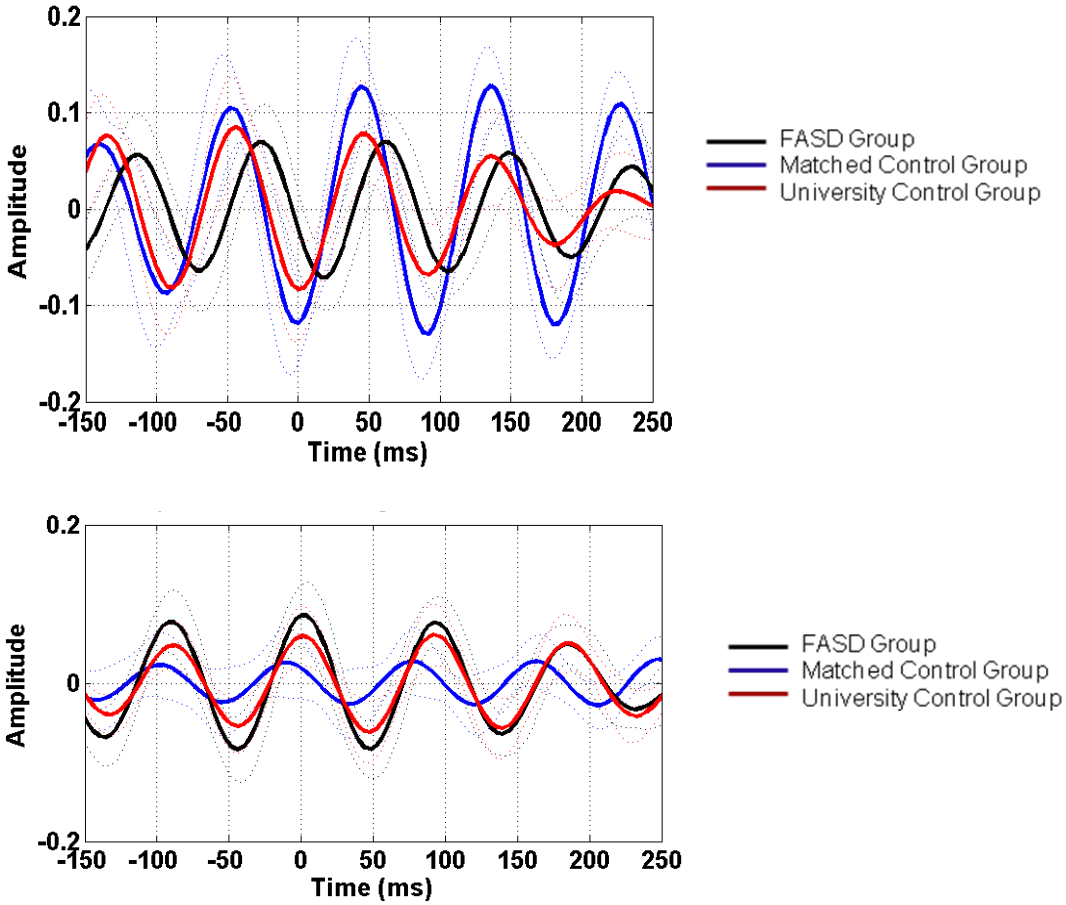
Although visual inspection of waveforms indicated that phase differences may be present (Figure 3), no significant effect for the between-subject factor, GROUP, was found, $F_{(2, 27)} = 0.656$, $p = .527$. As with the power measures, phase values differed significantly across the four frequency bands, $F_{(3.000, 81.000)} = 9.690$, $p = .000$. A pairwise comparison showed that theta phase values were significantly larger than those calculated for lower alpha, upper alpha and gamma.

A main effect of Components, $F_{(2.000, 54.000)} = 15.149$, $p = .000$, was recorded. Phase values for Component 24 were significantly larger than the phase values recorded for Component 52 and 56. Only one significant interaction effect was found, Frequency X Component $F_{(6.000, 162.000)} = 5.026$, $p = .000$. Component 24 phase values were greater within the theta, lower alpha and gamma frequency bands, while Component 56 phase values were larger than corresponding values for Component 52 within the theta, lower alpha and upper alpha frequencies.

A



B


0.2
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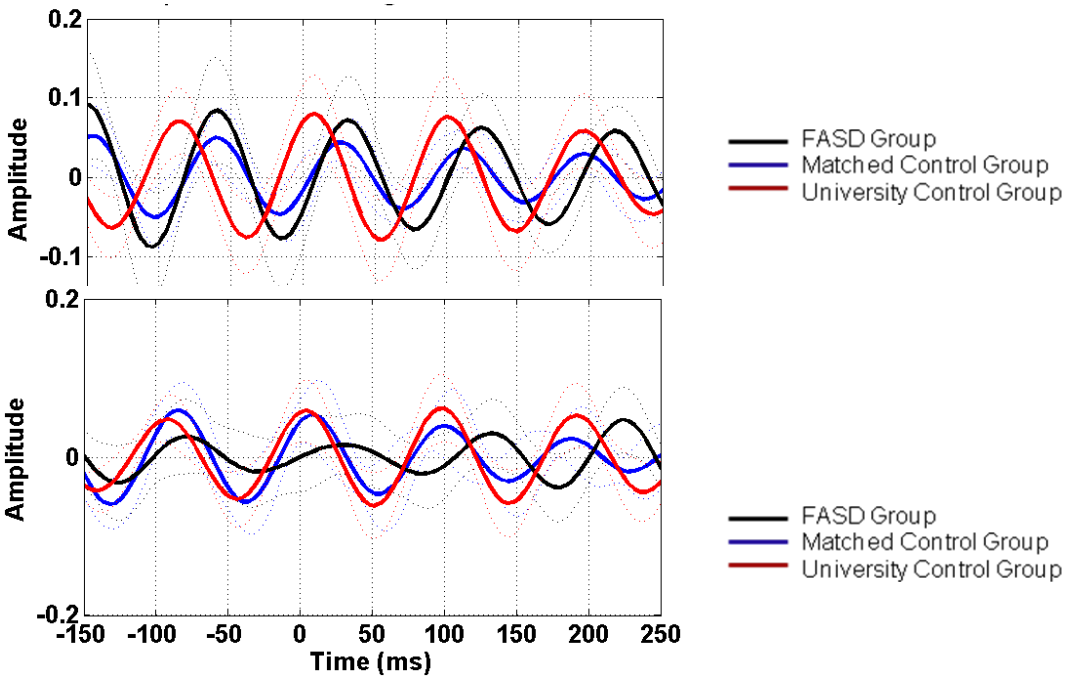
-0.1
-0.2
Amplitude
-150 -100 -50 0 50 100 150 200 250
Time (ms)
FASD Group
Matched Control Group
University Control Group
0.2
0
-0.2
Amplitude
-150 -100 -50 0 50 100 150 200 250
Time (ms)
FASD Group
Matched Control Group
University Control Group

C


0.2
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Amplitude
FASD Group
Matched Control Group
University Control Group
0.2
0
-0.2
Amplitude
-150 -100 -50 0 50 100 150 200 250
Time (ms)
FASD Group
Matched Control Group
University Control Group

Figure 3. Comparison of upper alpha RMS values for the three components projected to the occipital cortex. X-axis: time in ms centered at trial onset (0 ms). Y-axis: RMS values in μV. (a) RMS values for the cue and place trials in the upper alpha frequency band for the three participant groups for Component 24. (b) RMS values for the cue and place trials for the three participant groups for Component 52. (c) RMS values for the cue and place trials for the three participant groups for Component 56.

Discussion

Individuals diagnosed with mild to moderate FASD typically do not display the typical facial features associated with FAS. However, the effects of prenatal alcohol exposure on occipital functioning in individuals without the more severe diagnosis of FAS are unknown. This study evaluated processing in the occipital region at stimulus onset by individuals with the FASD.

Power (RMS) and phase measures confirmed no group differences across the FASD, matched control and university control groups for the three components projected to the occipital cortex. For both the cue and place trials, the initial image on the computer screen consisted of a virtual pool containing two visible platforms and a picture on each wall in the room. The expected result, of no main effect of condition, was confirmed.

The significant main effect of Frequency, with theta values being significantly larger than the other three frequencies, must be interpreted with caution. The larger values for theta, may reflect lower alpha values

typically associated with visual tasks rather than increased activation within the theta band. In addition, physiologically, theta waveforms display more power due to the longer time frame within which postsynaptic potentials can accumulate. However, this same rationale would predict that the power would gradually decrease in a stepwise manner across the four frequency bands. The mean RMS value for upper alpha, though, was larger than the values for lower alpha while mean RMS values for lower alpha and gamma were similar. One complication in interpretation involves the slightly larger frequency window for theta than lower and upper alpha, although the sizes of the frequency windows for lower and upper alpha were identical. Klimesch and colleagues (Klimesch et al., 2004; Gruber, Klimesch, Sauseng and Doppelmayr, 2005) have linked theta and alpha phase resetting with N1 and P1 waveforms. The theta and alpha results found here follow a similar pattern described by Klimesch and colleagues.

Overall, the FASD group displayed similar occipital waveform patterns to those of the matched control and university control groups. This implies that prenatal alcohol exposure resulting in less severe expressions of FASD does not affect primary visual processing within the occipital cortex.

8. PRENATAL ALCOHOL EXPOSURE, VIRTUAL MORRIS WATER TASK PERFORMANCE, AND TASK-RELATED EEG.

Chronic maternal consumption of alcohol leads to debilitating deficits in the developing fetus. Fetal alcohol syndrome (FAS), a disorder characterized by growth deficiency, distinctive craniofacial dysmorphology, and cognitive and behavioural impairments, has been extensively documented since first described by Lemoine and colleagues in 1968 (Lemoine et al., 2003) and Smith and Jones in 1973 (Smith & Jones, 1973).

The cognitive and behavioural deficits resulting from prenatal alcohol exposure are extensive (Streissguth et al., 1991, 1994; Olson et al., 1998; Kelly et al., 2000, Coles, 2001; Kodituwakku, Kalberg & May, 2001). Equivalent cognitive and behavioural impairments were reported in individuals with a history of chronic prenatal alcohol exposure but without the physical features associated with FAS (Mattson et al., 1997). Cognitive and behavioural dysfunctions have also surfaced in studies evaluating the effects of moderate or social drinking during pregnancy (Gusella & Fried, 1984; Streissguth, Barr & Sampson, 1990), although the effects were typically not as deleterious as those seen with higher levels of maternal alcohol consumption.

Central to many of the cognitive impairments are learning and memory deficits. The role of the hippocampus in learning and memory tasks has been well documented in both animal and human research (Milner, 1972; Squire, 1992), although the exact nature of the mechanisms underlying learning and memory are still contested. The

hippocampus has consistently been associated with the learning and memory of spatial and contextual information (White & McDonald, 2001; Silva et al., 1998; Eichenbaum et al., 1999).

Primate and rodent researchers frequently employ the Morris water task (MWT) as a routine behavioural protocol to evaluate hippocampal functioning. Numerous studies have reported that hippocampal-lesioned rats display an impaired ability to locate a hidden platform in the MWT paradigm (Morris et al., 1982; Burwell et al., 2004; de Bruin et al, 2001, Sutherland et al., 1983, 2001; Mumby et al., 1999; Wright et al., 2004). Medial prefrontal lesions also interfered with spatial navigation. However, this impaired performance was thought to reflect reduced behavioural flexibility when task demands or the appropriate strategy to complete the spatial paradigm were altered (de Bruin et al., 1994, 1997; Ethier et al., 2001; Compton et al., 1997; Granon & Poucet, 1995).

Prenatal alcohol exposure has been correlated with impaired performance on the MWT. Richardson and colleagues (2002) reported that guinea pigs subjected to chronic prenatal ethanol exposure took longer to learn the location of the hidden platform in the MWT. Impaired performance was also reported in rats exposed prenatally to ethanol by, for example, Blanchard and colleagues (1987), Gianoulakis (1990) and Kim and colleagues (1997).

Researchers have created virtual spatial navigation tasks for humans based on the Morris water task (Hamilton et al., 2003), virtual “tunnels” (Gramann et al., 2005), virtual T mazes (Bischof and Boulanger, 2003) and virtual “towns” (McGuire et al., 1998; De Araujo et al., 2002). Functional medical imaging studies have reported activation of temporal and frontal regions such as the posterior cingulate (Gron et al., 2000),

medial temporal lobe structures (Shelton & Gabrieli, 2002) and the parahippocampal gyri and right hippocampus during spatial navigation tasks (Gron et al., 2000; Hartley & Burgess, 2005; Iaria et al., 2003; Moffat et al., 2005; Parslow et al., 2004).

Although functional medical imaging studies, typically functional medical resonance imaging (fMRI), have investigated cortical activity during spatial navigation, the high temporal resolution seen with EEG and MEG would better capture the neural interactions. Despite the inherent advantages of EEG/MEG, investigation of human spatial navigation using EEG/MEG has been extremely limited. Consistent with findings from primate and rodent research correlating theta activity with spatial navigation, Bischof and Boulanger (2003) reported increased theta episodes when subjects viewed new hallways in a virtual T maze, or after navigational mistakes were corrected. De Araujo et al. (2002) required subjects to navigate through a computer-generated virtual reality town. They reported a peak frequency of theta oscillations during the two periods of navigation. Recording from intracranial electrodes implanted in patients with medically intractable epilepsy, Kahana, Caplan and Ekstrom (Kahana et al., 1999; Caplan et al., 2001, 2003; Ekstrom et al., 2003, 2005) evaluated theta activity during a multiple T-junction maze. They discovered theta oscillatory activity appeared during study and, more frequently, during test trials in “distinct, well defined episodes”.

Increases in theta have not been limited to spatial navigation. Theta power increases have been consistently reported during retention intervals in a variety of working memory tasks including the Sternberg (old/new) and n-back tasks. In these tasks, theta is hypothesized to reflect active maintenance of information in working memory. Increases

in theta power localized to frontal midline sites are correlated with tasks requiring sustained attention. Post-onset parietal increases in theta power have been associated with encoding and retrieval of episodic memory. These increases have successfully predicted later memory performance (Klimesch et al., 1996, 1997).

Alpha and gamma oscillations, although correlated with behaviours associated with learning and memory, have not been addressed during spatial navigation tasks. Originally, alpha was purported to represent "cortical idling" as widespread alpha power decreases topographically have been recorded at the onset of numerous test paradigms. In contrast, localized increases in alpha power, sometimes referred to as "event-related synchronization", have been reported. Several research groups (Klimesch et al., 1999; Jensen and Tesche, 2002; Sauseng et al., 2005) have reported increased alpha during the retention period in tasks where the subject must withhold a response until after the probe item is presented. Enhanced alpha has been hypothesized to reflect an inhibitory process that suppresses task-irrelevant processes or processes that might interfere with retention of the target information (Palva and Palva, 2007; Freunberger et. al., 2008).

Gamma research has principally focused on its role in object recognition, attention and working memory. One prevailing hypothesis attributes "binding", the construction of object representations, to synchronous gamma activity (Tallon-Baudry & Bertrand, 1999; Ross et al., 2006). Bastiaansen and Hagoort (2006) summarized language comprehension research and concluded that gamma synchrony represented the "unification of lexical information" (phonological,

syntactic and semantic information). Fan and colleagues (2007) proposed that gamma activity reflected the orienting (attention) network whereas Summerfield and Mangels (2006) linked gamma with top-down attentional processes. Although other authors (Jokisch and Jensen, 2007; Sederberg et al., 2003; Gruber et al., 2004) have identified gamma as necessary for successful encoding, gamma has also been linked with rehearsal or "neuronal maintenance of the [visual] representation" (Jokisch and Jensen, 2007). Gamma has not been investigated in a spatial navigation task.

Phase and cross-frequency phase synchronization (multiplexed oscillations; Lisman, 2005) have been reported for theta and alpha during memory tasks (Klimesch et al., 2004), for theta and gamma during word processing (Canolty et al., 2007), and for alpha and gamma during working memory and for object representation (Palva and Palva, 2007). Rizzuto and colleagues (Rizzuto et al., 2003)reported preferential phase reset in intracranial electrodes located in the right parietal lobe, and the inferior temporal lobe and occipital lobes upon presentation of test and probe items respectively, in the Sternberg recognition task. Using intracranial depth recordings from epileptic patients, Fell and colleagues (Fell, Ludowig, Rosburg, Axmacher & Elger, 2008)reported that phase-locking successfully predicted memory performance on a continuous word recognition experiment.

A limited number of studies of cortical functioning using electroencephalography (EEG) have been completed with individuals with FASD (for a review, please refer to D'Angiulli et al., 2006). Mattson and colleagues (1992) reported EEG data from two case studies. The authors found "dominant theta rhythms" and delta bandwidth activity for both

FAS children. These two subjects also displayed reduced cortical volumes and corpus callosum abnormalities. Not surprisingly, the authors reported severe cognitive deficits for both children. Kaneko and colleagues (1996) completed a passive, auditory "oddball-plus-noise" paradigm with children with FAS and Down syndrome. They stated that the FAS children displayed significantly longer P300 latencies in the parietal region than either the Down syndrome or the control children. They also reported that reduced theta and alpha power in the resting EEG identified the FAS children. In contrast, the N100, which is thought to be an indicator of attention, did not differ between the FASD and control groups. Differences in the contingent negative wave (CNV), an indicator of anticipation of an expected event, have also been examined. Although Buffington and colleagues' (1981) results did not reach statistical significance, they reported that eight of the ten control children displayed the CNV whereas the CNV was only evoked in four of the ten FAS children. Spohr and Steinhausen (1987) presented data showing inconsistency within the FAS population. Just over half of the 72 FAS children in the study (56%) displayed "normal" EEG activity. Following "rehabilitation measures", 45 of the FAS were reassessed 3 to 4 years later. The number of children with "normal" EEG activity increased to 71%.

Currently, there are no known published EEG data relating to fetal alcohol spectrum disorders and spatial navigation. Nor has EEG data been investigated in adults with a diagnosis of mild to moderate FASD.

We hypothesized that abnormal cellular functioning, resulting from damage caused by prenatal alcohol exposure, will be detected as

abnormal oscillatory patterns in the EEG. Given the research relating the hippocampus, spatial navigation and the theta bandwidth, and given the animal and human research describing hippocampal damage as a consequence of prenatal alcohol exposure, we hypothesized that individuals with mild to moderate FASD would display abnormal theta waveforms while completing a spatial navigation task, the virtual Morris water task (vMWT).

The behavioural phenotype of FASD implicates impaired functioning of the prefrontal cortex. Attentional and working memory deficits are well-documented with this population, even though MRI studies have not shown the prefrontal cortex to be disproportionately affected. As a result, we predicted abnormal waveforms or reduced mean power in the alpha and gamma bandwidths within the temporal and prefrontal regions.

Methodology

Participants

The home visitation program of the Chinook Health Region referred 9 females with a diagnosis of FASD and 10 female matched control subjects. The FASD control subjects were matched to the FASD subjects with respect to age, educational background, socioeconomic status, history of abuse, and past and current drug and alcohol use. Informed consent was obtained from each subject. Eleven female, right-handed university students from the University of Lethbridge participated in this study. Approval for this experiment was granted by the ethics committee of the University of Lethbridge, Alberta, Canada.

Neuropsychological Assessment

A complete neuropsychological assessment was administered to the FASD and matched control groups as described earlier in this report.

EEG Task Protocol

For the visible platform version of the virtual Morris Water Task (vMWT), the subjects were required to remember the location of a platform in a virtual pool by orienting themselves to either the color of the platform (nonspatial cue condition) or to the location of the platform relative to pictures on the walls of the virtual pool room (spatial place condition; Figure 1). Subjects were seated comfortably approximately 180 cm from a Dell Trinitron 40 cm CRT computer screen. Before the commencement of each trial, the subjects viewed a blank screen for 2000 ms. The trial commenced at 0 ms, with the subject moving forward in a first person virtual environment.

The virtual environment consisted of a round pool placed in a square room. A different image, framed as a picture, was placed on each of the four walls. Two visible square platforms were located in different quadrants of the pool (Figure 1). To navigate in the virtual pool, the subject pressed the left or right arrow key on a keyboard. The participants moved forward through the pool at a constant pace controlled by the computer program. For each trial, the subject began in a random starting location along the pool wall. Each block consisted of four trials during which the platform locations and the distal cues on the four walls remained constant. When the subject reached the incorrect platform, forward motion would continue and the subject would appear to "swim through the platform". When the subject reached the correct

platform, forward motion would stop and the phrase “Platform Found” was presented on the screen.

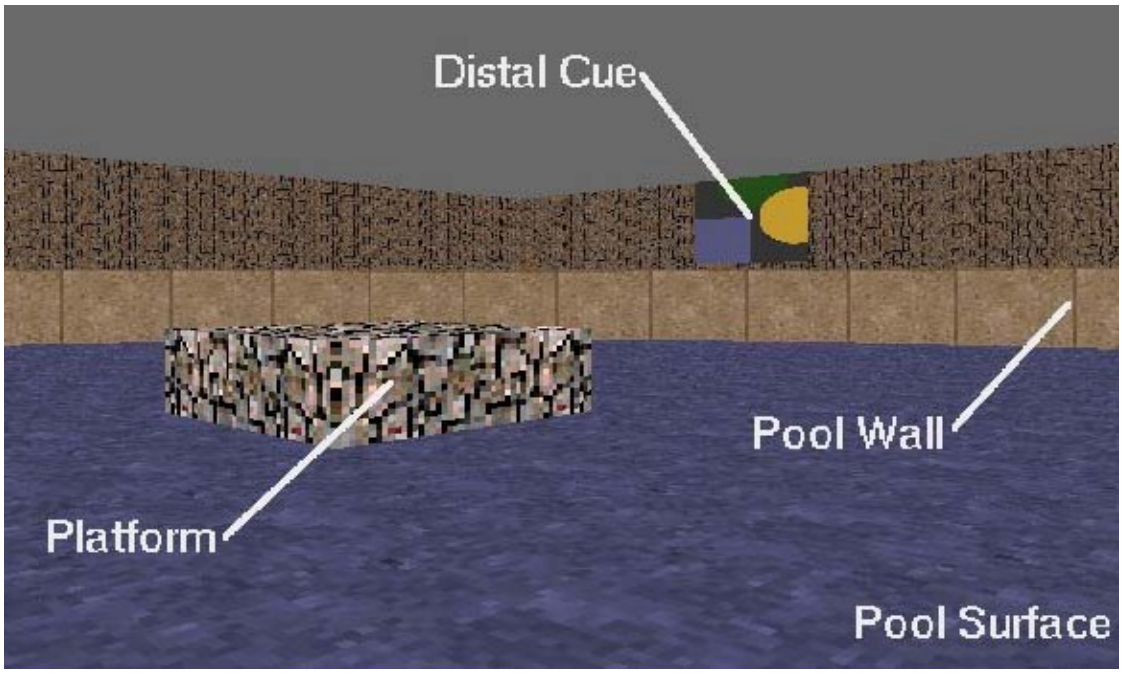


Figure 1: A sample view of the virtual Morris Water Task (vMWT).

During the place condition, the two platforms were visually identical while in the cue condition, the platforms displayed visually distinct color patterns. For the first presentation (trial one), the subjects were required to look around the room and then pick one platform and swim towards it. If that was the incorrect platform, they were to then swim to the second platform. For the second, third and fourth trials of each block, the subject had to remember the location (place trials) or color pattern (cue trials) of the correct platform. To lessen the use of unknown or idiosyncratic strategies, subjects were specifically instructed to look at

the distal cues during the place trials and determine where the correct platform was in the pool in relation to those cues. They were also told to focus on the color of the platform during the cue trials. The word "Place" was presented on the screen at the beginning of each place condition block. The word "Cue" was presented on the screen at the beginning of each cue condition block. Participants were given practice trials until she displayed an understanding of the task. Participants completed 20 blocks of each condition. Different distal images and platform colors were randomly created for each subsequent block. Place and cue conditions alternated throughout the session. Accuracy and latency to the correct platform were collected for all trials.

Data Acquisition

Data was collected using a 128-channel Geodesics dense-array sensor net and Net Station acquisition software (Electrical Geodesics, Inc., Eugene, Oregon). Data was initially recorded at 500 Hz with a high pass filter of 0.1 Hz and a low pass filter of 200 Hz but later downsampled to 250 Hz to reduce memory demands during analysis. The data for each participant was average referenced, segmented into epochs centered on the onset of each trial (-1000 to 2500 ms) and band-pass filtered from 1.0 to 50 Hz. Trial one from each block was omitted from data analysis as, during that trial, the subjects found the correct platform by chance. All epochs for each subject for trials two, three and four, were manually inspected to discard those contaminated with non-stereotyped artifacts. Artifacts due to eye and muscle movement were removed using Independent Component analysis (ICA), following the procedure described by Makeig and colleagues (Delorme et al., 2004; Jung et al., 2000, 2001). Twenty-nine trials per subject for each condition were included

for analysis. Three of the subjects from the FASD and matched control groups had fewer trials included (23, 26 and 27 trials) due to fewer accurate responses and/or more contaminated epochs.

Data files for all participants were concatenated to create a common dataset for analysis. Using Multiple Origin Spatio-Temporal Modelling for Electroencephalography (MOST-EEG, Zeman et al., 2007; Zeman, 2008), the dataset was decomposed into independent components. The components were projected onto a three dimensional volume using a modified LCVM Beamform algorithm. The components were then ranked along three dimensions: volume representation (voxel specificity of the volume domain), volume uniqueness (a measure of volume overlap) and quality of convergence (a measure of volume stability). Three components were chosen for further analysis.

Power measures (root mean square values) for the pre-onset (-250 ms to 0 ms) and post-onset (0 to 250 ms) epochs were calculated across four frequency bands: theta (4 to 7 Hz), lower alpha (7.5 to 9.5 Hz), upper alpha (10 to 12 Hz) and gamma (36 to 44 Hz). A repeated measures ANOVA was conducted using the between-subject factor of GROUP (FASD, Matched Controls and University Controls), and within-subject factors of Frequency (theta, lower alpha, upper alpha and gamma), Components (C1, C2, C3), Condition (cue, place), and Timing (pre-onset, post-onset). The phase measures were determined by calculating the phase in radians (0 to 2pi; 2 pi [2π] radians = 360 degrees) at trial onset. For the phase measures, a repeated measures ANOVA was conducted using the between-subject factor of GROUP (FASD, Matched Controls and University Controls), and within-subject factors of components (C1, C2 and C3), condition (cue, place) and

frequency (theta, lower alpha, upper alpha and gamma). All significance levels were set at $p = .05$. Huynh-Feldt corrections were used throughout the analyses.

Results

Neuropsychological Results

The FASD and matched control groups tested in the vMWT scored within two standard deviations of published test means for the WAIS verbal, performance and full scale intelligence quotients and for the WMS working and general memory indices. These results demonstrate that the two groups displayed within average intelligence and memory as measured using formal, structured tests.

The neuropsychological test results were analyzed using a repeated measures ANOVA (SPSS 16.0). Significant main effect for GROUP, $F_{(1, 19)} = 5.082$, $p = .035$, and for the within-subjects factor, Test, $F_{(5.271,110.686)} = 613.836$, $p < .001$, were obtained. There were no significant interactions.

One-way ANOVAs completed on the within-subject factor, Test, showed that the performance intelligence quotient from the WAIS-III (WAISPIQ)and the recall scores of the Rey-Osterrieth Complex Figure Test were significant (WAISPIQ: $F_{(1,17)} = 7.876$, $p = .011$; Recall: $F_{(1,17)} = 4.814$, $p = .040$). Although the WAISPIQ means were within average for the test norms, the score was lower for the FASD group ($X = 97.33$, $SD = 12.507$) than for the matched control group ($X = 111.45$, $SD = 11.536$). The FASD group also scored lower on the Rey-Osterrieth recall ($X = 13.42$, $SD = 7.489$) than the matched control group ($X = 19.73$, $SD = 6.166$). All other test scores were non-significant.

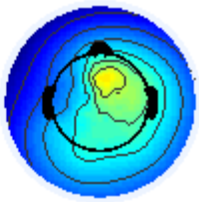
Behavioural Results

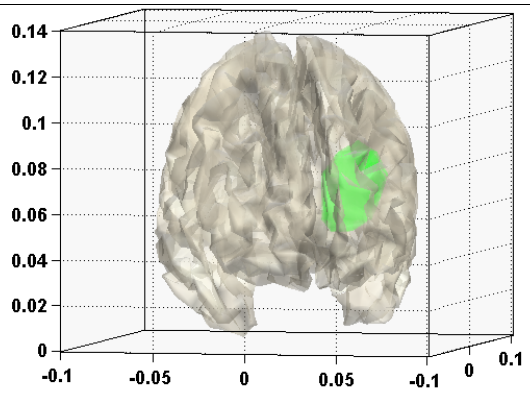
All three groups obtained similar accuracy rates for the cue, $F_{(2,26)}$ = 1.699, p = 0.203, and place, $F_{(2,26)}$ = 0.976, p = 0.390, conditions. Latency to the correct platform was also statistically nonsignificant for the three groups (cue: $F_{(2,26)}$ = 2.217, p = 0.129; place: $F_{(2,26)}$ = 1.375, p = 0.271). The FASD and matched control groups, therefore, were competent at both the cue and place conditions of this version of the vMWT.

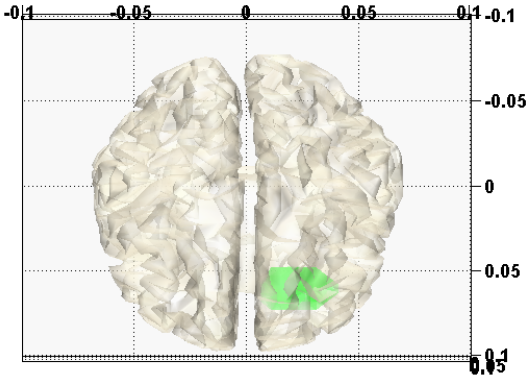
EEG Results

No components, potentially representing temporal lobe, met the criterion cut off of a "good" component. The components either did not demonstrate appropriate volume representation, as the projected volume was not restricted to the temporal lobe region, did not demonstrate volume uniqueness, as the projected volume displayed significant overlap with adjacent components, or did not demonstrate convergence, indicating the projected volume was not well-defined. Three components, whose volumes were represented within the prefrontal regions, were chosen for further analyses: Component 1 (C1) had been projected to the anterior portion of the cingulate cortex, component 2 (C2) to the right, lateral middle frontal gyrus, and component 3 (C3) to the left, lateral middle and inferior frontal region (Figure 1).

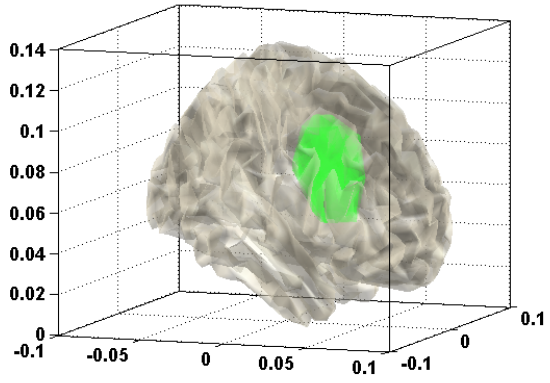
A Component 1







B Component 2



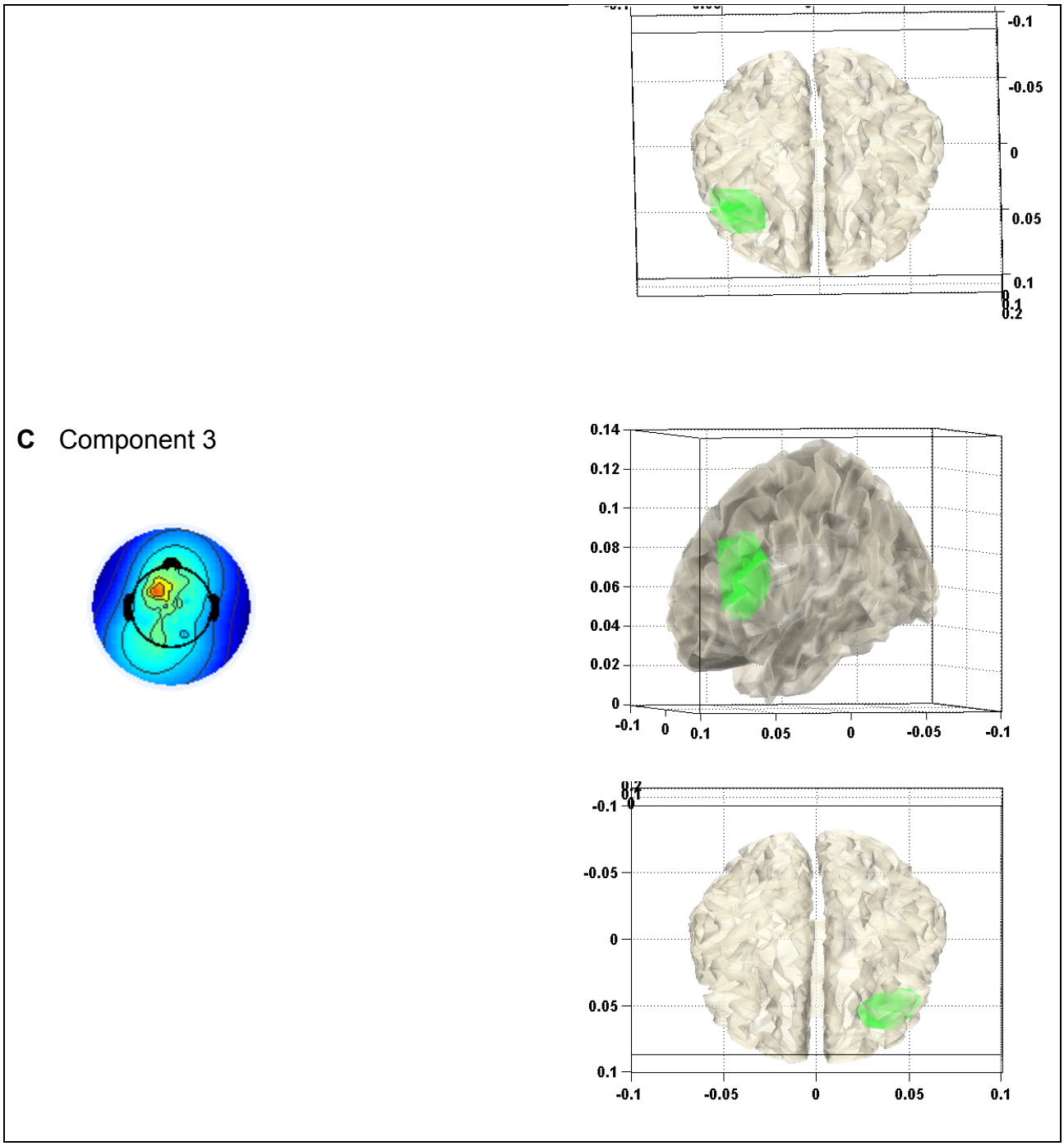


Figure 2. Scalp topographies (left) and Beamform volume projections (right) for the three components. (A) Component 1, (B) Component 2 and (C) Component 3.

Amplitude.

Visual inspection of the waveforms indicated that the amplitudes of the components would not distinguish among the three groups (Figure 3). For example, within the upper alpha frequency bandwidth for C1, amplitudes were similar for the matched control and university control groups in the cue condition(Figure 3a) and for the FASD group and the matched control group in the place condition (Figure 3b). The repeated measures ANOVA confirmed no significant main effect of GROUP, $F_{(2, 27)} = 2.032$, $p = .151$.

The within-subjects factor of Frequency was significant, $F_{(1.685, 45.482)} = 22.503$, $p = .000$, as was the within-subjects factor of Component, $F_{(1.646, 44.449)} = 4.671$, $p = .020$). No main effects were recorded for Condition and Timing. A stepwise comparison of Frequency indicated that theta RMS values were the largest ($X = 0.569$, $SE = 0.034$) and differed significantly from the other frequency bands (Least Significance Difference $p = .000$ for all three comparisons). Lower alpha RMS values and upper alpha RMS were significantly different from each other (LSD $p = .000$) but not from gamma RMS values (lower alpha: $X = 0.376$, $SE = 0.032$; upper alpha: $X = 0.331$, $SE = 0.032$; gamma: $X = 0.353$, $SE = 0.035$). C1, the component projected to the anterior cingulate, displayed the largest RMS value ($X = 0.454$, $SE = 0.037$), followed by C3 ($X = 0.405$, $SE = 0.025$) and C2 ($X = 0.364$, $SE = 0.032$). A pairwise comparison indicated that the RMS values between C1 and C2 were significant (LSD $p = .023$) but the difference between C1 and C3 and between C2 and C3 were not significant.

A significant interaction, Frequency X Component, was also seen, $F_{(2.657, 71.749)} = 16.171$, $p = .000$. C1 displayed the largest RMS values in the theta, lower alpha and upper alpha frequency bands (theta: $X = 0.676$, $SE = 0.049$; lower alpha: $X = 0.451$, $SE = 0.050$; upper alpha: $X = 0.391$, $SE = 0.050$) while C2 displayed the largest gamma RMS value ($X = 0.391$, $SE = 0.061$). There were no significant interactions among the within-subjects factors and no significant interactions between the within-subject factors and GROUP.

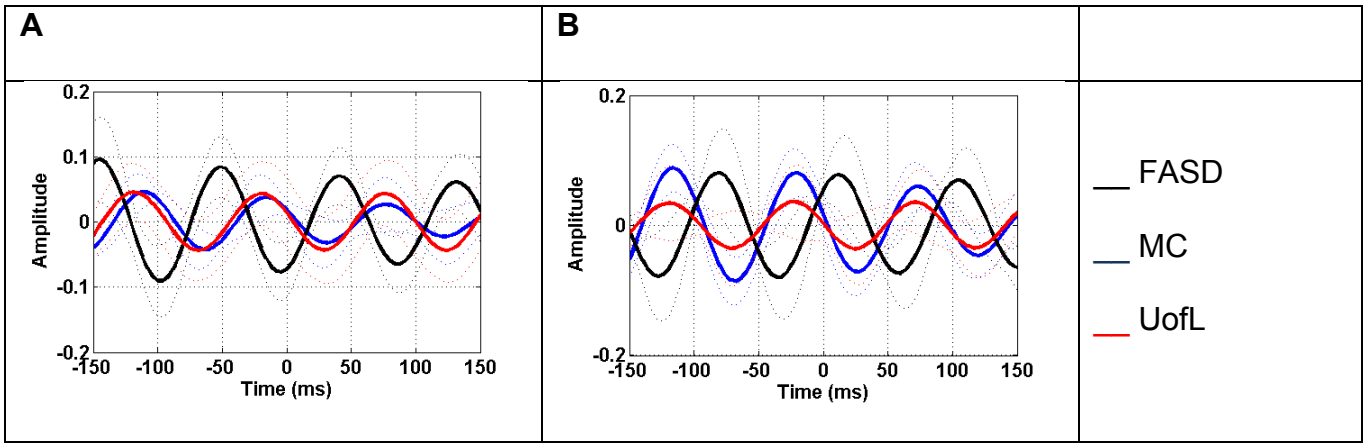
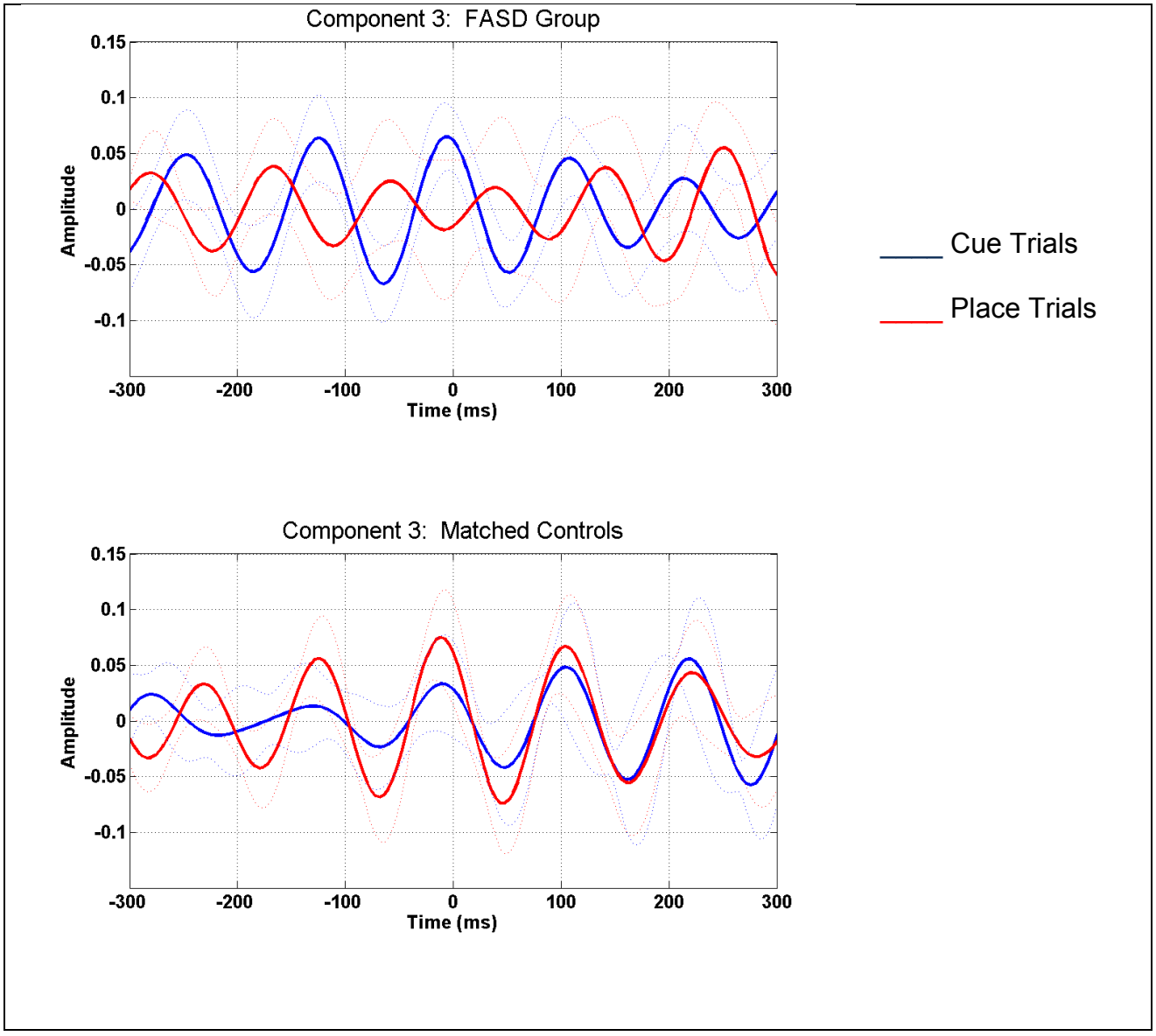


Figure 3. Waveforms for component 1 in the upper alpha frequency from -150 ms to 150 ms trial onset. Black = FASD group, blue = matched control group, red = university control group (a) cue trials; (b) place trials

Phase.

Although visual inspection of the waveforms indicated a potential phase effect (for example, Figure 4), no significant main effect for component, frequency or condition were found. There was no main effect

found for the between-group factor GROUP. Not surprisingly, no significant interactions were recorded.



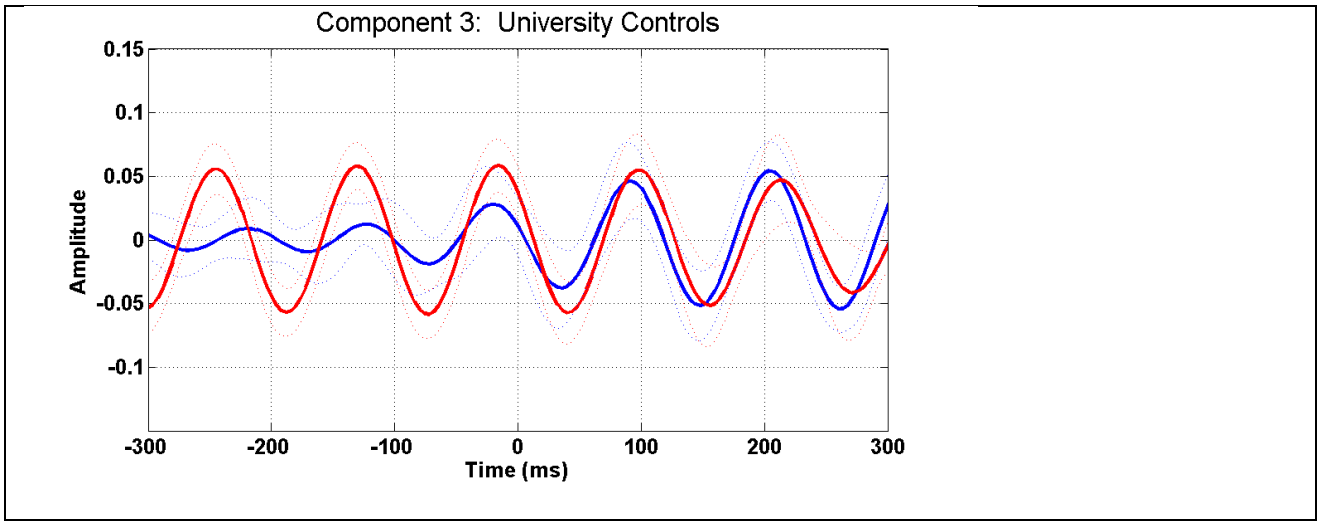


Figure 4. Waveforms of place and cue trials for Component 3, lower alpha frequency band, from -300 to 300 ms trial onset for the FASD, matched control and university control groups. A change in phase oscillation prior to onset of cue trials is visible in the waveforms for both control groups. Blue = cue trials, red = place trials.

Discussion

Significant effects of frequency (with theta being statistically significant from the other frequencies) and components (with an emphasis on the component projected to the anterior cingulate) were found in this study. Frontal theta has been associated with attention and memory processes, such as updating working memory and sustaining attention during maintenance periods in working memory tasks (Deiber et al., 2007; Krause et al., 2000; Missonnier et al., 2006). The lack of group differences in the behavioural results and the WMS–III results would support an interpretation of similar attention to task or working memory skills during the vMWT among the three groups.

This study examined a control group that was matched on many more factors than just age, educational level and socioeconomic status.

Individuals from the matched control group were enrolled in the same program at the Chinook Health Region as the individuals with FASD as they also had difficulty with daily living skills, managing finances, obtaining and maintaining employment and providing an appropriate home environment for their children. Although the waveforms from the components evaluated for the matched control group did not always resemble those obtained for the FASD group, there were enough similarities that the main effect of GROUP was nonsignificant. This may imply that the results were more indicative of underlying disabilities, such as a learning disability or attention deficit disorder, that affected members of both the FASD group and the matched control group. In addition, the matched control group typically displayed greater variability across subjects than the other two groups as evidenced by the larger standard deviations. This would also reduce the ability of the task and the analyses to distinguish between the FASD and matched control groups.

Although frontal theta activity was seen during the vMWT trials, hippocampus/temporal lobe theta could not be depicted from the results of this study. Some animal research studies have reported that hippocampal-lesioned rats display an impaired ability to locate a hidden platform whereas they display an unimpaired ability to locate the visible platform in the MWT paradigm (Burwell et al., 2004; Sutherland et al., 1983; Sutherland et al., 2001; Wright et al., 2004). In addition, animal and human research correlates low and moderate levels of prenatal alcohol exposure with abnormal hippocampal functioning, albeit at a more subtle level. By extension, deficits in spatial memory may not be evident unless the spatial task challenges the hippocampal system to a greater

degree. In line with this hypothesis, Sutherland, McDonald and Savage (2000) reported that rats exposed to a moderate level of prenatal ethanol did not exhibit impaired performance on the standard (fixed platform) version of the MWT. However, with a more challenging, moving platform version of the MWT, the ethanol group displayed abnormal performance in relation to the control groups.

The visible platform version of the vMWT in this study was chosen to ensure that the FASD subjects could successfully complete enough trials to compare with successful completion by the control groups. During initial trials with the standard (invisible platform) version of the task, the FASD subjects became frustrated and refused to continue the task, or, more commonly, would simply wait in the virtual pool for the platform to appear at the end of each 60 second trial. In addition, a female participants have, in general, significantly more difficulty with the standardized version of the vMWT than males (Astur, Ortiz & Sutherland, 1998; Astur, Tropp, Sava, Constable & Markus, 2004; Mueller, Jackson & Skelton, 2008). It would have been difficult to decipher differences in waveforms and projected volumes attributable to gender effects, effects of prenatal alcohol exposure or effects of nonspatial strategies (such as waiting for the platform to reappear).

However, the task presented in this study may have been too simplified. First, as the accuracy rate was similar for all three groups, the demands of the visible platform version of the Morris Water Task may not have been sufficient to result in differing theta activations across treatment groups. Secondly, although the participants were specifically instructed to use the distal cues on the walls to remember the location of the platform, the visible platforms limited the amount of search behavior

needed to complete the task. The participants may have been able to use a single picture or landmark to correctly remember the location of the platform in the place trials. This would have reduced the place trials to a "nonspatial" trial and hence, eliminated differences in strategy and cognitive processing between the cue and place trials.

Although tempting, it would be premature to conclude that prenatal alcohol exposure associated with less severe forms of FASD does not affect cognitive functioning during spatial navigation. As the data from all three groups were concatenated prior to ICA analyses, the methodology favored components that were common to all three groups. This analysis more likely evaluated whether individuals with FASD displayed differences in components that were active in control groups. As such, it reflected whether FASD individuals differed in "degree" and not if FASD individuals displayed compensatory or unique activations. Components that may have been specific to only one group, such as the FASD group, may not have had strong enough RMS values to be classified as a viable component. As such, an alternate explanation, that the FASD group (and perhaps the matched control group) did not display strong temporal activation during the task, may also account for the lack of components whose volume projected to the temporal regions. Therefore, the next step in the analysis is to analyze the FASD group and compare the components or patterns predominant in the FASD group against the matched control and university control groups.

9. PRENATAL ALCOHOL AND SPATIAL WORKING MEMORY PROJECT

Working memory is frequently typified as the encoding, maintenance, manipulation and retrieval of information. A common working memory paradigm is the n-back task where the participants are required to encode and maintain an item in memory, encode and maintain a subsequent item(s) and match the current item with the prior items presented. Research focusing on working memory has yielded a labyrinth of neuroanatomical regions and neurophysiological processes dependent upon the modality, levels of complexity and functional processes evaluated.

Neuroanatomy of Working Memory

Published research does, however, consistently converge on the frontal and parietal regions (Levy and Goldman-Rakic, 2000; Owen et al., 1996; Smith and Jonides, 1999; Suchan, 2008; Thomas et al., 1999; Wagner et al., 2001), although the exact nature of the anatomical and functional framework for working memory remains elusive. In a meta-analysis of 24 neuroimaging studies employing the n-back paradigm, Owen and colleagues (2005) reported numerous cortical regions routinely activated across all studies: lateral and medial premotor cortex, dorsal cingulate, dorsolateral and ventrolateral prefrontal cortices, frontal poles, and medial and lateral posterior parietal cortices. Researchers have attempted to attribute varying functions to these reported cortical regions. For example, in a meta-analysis of neuroimaging studies completed by Wager and Smith (2003), the authors summarized that the superior frontal cortex was activated when working memory had to be

continuously updated, the (right) ventral frontal cortex responded during situations requiring manipulation or during dual-task situations, while the posterior parietal cortex was activated in a variety of "executive functions". Finally, they correlated activation of the medial prefrontal cortex with "selective attention to features of a stimulus" that was to be stored in working memory. In a similar vein, Wolters and Raffone (2008) localized error monitoring within the medial regions of the prefrontal cortex (PFC), goal directed behavior to the lateral and anterior PFC and processing of reward and affective information to the ventromedial and orbitofrontal regions. The parietal cortex has been linked with retrieval-related activity and task relevance (Vilberg & Rugg, 2008). In addition, top-down versus bottom-up attentional processes are attributed to the superior and inferior parietal lobes respectively (Cabeza, 2008; Ciaramelli et al., 2008).

More recently, researchers have altered their concept of working memory localization to acknowledge not only the networks or recurrent loops of activation (i.e., Ranganath et al., 2005; Ranganath, 2006), but also the differing patterns of activation with increasing cognitive demands (such as increased memory loads during n-back paradigms). Du Boisgueheneuc and colleagues (2006) reported that although some cortical regions, such as the left superior frontal gyrus, favored a specific domain (e.g., verbal versus spatial), these same regions could be engaged regardless of the modality when cognitive demands increased. Similarly, Volle and colleagues (2008) concluded that although the left posterior lateral prefrontal cortex was domain specific, it was also critical for higher levels of cross-domain "executive" control. This dual-function ability

could reflect Duncan's (2001) proposed "adaptive coding" model, where neurons in the prefrontal cortex adapt or adjust to different kinds of input from different cortical regions in order to complete the task presented.

Electrophysiology of Working Memory

McEvoy, Smith and Gevins (1998) evaluated spatial and verbal versions of a visual n-back task while recording evoked potentials and ongoing electroencephalographic (EEG) data. They interpreted the midline central P250, larger in spatial tasks and larger to nonmatching trials, as reflecting memory for updating or comparing the spatial attributes of target stimuli. In contrast, they concluded that the parietal P300, sensitive to memory load but not task domain (verbal versus spatial), reflected a common underlying component, such as maintenance or rehearsal. Slow waves originating from the left frontal and right parietal cortex, again, sensitive to task load but not to modality, were interpreted as representing higher-order attentional demands of the task such as sustained attention during the maintenance period between successive stimulus presentations.

Watter and colleagues (2001) credited different cognitive functions to the P300 peak during a spatial n-back task. They described a constant P300 peak latency but an inversely related peak amplitude in relation to memory load. The authors attributed the decreasing amplitude with increasing memory load to a reallocation of attention and processing capacity away from the task of stimulus matching to working memory.

Several groups of researchers evaluated ongoing EEG data within frequency bands during n-back tasks. Differing patterns of activation across frequency bands were associated with reaction time, target versus non-target stimuli and memory load (e.g., Pesonen et al., 2007). In a

verbal n-back paradigm, Deiber et al. (2007) recorded evoked theta phase-locked to the stimuli in the parieto-occipital region for all tasks while induced theta was recorded in the frontal region. In addition, the authors reported sustained theta and beta activity within a frontal and parietal topographical distribution (respectively).

In a letter n-back task, Krause and colleagues (2000) noted that increased memory load was associated with anterior event-related synchronization (ERS) in theta and low alpha frequency bands. Gevins, Smith & McEvoy (1997) recorded increased frontal midline theta, localized to the anterior cingulate, with increasing memory load, regardless of whether the stimuli were verbal or spatial. Similarly, Meltzer and colleagues (2008) reported increases in theta and alpha power in midline frontal regions with increasing load during a Sternberg task in intracranial EEG recordings. These authors (Gevins et al., 1997; Krause et al., 2000; Meltzer et al., 1997) interpreted theta increases in frontal regions as attentional processes or shifts in allocation of attention. Gevins, Smith & McEvoy (1997) attributed the theta increase to greater effort required to maintain attention on the task whereas Krause and colleagues (2000) hypothesized that when attentional capacities were exceeded, the frontal cortices were inhibited (as reflected by increased ERS) and alternative strategies were utilized.

Fetal Alcohol Spectrum Disorders (FASD)

Clinical descriptions of individuals with FASD often cite difficulties with attention and working memory, cognitive skills attributed to the prefrontal and parietal cortices. In addition, animal research has demonstrated a link between FASD, impaired spatial skills and damage to

the temporal regions (most notably the hippocampus; for a review, see Berman & Hannigan, 2000).

Malisza and colleagues (2005) hypothesized that individuals with FASD would display damage or dysfunction in cortical regions associated with working memory. On their one-back task, children and adults with FASD displayed increased errors, increased latencies to respond and increased rates of incorrect- and non-responding. Children with FASD displayed increased functional activity in the inferior and middle frontal cortex and reduced superior frontal and parietal activity relative to the controls. Adults with FASD also displayed greater orbital and inferior-middle frontal activation, as well as greater activation in the superior frontal cortex, than the control participants. The authors concluded that individuals with FASD displayed abnormal functioning of prefrontal areas. Similarly, Connor and Mahurin (2001) stated that FASD subjects, in contrast to their control subjects, displayed minimal activity in the left dorsolateral prefrontal cortex and significantly poorer behavioural results for a two-back working memory task.

Encoding Versus Retrieval

Several researchers have noted that individuals with FASD have greater difficulty learning test material but are able to retain and recall information eventually learned (e.g., Kaemingk, Mulvaney & Halverson, 2003; Mattson et al., 1992; Mattson, Riley, Delis, Stern & Jones, 1996; Mattson & Roebuck, 2002; Uecker & Nadel, 1996). One conclusion was that the memory deficits displayed by individuals with FASD resulted from difficulty encoding material, rather than from difficulties with retrieval (Mattson et al., 1996).

Research Questions

Three questions were examined in this study. First, do individuals with FASD encode information during a spatial working memory task in a similar manner to individuals without a diagnosis of FASD (as evidenced by similar EEG patterns recorded during the presentation of the target stimuli)? Second, is the pattern of EEG activity during the presentation of the test stimuli (recall/recognition) similar or distinctive for the FASD group compared to the matched control and university control groups? Third, is the pattern of activity altered by memory load?

Given prior research, I hypothesized that abnormal EEG patterns would be recorded from frontal regions during encoding but not during retrieval. As the task presented is spatial, abnormal patterns in right temporal regions would also be expected. In addition, the abnormal patterns were be more evident with increasing memory load.

Methodology

Participants

The home visitation program of the Chinook Health Region (now Alberta Health Services) referred 8 adult females with a diagnosis of FASD and 12 female controls. The matched control participants were equivalent to the FASD group with respect to age, educational background, socioeconomic status, history of physical and emotional abuse, and past and current drug and alcohol use. A worker from the home visitation program drove the participants to the test sessions. Six female, right-handed students enrolled at the University of Lethbridge also participated in this study. They received an additional 1% for their final grade in an undergraduate psychology class. Informed consent was obtained from each subject. Approval for this study was granted by the

ethics committee of the University of Lethbridge, Alberta, Canada.

Neuropsychological Protocol

FASD and matched control participants were administered a neuropsychological battery as described elsewhere in this report.

Spatial Working Memory Protocol

The n-back test was modified for use with individuals with FASD. The task needed to be designed to avoid penalizing participants whose working memory was intact but processing or response times were slower. It also needed to identify memory processes uncontaminated by interference from prior trials. At a practical level, the participants needed short, discrete trials to maintain attention and motivation. The task needed to be structured so that it could be stopped at any point in the session; in addition, the trials needed to be structured to avoid non-responding by the participants. (Several participants displayed tendencies to not respond when frustrated or when they felt they couldn't answer correctly during a prior spatial task. Non-responding has also been reported as a problem with this population in other studies, for example, the n-back study conducted by Malisza et al., 2005.)

The spatial working memory task was written with Microsoft's Visual Studio C++ software. The program pseudorandomly presented trials for 1-back, 2-back and 3-back memory loads. Five locations on the screen were identified: the left upper corner, left lower corner, right upper corner, right lower corner and center. The participants initially saw the word "Ready" presented on the screen for 500 ms to alert them to the start of a new trial. A fixation cross was then presented and remained in the center of the screen throughout the trial. The intertrial interval, between

onset of the fixation cross and presentation of the first symbol, between presentations of the symbols, and from the end of one trial to the presentation of the word “Ready” to start the next trial, were randomly jittered between 750 and 1000 ms. Each symbol remained on the screen for 750ms.

For the one-back trials, one symbol (from a selection of five taken from the computer keyboard, “*”, “&”, “#”, “@” and “$”) was presented on the screen in one of the five locations. A question mark was then presented and remained in the center of the screen for a randomly jittered interval of 750 to 1000 ms. The question mark alerted the participant that the next symbol presented would be the test symbol. The test symbol remained on the screen until the participant responded. (The same symbol was used throughout each trial.) If the location of the symbol matched the location of the symbol presented in the trial period, the participant was to push the “1” key on the computer keyboard. If it did not match, the participant was to push the “0” key. After the participant had responded, the word “Ready” again appeared on the center of the screen to indicate that the next trial had begun.

For the two-back trials, a symbol was presented on the screen in one of the five locations. The symbol was then presented in a second location. This was followed by the question mark and then the symbol in the test location. If the test location matched the location of the first symbol, the participant was to push “1”. If the test location matched the location of the second symbol, the participant was to push “2”. And if the test location did not match either of the trial locations, the participant was to push “0”. For the three-back trials, a symbol was again presented on the

screen in one of the five locations, then in a second location and finally, in a third location. Following the question mark, the symbol was presented in the test location. Again, if the test location matched the location of the first symbol, the participant was to push "1". If the test location matched the location of the second symbol, the participant was to push "2" whereas if the test location matched the location of the third symbol, the participant was to push "3". And if the test location did not match either of the trial locations, the participant was to push "0".

The program was designed to present up to a total of 300 trials; one-third of the trials were one-back, one-third were two-back and the remaining one-third were three-back. In 10% of the trials, the test location did not match the trial location(s). Eight practice trials were presented with the researcher in the room explaining (and demonstrating if necessary) the procedure to the participant. If the participant was having difficulty understanding what she was to do, the eight practice trials were repeated. A break was scheduled after every 40 trials. To signal the break, the participant saw "Take a break. Press the space bar to continue." on the computer screen. If the participant did not press the space bar within three minutes, the researcher entered the testing room to encourage the participant to continue.

Data Acquisition

Using the 128-channel EGI Geodesic dense-array sensor net and Net Station acquisition software (Electrical Geodesics, Inc., Eugene, Oregon), EEG data was recorded at 500 Hz with a high pass filter of 0.1 Hz and a low pass filter of 200 Hz. Electrode locations for each participant were recorded using the Locator program from EMSI (Source Signal Imaging,

Inc., San Diego, CA) in conjunction with Polhemus (Polhemus, Colchester, VT).

Pre-Analysis Processes

The data were down-sampled to 250 Hz to reduce memory demands during analyses and were then digitally filtered (band-passed filter 1 to 50 Hz) to minimize line noise artifacts and drifts using a zero-phase linear filter. Finally, the data were re-referenced to an average reference. Extracted data epochs began 750 ms prior to stimulus presentation (when the participants were viewing a blank, black screen) and terminated 2500 ms after the onset of the stimulus. Extracted epochs were coded for memory load and accuracy. Epochs for "correct encoding" were centered on the initial presentation of the target stimulus in trials that the participant subsequently answered correctly. Epochs for "correct recall" were centered on the presentation of correctly answered test stimulus. The files were then formatted for Matlab (Matlab 7.0.1, The Mathworks Inc., Natick, MA).

Data of each subject were decomposed using ICA. Topographies were manually inspected to identify components representing artifacts. The data was re-constituted using all components except those marked as artifacts. Electrode channels with consistent noise for multiple participants were removed. The subject files were subsequently concatenated across groups (FASD, matched controls and university controls).

Data Analyses

The concatenated data file was analyzed using Multiple Origin Spatio-Temporal Modelling for Electroencephalography (MOST-EEG, Zeman et al., 2007; Zeman, 2008). This software program decomposed the dataset into independent components. The components were then projected onto a three-dimensional canonical volume using a modified LCVM Beamform algorithm. The components were ranked along three dimensions: volume representation (voxel specificity of the volume domain), volume uniqueness (a measure of volume overlap) and quality of convergence (a measure of volume stability; Zeman, 2008).

Ten components were chosen for further analyses. Two components modeled within the frontal regions, five components modeled within the occipitotemporal and temporal regions, and three components projected to the parietal region. Power (root mean square) values, for the pre-onset (-250 ms to 0 ms) and post-onset (0 to 250 ms) epochs were calculated across a broadband frequency of 4 to 40 Hz.

Statistical Analysis

All statistical analyses were completed using SPSS 16.0 (SPSS, Inc., Chicago, Il.). Repeated measures ANOVAs were conducted to evaluate performance on neuropsychological tests, behavioural performance and the EEG results. Huynh-Feldt corrections were applied to all univariate ANOVA results.

Results

Neuropsychological Testing

A repeated measures ANOVA was completed with the between-subjects factor of GROUP and the within-subjects factor of Tests. Eleven scores were included in the analysis. The WAIS summary scores of Verbal IQ, Performance IQ and Full Scale IQ (Figure 1) were included as were the WMS summary indices of General Memory and Working Memory. Given the spatial nature of the study, spatial subtests and tests were also included: WAIS Block Design, WMS spatial index, Rey-Osterrieth Complex Figure test (copy and recall), Semmes Body Placing Test and the Test of Right/Left Differentiation. Finally, given the visual memory component of the study, the WMS visual immediate memory index was also included. All of the participants scored within two standard deviations of the published means for the WAIS-II verbal, performance and full scale intelligence quotients (Figure 1) and for the WMS General Memory and Working Memory indices. (For additional information, please refer to the "Neuropsychological Effects of FASD" draft.)

A significant main effect of GROUP was found, F (1, 21) = 6.205, p = .021. To further delineate the group effect, the scores for the same group of tests were analyzed using a stepwise linear regression with GROUP as the outcome (dependent) variable and the neuropsychological test results as the predictor (independent) variables. Of the tests evaluated, only the WAIS performance IQ (WAISPIQ) score significantly predicted the group membership, R^2 = .457, F(2,21) = 8.839, p = .002. Although the WAISPIQ means were within average for the test norms, the score was lower for the FASD group (X = 97.33, SD = 12.507) than for the matched control group (X = 111.45, SD = 11.536).

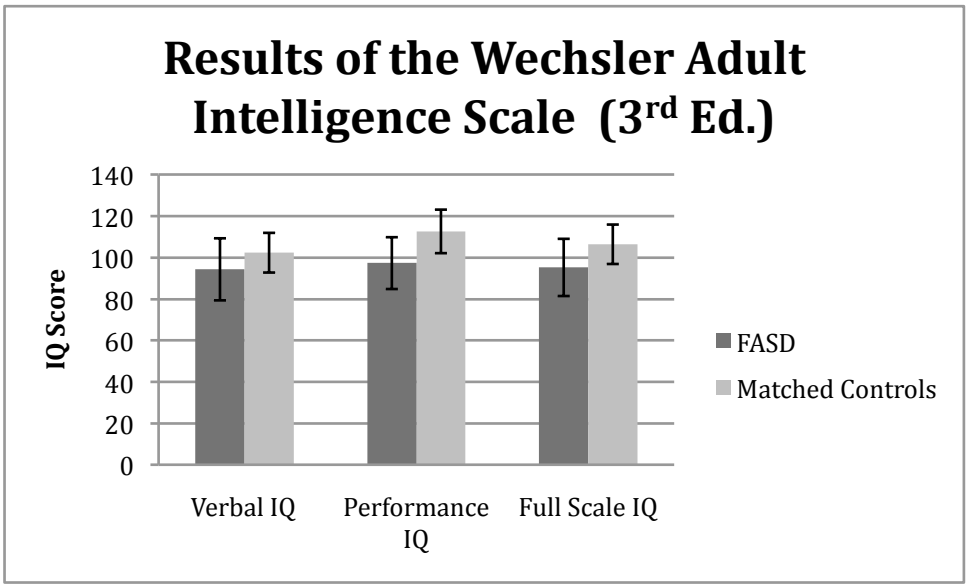


Figure 1. Scores on the verbal (verbal IQ), performance (performance IQ) and full scale (full scale IQ) intelligence quotients of the Wechsler Adult Intelligence Scale (3rd Edition).

Behavioural data

Accuracy was analyzed using repeated-measures analysis of variance (ANOVA) with the between-subject factor of GROUP (FASD, FASD matched controls, university controls) and the within-subject factors of Load (1-back load, 2-back load, 3-back load). All three groups achieved 100% accuracy on the 1-item memory load trials. The accuracy on the 2-back and 3-back trials were similar for the FASD group (Table 1). The accuracy across the two memory loads was also similar for the university control group. The accuracy on the 3-back trials dropped compared to the 2-back trials for the matched control group. The main effect of GROUP, though, was non-significant, $F_{(2, 23)} = 2.134$, $p = .141$.

	2-back	3-back
FASD	81.17% (27.084)	81.76% (20.072)
FASD Matched Controls	82.03% (17.473)	74.72% (20.942)
University Controls	97.26% (4.555)	96.96% (2.560)

Table 1. Mean percent accuracy (and standard deviations) for the 2-back and 3-back memory loads.

In contrast, the main effect of Memory Load was significant, $F_{(1.341, 30.840)} = 13.350$, $p = .000$. In a pairwise comparison, the accuracy on the 1-back items was significantly different from the two- (*LSD* $p = .003$) and three-back (*LSD* $p = .000$) trials; however, accuracy on the two- versus three-back trials did not differ significantly.

Although accuracy on the 1-back trials differed significantly from the 2- and 3-back trials, the 1-back trials did not distinguish between the three groups. Not surprisingly then, the interaction of Memory Load*Group was non-significant, $F_{(2.682, 30.840)} = 2.297$, $p = .103$.

As subjects achieved 100% accuracy on the 1-item load trials, the 1-item load trials were not included in any further statistical analyses.

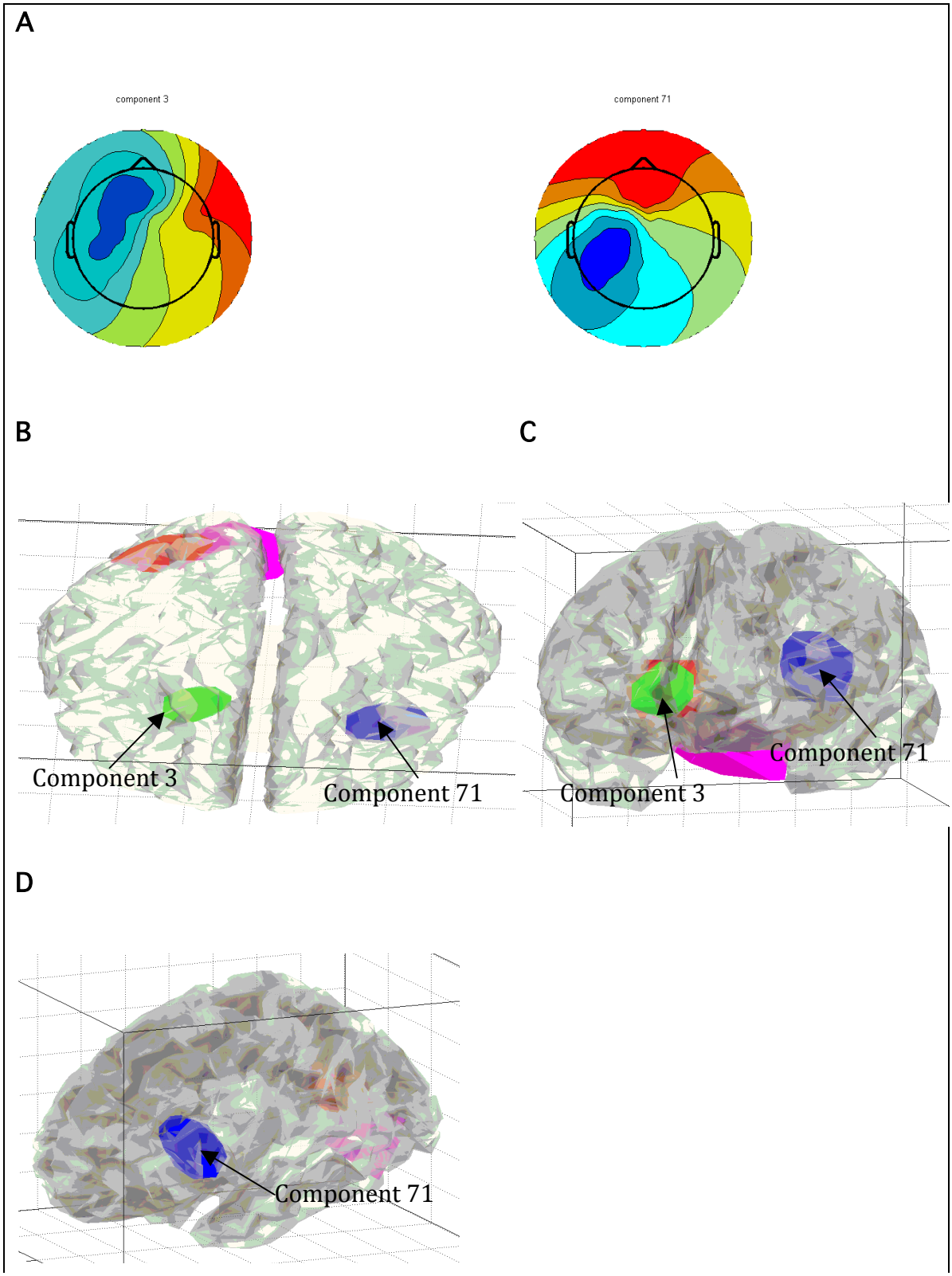
Electrophysiological Data

EEG data from two participants was not included in the EEG analysis. The accuracies for the two participants (one FASD participant

and one MC participant) on both the 2-back and 3-back memory load items were below chance. The RMS values of the correct trials for these two participants were therefore assumed to more likely reflect chance responding and not accurate memory encoding and recall.

Components Projected to the Frontal Cortex.

Two components, labeled C3 and C71, were modeled within the frontal regions (Figure 2). C3 was projected to the region of the cingulate cortex while C71 was projected to the dorsolateral prefrontal region. To determine if these two components differentiated the FASD group from the matched control and university control group, a 3 (GROUP) X 2 (Components) X 2 (Memory Process) X 2 (Memory Load) repeated


A
component 3
component 71
B
C
Component 3
Component 71
Component 71
Component 3
D
Component 71

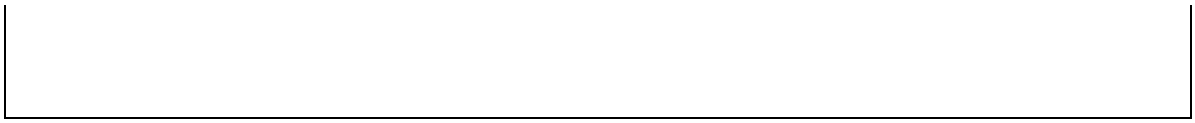


Figure 2. Frontal components C3 and C71. (A) topographical maps of each component. (B) – (D) The components projected in a three-dimensional volume using a modified version of the LCVM Beamform algorithm. (B) The virtual cortex viewed from above. Frontal cortices are closest to the viewer. (C) A coronal view with the frontal cortices facing the viewer. (D) A saggital view of the virtual cortex with the left hemisphere facing the viewer.

measures ANOVA was used. There were no main effects for the between-subject factor of GROUP, and the within-subject factors of Components and Memory Load. A main effect was found for Memory Process (encoding versus recall), $F_{(1, 21)} = 11.187$, $p = .003$, indicating that EEG power was significantly stronger during encoding ($M = 0.855$, $SE = 0.041$) than during recall ($M = 0.756$, $SE = .040$). There were no interaction effects with the exception of Components X Memory Process, $F_{(1, 21)} = 13.047$, $p = .002$. The mean power of Component 3 for encoding exceeded that for recall (encoding $M = 0.856$, $SE = 0.047$; recall $M = 0.723$, $SE = 0.041$). The difference between encoding and recall was not as great for Component 71 (encoding $M = 0.0.854$, $SE = 0.040$; recall $M = 0.789$, $SE = 0.039$).

Components Projected to the Parietal Cortex.

Three viable components were localized in the parietal cortex. Components labeled C70 and C104 projected to the left hemisphere while C86 projected to the right (Figure 3). All three were localized in the region of the superior parietal lobe. As with the

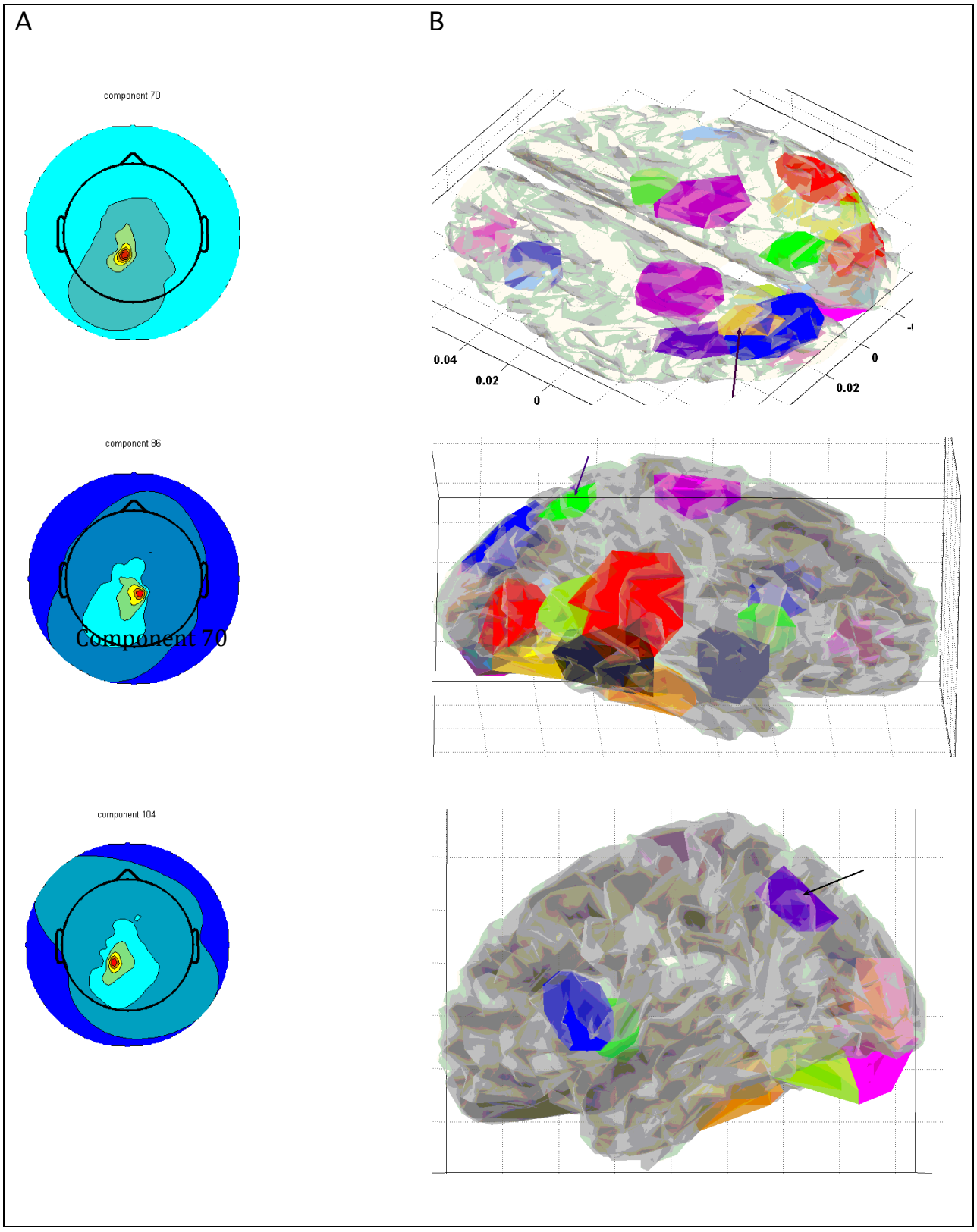
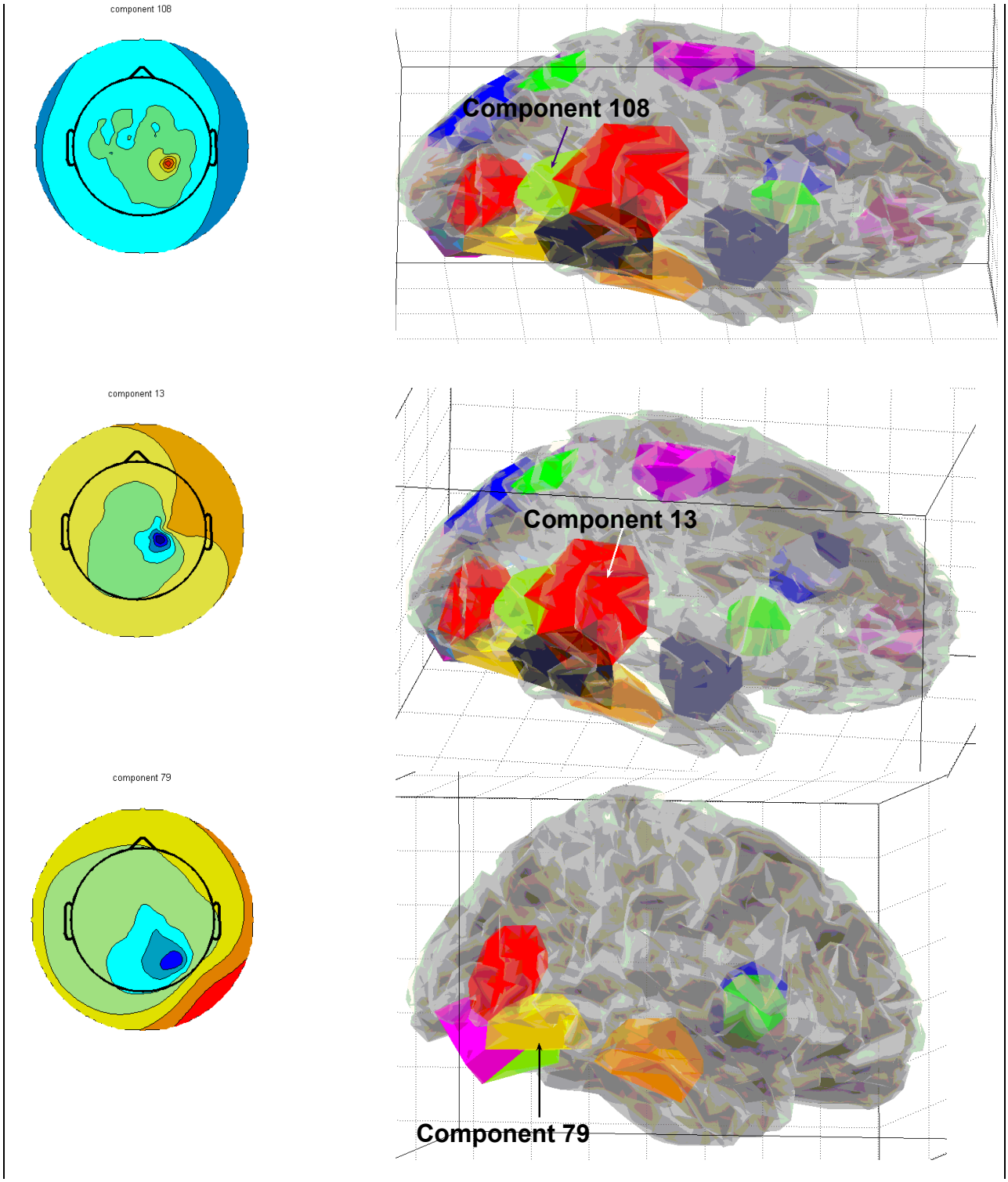

A
B
component 70
component 86
component 104
0.04
0.02
0
0
0.02
Component 70

Figure 3. Topographical maps and corresponding three-dimensional volume projections for three components. (A) Topographical maps for Components 70, 86 and 104. (B) Beamform projections for the three components. The top projection, C70, is viewed from the top with the occipital lobes facing the bottom right corner. The middle projection, C86, is a coronal view of the lateral surface of the right hemisphere while the bottom projection, C104, is a coronal view of the lateral surface of the left hemisphere.

frontal components, there was no between-subjects GROUP effect. There were also no main effects for within-subject factors of Components and Memory Load. There was however, a main effect for the within-subject factor of Memory Process, $F(1, 21) = 4.910$, $p = .038$. Again, the power (root mean square) value was greater for encoding than for recall (encoding $M = .826$, $SE = .127$; recall $M = .645$, $SE = .190$). There were no statistically significant interactions

Components Projected to the Temporal Cortex.

Five components projecting to occipitotemporal and temporal regions were analyzed further (Figure 4). All five components localized to the right hemisphere. Two components, C108 and C13, were rendered in the region of the angular and supramarginal gyri. In contrast, the remaining three components, C79, C89 and C106, were rendered along the inferior temporal gyrus.


component 108
Component 108
component 13
Component 13
component 79
Component 79

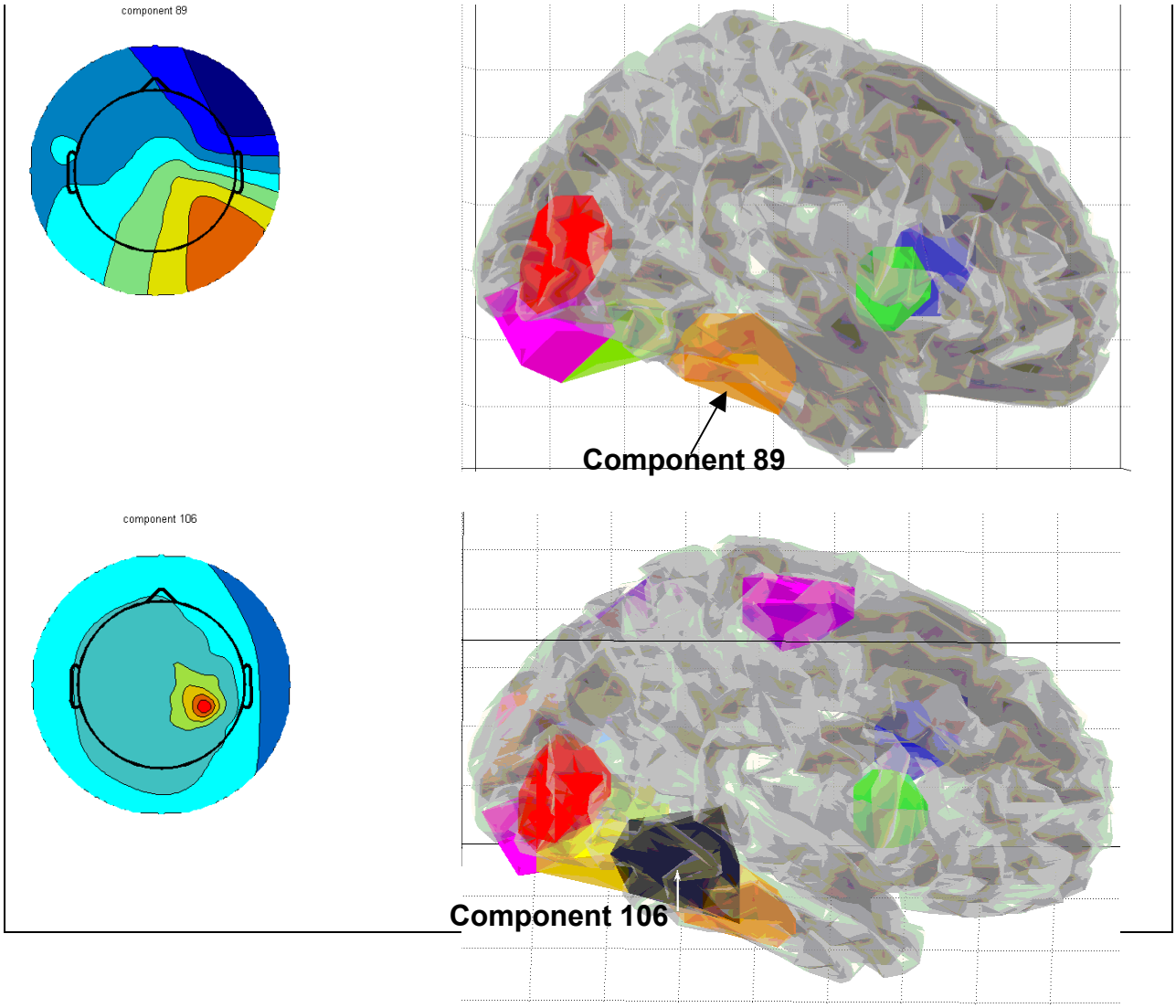


Figure 4. Topographical maps and three-dimensional volume projections for five components. (A) Topographical maps for Components 108, 79, 89, 106 and 13. (B) Beamform projections for the five corresponding components. All images are coronal views of the lateral surface of the right hemisphere.

In contrast to the results seen for the frontal and parietal components, a significant main effect of GROUP was found for the five occipitotemporal and temporal located components, $F_{(2, 21)} = 5.325$, $p = .013$. No main effect was found for Components or Memory Load. A main effect for Memory Process was found again, $F_{(1, 21)} = 8.757$, $p =$

.007, with the mean measure of power greater for encoding (M = 0.845, SE = 0.086) than for recall (M = 0.660, SE = 0.081). Two interactions were significant, Components X Memory Load, $F_{(3.427, 71.959)} = 3.624$, p = .013, and Components X Memory Load X Memory Process, $F_{(3.995, 83.901)} = 3.604$, p = .009. No other interactions were significant.

For the Component X Memory Load interaction, the greatest difference between the 2-back and 3-back memory loads were recorded for C108 (2-back: X = 0.827, SE = 0.089; 3-back: X = 0.755, SE = 0.082) while the lowest difference (and the lowest RMS values) between the two memory loads was recorded from the more ventral C106 (2-back: X = 0.680, SE = 0.101; 3-back: X = 0.694, SE = 0.110). The Components X Memory Load X Memory Process interaction displayed two patterns. For components 106, 108 and 13, greater RMS power was recorded during encoding than during recall (C108 mean difference 2-back = 0.329 and 3-back = 0.201; C106 mean difference 2-back = 0.168 and 3-back = 0.202; C13 mean difference 2-back = 0.286 and 3-back = 0.235). These three components form a cluster at the occipital-parietal-temporal junction in the region of the angular and supramarginal gyri. Components 79 and 89, more inferiorly located components, displayed greater RMS power during encoding for 2-back memory loads (C79 difference mean = 0.175; C89 difference mean = 0.148) but similar RMS power values for encoding and recall for 3-back memory loads (C79 difference mean = 0.042; C89 difference mean = 0.062)

Discussion

In their review of n-back neuroimaging studies, Owen and colleagues (2005) reported cortical regions consistently activated during working memory, including the dorsal cingulate and lateral prefrontal cortices, and the medial and lateral posterior parietal cortices. Spaniol and colleagues (2009), in a meta-analyses of fMRI studies of encoding and retrieval of episodic memory, reported similar regions of activation such as the dorsolateral and ventrolateral prefrontal cortices, anterior cingulate and inferior and superior parietal gyri. They associated the ventrolateral PFC with selection and recollection of cues associated with the target or selection of the appropriate response from the potential alternatives, and the dorsolateral PFC with associative encoding and monitoring and verifying retrieval. The functional significance of parietal activation was more controversial. The superior parietal regions have been associated with salience of cues and task relevance, and also top-down attentional control during retrieval. The inferior parietal regions, while also playing a role in retrieval, have been associated with bottom-up attentional processes.

The frontally projected components analyzed in this study are consistent with cingulate (component 3) and lateral prefrontal regions (component 71). The three parietal components found (components 70, 86 and 104) are also congruent with the parietal regions noted in the n-back and fMRI reviews. Two FASD studies reported differential activation within the frontal and parietal regions between the FASD and control groups. Malisza et al. (2005) noted increased activity in the inferior and middle frontal cortex and reduced superior frontal and parietal activity in

children and adults with FASD during a one-back task. Similarly, Connor and Mahurin (2001) noted reduced activity in the left dorsolateral prefrontal cortex, in conjunction with significantly poorer behavioural results, for FASD individuals during a two-back task. The lack of a group effect for the power measures recorded from frontal and parietal components in this study may have resulted from differences in the task protocols and the neuroimaging technique used. However, there are several other potential interpretations. The lack of a group effect may have reflected the differences in severity of the FASD in the participants across the studies or may have reflected the resulting differences in behavioural performance. Malisza and colleagues' FASD participants were only able to complete a one-back task. Connor and Mahurin's FASD participants performed significantly poorer than control subjects on a two-back task. In contrast, the FASD participants in this study achieved 100% accuracy on the one-back task and scored comparably to the matched controls in the two- and three-back items. It is also possible that, given the behavioural difficulties displayed, the matched control group included individuals with undiagnosed mild FASD. This may have led to a lack of statistically significant RMS values between the FASD and matched control groups.

The prefrontal and parietal activations may reflect attentional factors. Given the comparable accuracy levels, attentional skills needed to complete the task may not have been affected by lower levels of prenatal alcohol exposure, or conversely, the task may not have been challenging enough to differentially tax the attentional capabilities of the FASD participants. Hence, no group differences were found in components projected to these two regions.

Petrides (Petrides, 1994; Petrides & Milner, 1982) and Fletcher and Henson (2001) attributed maintenance of information to the ventrolateral prefrontal cortex. Component 71 localizes to a region congruent with the ventrolateral PFC. The anterior cingulate and the parietal cortex have also been implicated in the maintenance of information in working memory (Curtis, 2006; Woodward et al., 2006). Maintenance of information has been reported as a relative strength for individuals with FASD (e.g., Kaemingk et al., 2003; Mattson & Roebuck, 2002). The lack of a group effect found in this study for the frontal and parietal components analyzed may then reflect this relative strength.

As the task performed by participants of this study was spatial, a right, rather than left, hemisphere prefrontal and parietal components would have been expected. Given the analysis completed, where data from all groups were concatenated, differences between groups in right hemisphere activation may have reduced the strength of a right hemisphere component. As a result, a relevant, but much weaker, component may not have been selected for analysis. Conversely, left hemisphere activation may represent verbalization or sub-vocalization of the name of the location of each symbol to aid in maintaining that information in working memory.

Both the frontal and parietal components activated differentially for encoding versus recall but not for memory load or group. In their meta-analysis of fMRI studies, Spaniol and colleagues (2009) reported consistent activation in the dorsolateral and ventrolateral PFC during both successful encoding and successful retrieval, although left ventrolateral PFC activation was greater during encoding. In contrast to Spaniol and colleagues, activation during the spatial working memory task was greater

during encoding than retrieval for both the component projected to the ventrolateral PFC and the component projected to the cingulate cortex. The spatial working memory task in this study required encoding not only one, two or three locations but also the order of presentation. The tasks reviewed by Spaniol and colleagues focused on studies examining recognition of previously presented or studied items. As such, the encoding demands during the spatial working memory task may have been more extensive than those required for the old/new paradigms reviewed by Spaniol et al.

In contrast to the frontal and parietal components, a group effect was seen with the temporal components. The temporal components appeared to lie along two lines. Three components were projected along the inferior edge of the occipitotemporal and temporal cortices, which would correspond to the "ventral stream" associated with object identification and object memory. These three components displayed the smaller differences between amplitude measures for encoding versus recall epochs. The other two components (components 13 and 108) were projected to cortical regions consistent with the angular and supramarginal gyri, regions that are described as "associative". The larger differences between power measures for the encoding and recall epochs were recorded from these two components. These two groups of components may reflect differences in processing the symbol used in each set of trials versus the processing of the symbol's location and its' sequence of presentation. For C13 and C108, the encoding process, or integrating the information about the symbol presented, the sequence of presentation and the location, may require greater power than the retrieval process.

Spaniol and colleagues (2009) reported temporal activation during both encoding and retrieval although encoding was associated with greater activation within the fusiform gyrus, hippocampus and inferior temporal gyrus while retrieval was associated with greater activation within the paraphippocampal gyrus, superior temporal gyrus and the angular gyrus. Again, the difference in relative levels of activation between the meta-analysis of Spaniol and colleagues and the results in this study may reflect the potentially greater encoding demands of the spatial working memory task. Although, in Spaniol and colleagues' meta-analysis, hippocampal, parahippocampal, and middle temporal gyrus activations were in the left hemisphere, the majority of the studies they reviewed (20 of 26 encoding studies and 20 of 30 retrieval studies) involved words as stimuli. Only 3 of the 56 studies involved pictures of scenes and none of the studies looked at spatial skills. Cortical regions activated during encoding and retrieval reflect not only the cognitive demands of the task, but also the modality of the test stimuli (e.g., Uncapher et al., 2006). Right hemisphere activation see in this study would be consistent with the spatial demands of the working memory task.

A significant GROUP X Memory Process was not found. However, greater power measures for encoding and recall during both two-item and three-item load conditions were recorded by the FASD group. (The measures for encoding and recall for the matched controls and university controls were very similar, perhaps accounting for the lack of a group effect.) The greater power measures for the FASD group may reflect greater effort to complete the task or greater inefficiency encoding,

maintaining and recalling spatial information even when accuracy levels are high.

Although Kaemingk and Halverson (2000) reported no significant spatial memory differences between their FASD and control participants when differences in perceptual and verbal memory task performance were taken into consideration, other researchers have found spatial-specific differences. Uecker and Nadel (1998) reported that children with FAS had difficulty with spatial but not object memory. Hamilton and colleagues, in a spatial navigation task, observed that adolescents with FAS displayed difficulty navigating using spatial cues but did not differ from control participants during the non-spatial cue trials. The results from this study also indicate deficits specific to processing spatial information. The group difference in the temporal components, and lack of group difference in the frontal and parietal components, implies that the FASD group had greater difficulty with the spatial aspects of the task and not the encoding or maintenance of memory per se. Notably, these differences were present even though behavioural results on the spatial task did not differ from controls.

Overall, the results indicated that encoding was typically accompanied by larger levels of activation than recall in most components analyzed. EEG power measures for frontal and parietal regions, traditionally associated with attention and maintenance of items in memory, did not differ amongst the three groups. However, significant group differences were seen within the temporal regions. This implies that even when individuals with FASD respond accurately to test items on

a spatial working memory task, they display differential levels of activation in cortical regions associated with processing spatial information.

This study evaluated EEG patterns for components that were present in all three control groups. The next step is to evaluate EEG patterns that may be unique to the FASD group to determine if individuals with FASD also use compensatory strategies (and cortical regions) to complete spatial tasks accurately. In addition, given dominance of the theta frequency band in EEG research utilizing working memory tasks (e.g., Deiber et al., 2007; Gevins et al., 1997; Krause et al., 2000), further analyses of the data will focus on the theta bandwidth.

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noise ratio for statistical analysis of event-related potentials. Clin Neurophysiol., 118(12), 2591-2604.

APPENDIX A

Fetal Alcohol Spectrum Disorder Survey Database

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1. Installation

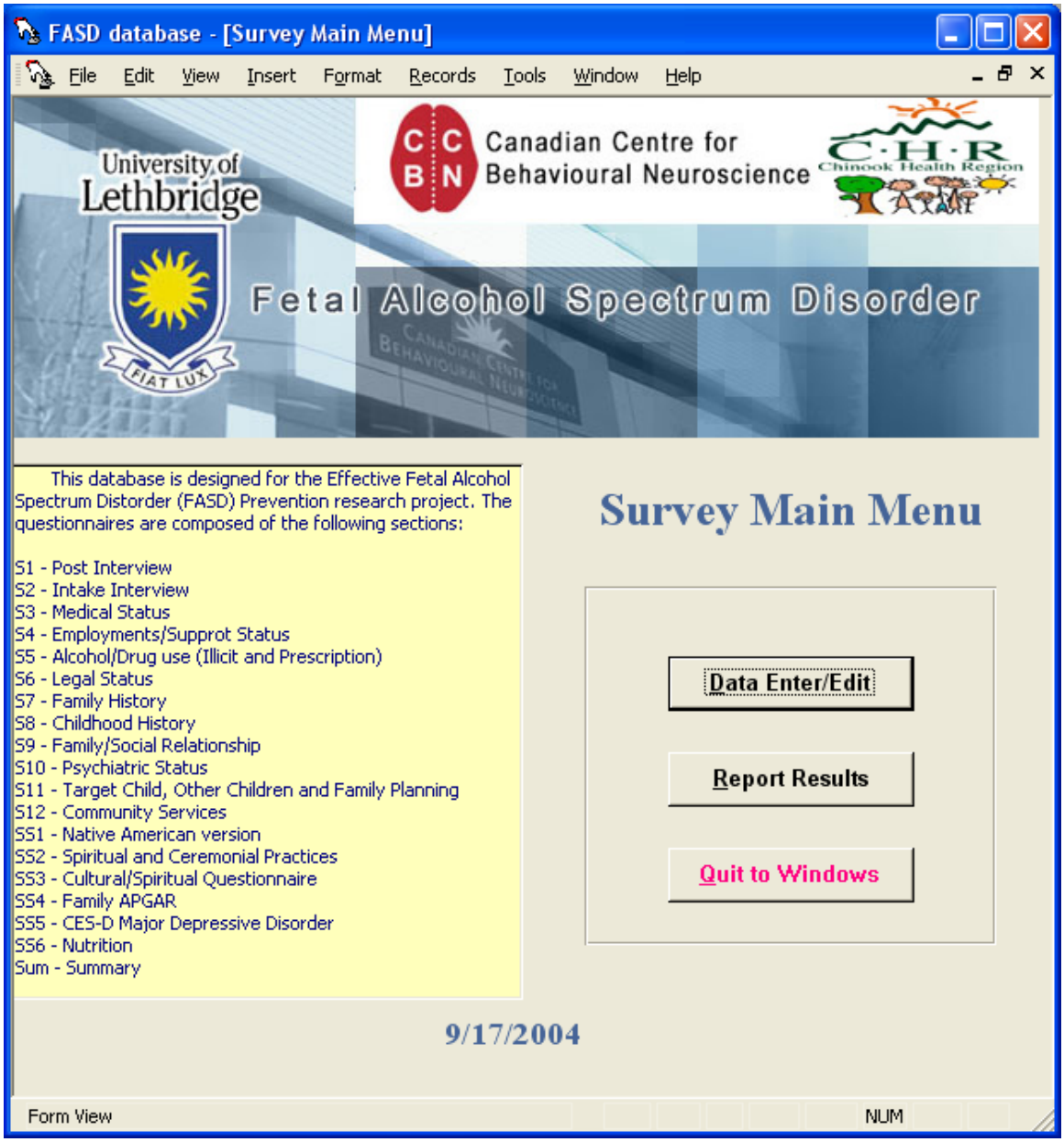
1. Make a folder named "FASD" under the root of C drive. Unzip three files "FASD.mdb, FASD.mde and Secured.mdw" into this folder (C:\FASD).
2. By clicking the FASD.mdb shortcut, user will see a logon box opened to let user enter the username and password to log on to the database.
3. Three usernames were created as lethbridge, lakeland and bloodtribe, and initial password is "FASDproject". After users login to the database, they can change their password by selecting Tools -> Security -> User and group accounts -> Change logon password.

2. Using FASD database

The first screen in FASD database is the Survey Main Menu. To select an option, user can do one of the following ways:

- Click a button
- Press [Alt]+ [underlined letter]

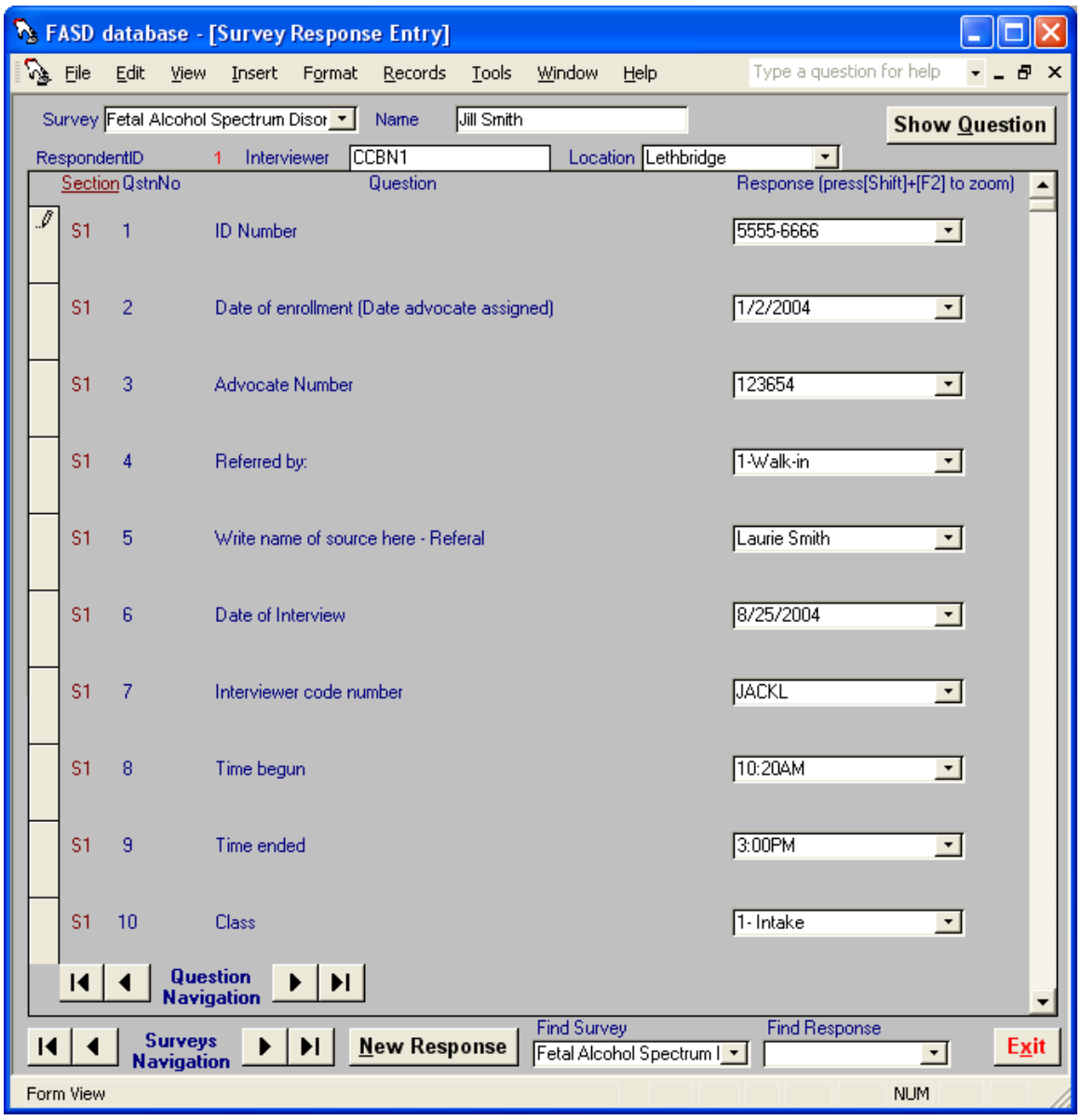
- Navigate to the proper button with the cursor keys and press [Enter]



Screen 1 – Main Menu

3. Entering/Editing Survey Data

Select "Data Enter/Edit" button from the Main Menu to begin entering survey responses. When the Survey Response Entry screen opens, a new blank survey will show. Select a survey from the Survey combo box and enter the respondent's name to create a new response. Click "Show Question" button to show all the questions for the selected survey. You can then begin to complete the survey by going through all questions under each section.



Screen 2 – Entering/Editing Data

To view the results from a previously entered survey, use the "Find Survey" and "Find Response" combo boxes at the bottom of the screen. The Survey Navigation buttons will view First, Previous, Next, and Last surveys in the total collection of surveys (here we just have one survey called FASD). Click the "New Response" button to enter a new survey response.

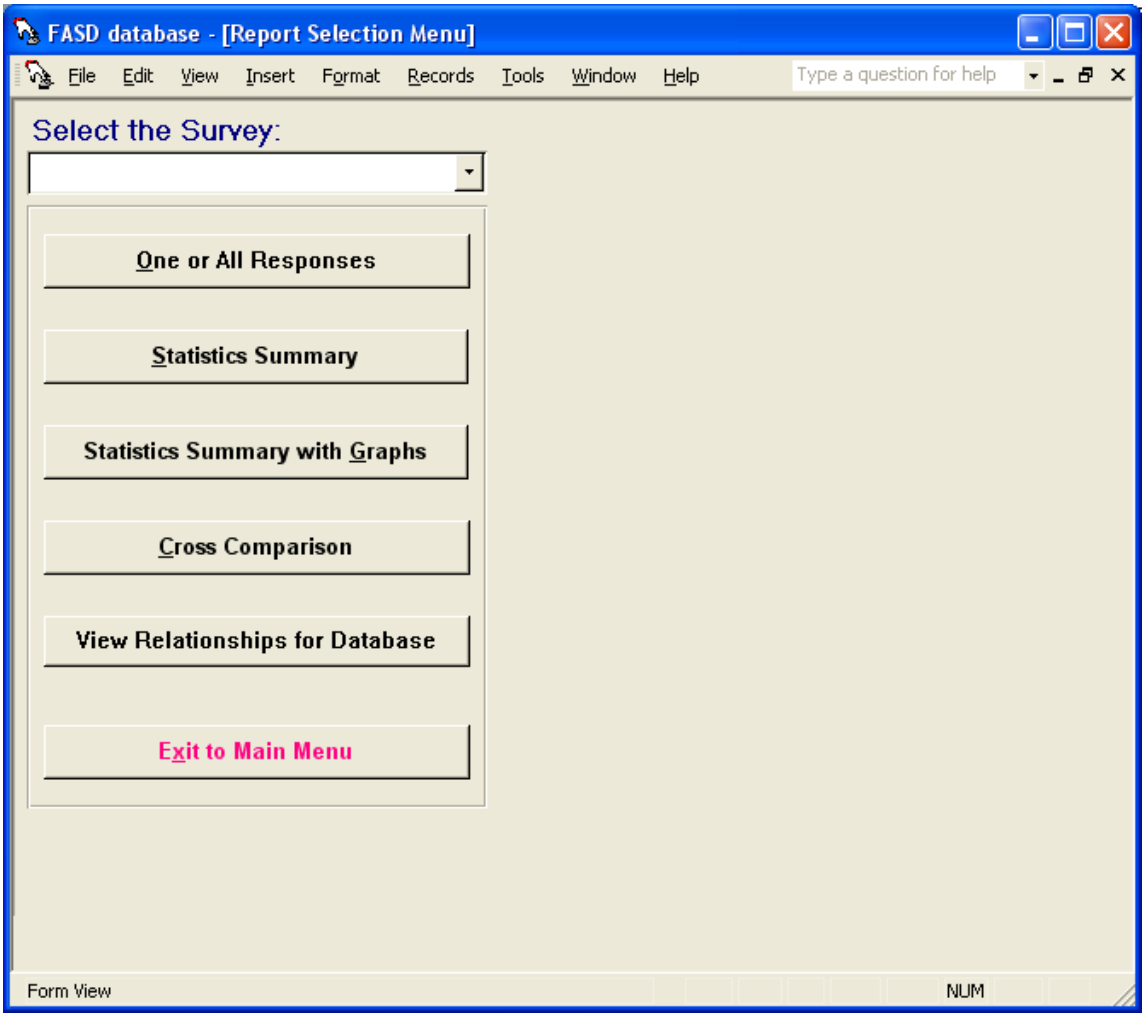
Enter data into each question. If a Response List has been created for a question, the responses list box will begin to show as entries typed previously when survey was designed. Press [F4] or [Alt] + [Down Arrow] to show the Response List. If the entered response does not meet the Validity Function set up by the designer the user will be notified.

If the response doesn't fit into the combo box, press [Shift] + [F2] key, a pop up zoom window will show the entire response.

Click the red "Exit" button to return to Main Menu window.

4. Reporting Results

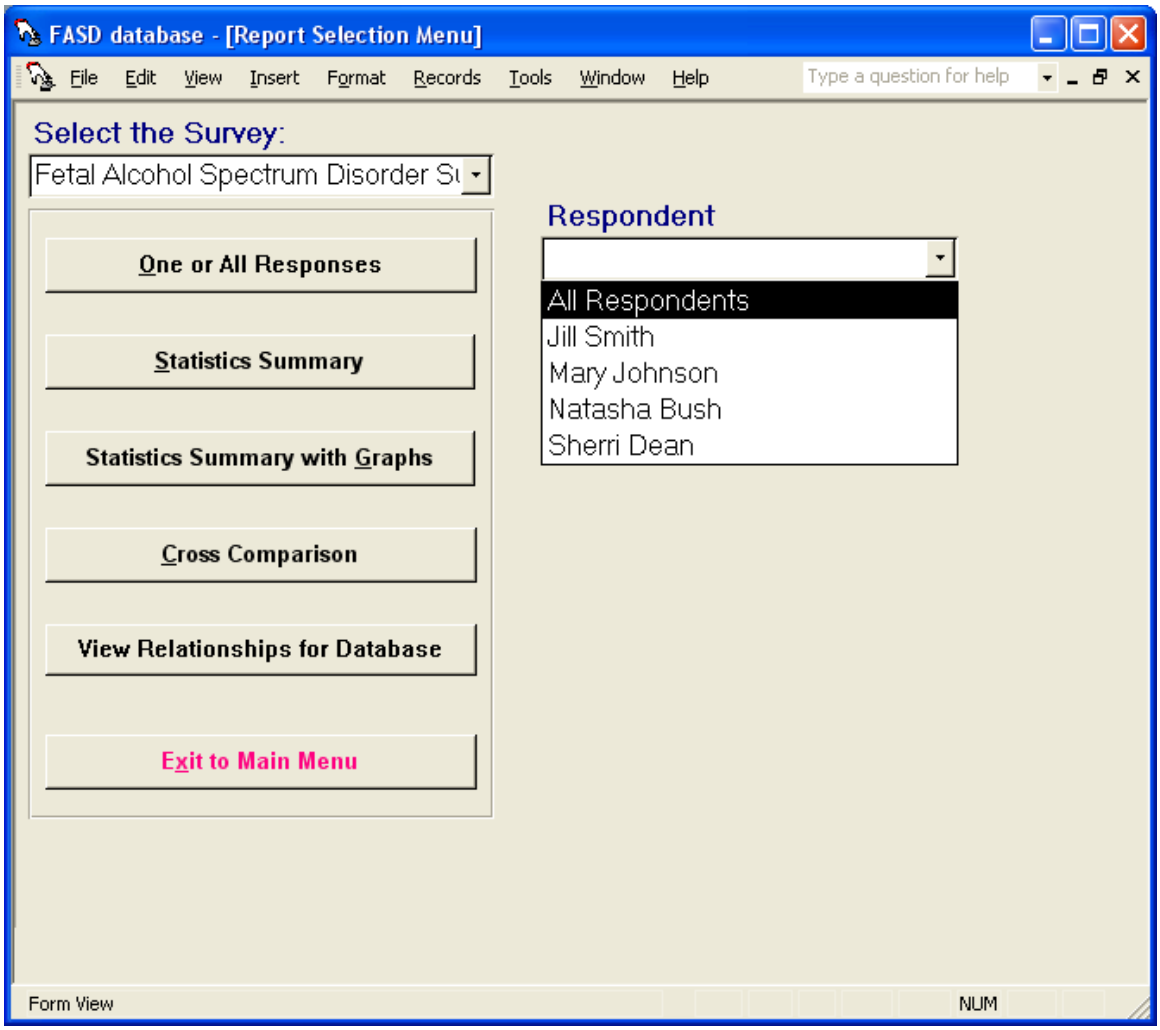
1. Click on "Report Results" button from the Main Menu to access the Report Selection Menu. First, select the Survey from the top combo box. Then click on the desired survey.



Screen 3 – Report Selection Menu

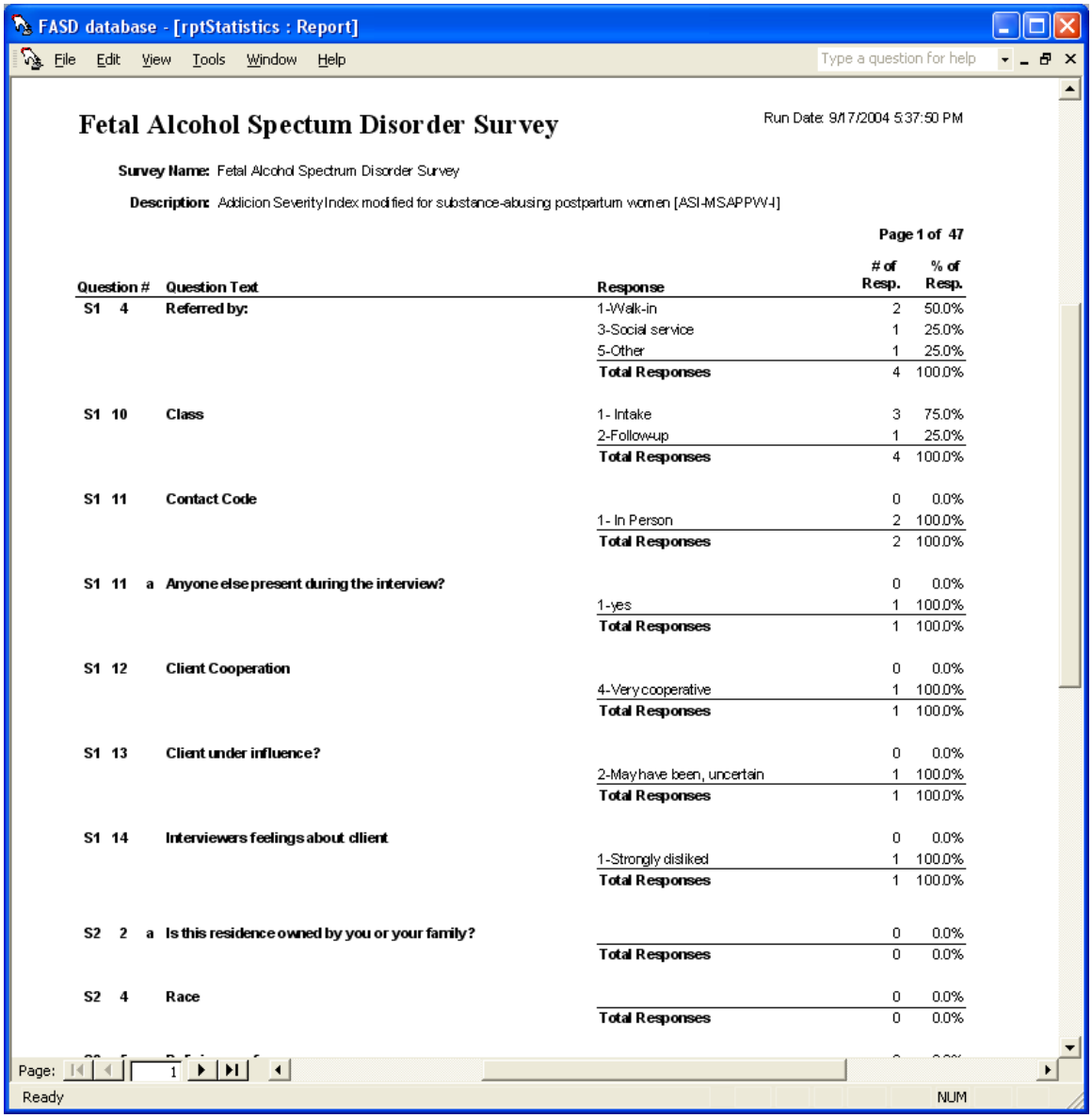
2. The "One or All Responses" report prints out a copy of the survey as the respondent might have completed it. Each respondent with location and interviewer's name will start on a new page. The survey's name and brief description are also printed in the report header. After selecting this

report, a combo box will appear at right hand side allowing the user to select either an individual respondent by name or all respondents.



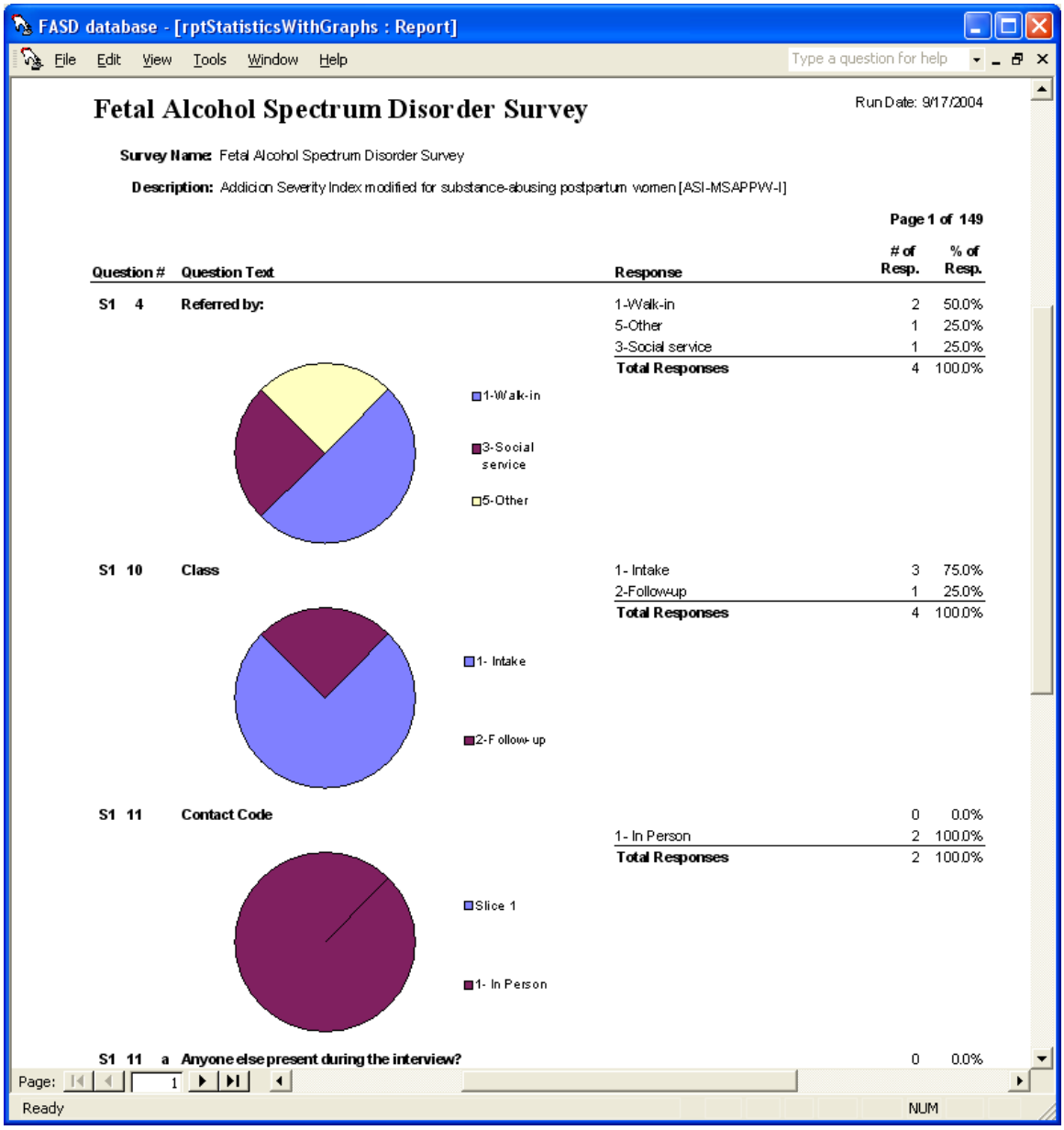
Screen 4 – Report individual respondent or all

3. The "Statistics Summary" button totals the responses to the questions of the "Statistics" type. Each statistic type question is printed on the left with every unique response and a count on the right. Percents of the total are also listed. The report can be printed out, or sent to Microsoft Word or Excel.



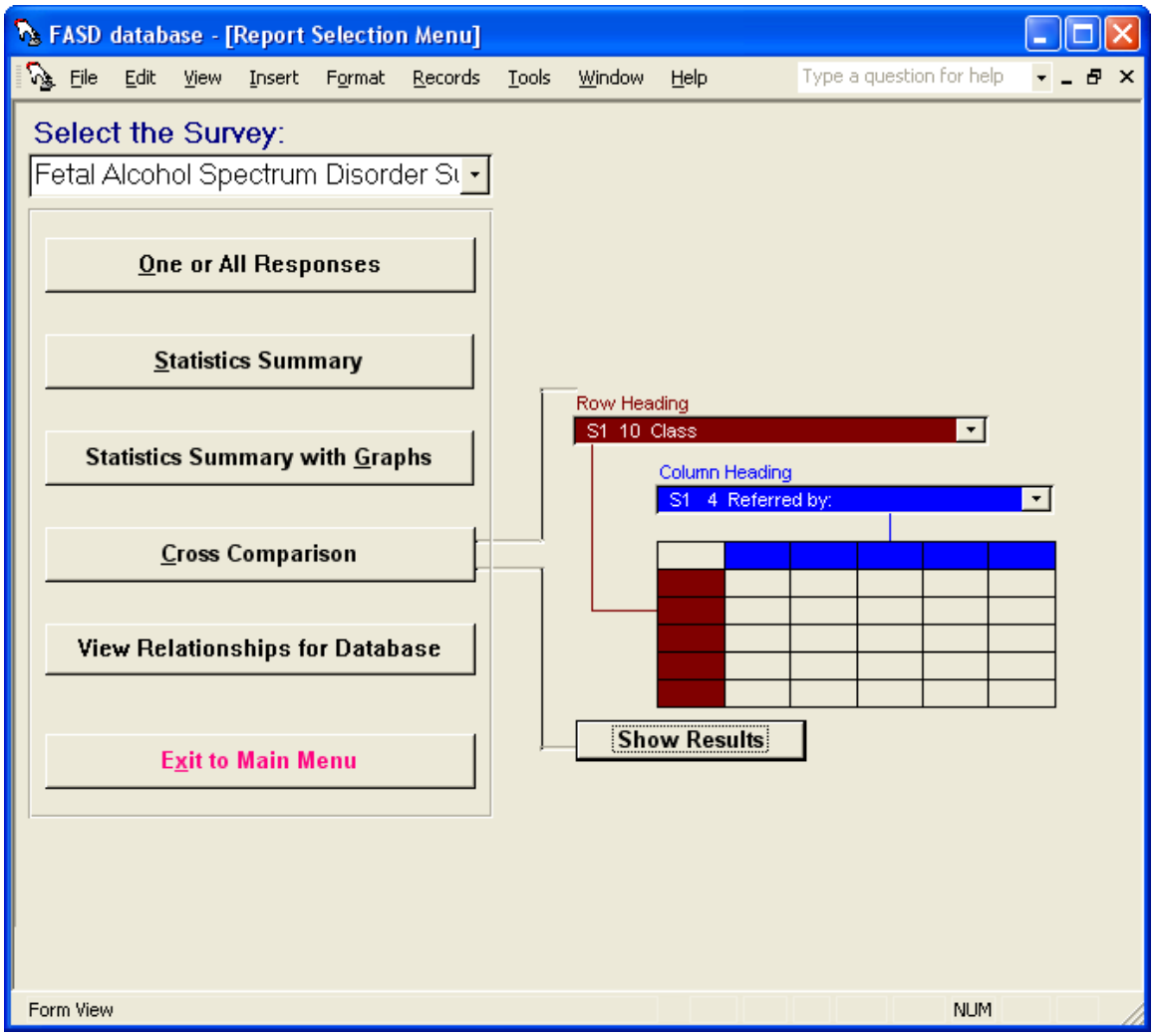
Screen 5 – Statistic Summary Report

4. The "Statistic Summary with Graphs" button is similar to the previous report except that each question includes a pie chart to visually present the information. In order for this report to run, MS Access must have been set up with the inclusion of the Microsoft Graph5 application. Same as previous statistic report, this report can also be printed out, or sent to Microsoft Word or Excel.



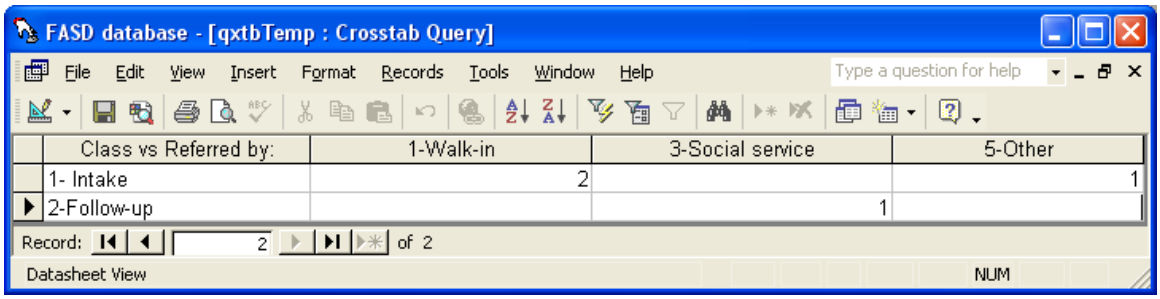
Screen 6 - Statistic Summary Report with Graphs

5. The "Cross Comparison" button allows the user to view how two questions relate to each other. For example, in FASD survey section 1, question 4 "Referred by" and question 10 "Class" could be shown versus the In-take or follow-up interview to how respondent was referred. Any two questions can be chosen to display their cross comparison.



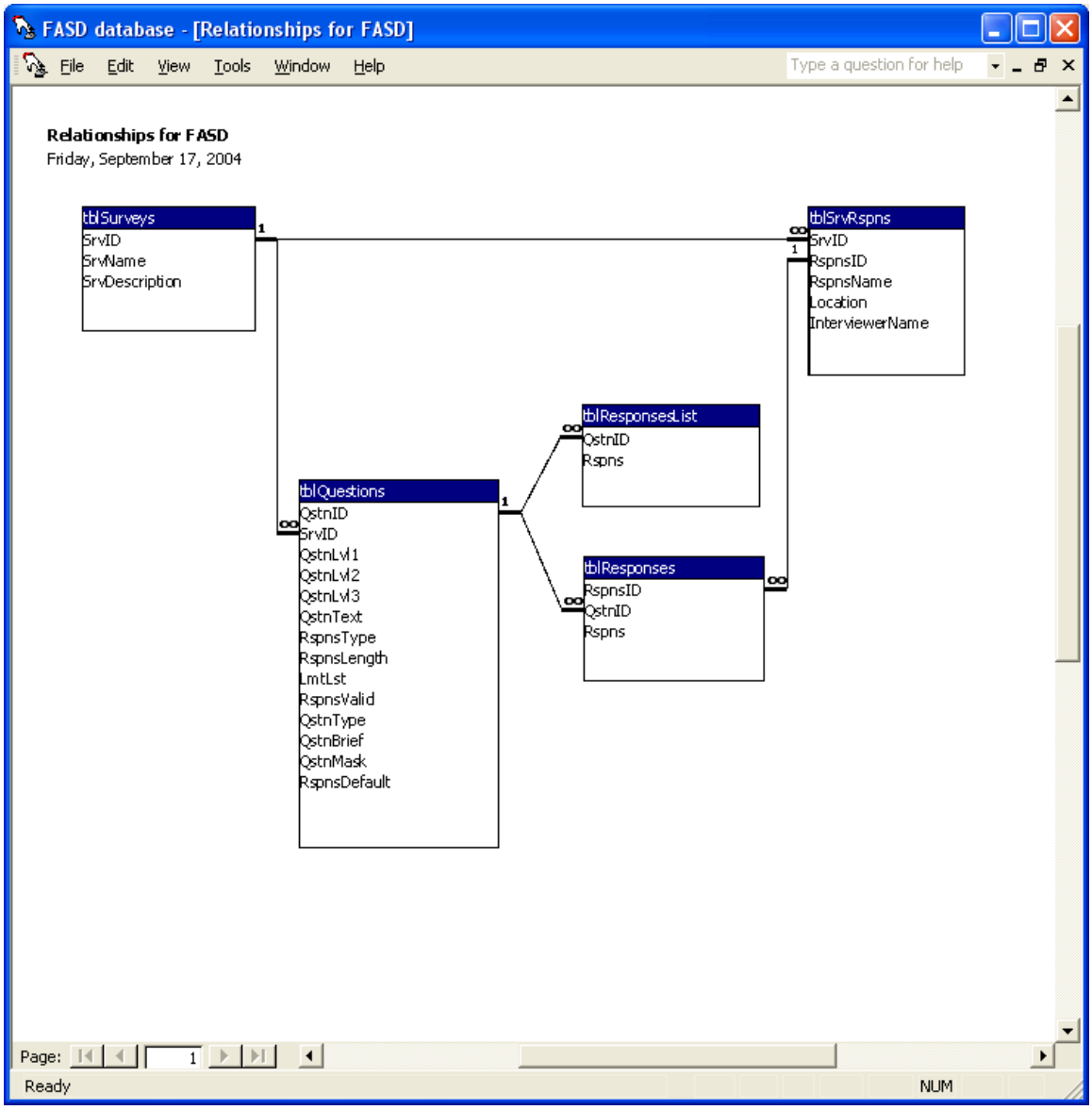
Screen 7 – Cross Comparison Definition

The result is displayed in sheet view. The view can be formatted, printed out, or sent to Excel.



Screen 8 – Cross Comparison Result

6. The "View Relationships for Database" button allows user to view the table relationships for the FASD database.



Screen 9 – Relationships for Database

7. Click the red button "Exit to Main Menu" to return to Main Menu window.

APPENDIX B

Research List

FASD Positive/Negative Risk Factor Research

Note: The selected clinical assessments tools have been selected and modified into an FASD Database for the sole purpose of conducting an FASD research project titled: Joint Blood Reserve, Lakeland, and Lethbridge Project on Prevention of Fetal Alcohol Spectrum Disorder.

Outline of the following assessment tools:

6. Addiction Severity Index (ASI)
7. Addiction Severity Index (ASI) North Dakota/Native American Version (ND/NAV)
8. Family APGAR
9. Center for Epidemological Studies (CES-D) Major Depressive Disorder Scale
10. CEBU Longitudinal Health and Nutrition Study

Questionnaire forms:

1. **Addiction Severity Index (ASI)**

The Addiction Severity Index is a relatively brief, semi-structured interview designed to provide important information about aspects of a client's life which may **contribute to her substance abuse syndrome.** We use a modified version of the 5th edition of the Addiction Severity Index that includes the following:

- General Information
  - Target Child, Other Bio. Children & Family Planning
- Legal Status
- Medical Status
- Psychiatric Status
- Employment/Support Status
- Family History

  - Childhood History
- Family & Social Relationships
  - Community Services

Reference:

http://depts.washington.edu/fadu/ASIExitManual.pdf

2. **Addiction Severity Index (ASI) North Dakota/Native American Version (ND/NAV)**

The Addiction Severity Index (ASI), used throughout the United States and in numerous other countries, is the most widely used assessment tool in the addictions field. It is a semi-structured assessment instrument designed for use with clients who present for substance abuse treatment. The ASI was developed in 1980 by A. Thomas McLellan, Ph.D., and colleagues at the University of Pennsylvania (McLellan et al. 1980). The ASI gathers information in seven important areas of a patient's life: medical, employment/support, drug and alcohol use, legal, family history, family/social

relationships, and psychological problems. **An eighth area, spiritual and ceremonial practices, has been added to the ASI adapted for North Dakota State, which was designed with consideration for Native American cultural and ceremonial practices.**

Addiction Severity Index (ASI) North Dakota/Native American Version (ND/NAV) that includes the following:

- Tribal Affiliation
- Spiritual and Ceremonial Practices

Reference:

http://www.treatment.org/documents/pdf/chapter1_3.pdf

3. Family APGAR

The **Family APGAR** is a 5-item measure of **family** function as assessed by the parent's report of satisfaction with 5 parameters of **family** function.

- FAMA1 - Can turn to **family** for help
- FAMA2 - **Family** talks over and shares problems
- FAMA3 - **Family** supports my new activities
- FAMA4 - Affectionate, responds to emotions
- FAMA5 - **Family** and I share time together

Reference

http://www.google.ca/search?q=cache:NOG-O54qZQ0J:www.sph.unc.edu/iprc/longscan/Measures%2520Manual/Baseline/s17.pdf++site:www.sph.unc.edu+Family+APGAR&hl=en&ie=UTF-8

4. Center for Epidemological Studies (CES-D) Major Depressive Disorder Scale

The Center for Epidemiological Studies-Depression Scale (CES-D) is a 20-item instrument that was developed by the National Institute of Mental Health to detect major or clinical depression in adolescents and adults.

The CES-D has 4 separate factors:

- Depressive affect
- Somatic symptoms
- Positive affect
- Interpersonal relations

The questions are easy to answer and cover most of the areas included in the diagnostic criteria for depression. It has been used in urban and rural populations, and in cross-cultural studies of depression. Studies using the CES-D indicate that it has very good internal consistency, acceptable test-retest stability, and construct validity.

The CES-D takes approximately 10 minutes to administer during a client interview or via self-report and is effectively used in a variety of mental health areas including primary care, psychiatric, and related clinical and forensic settings.

Reference:

http://www.assessments.com/catalog/CES_D.htm

5. CEBU Longitudinal Health and Nutrition Study

To better understand the relationships among childbearing, women's work, and women's autonomy in decision-making, researchers conducted a follow-up study to the 1983-86 Cebu Longitudinal Health and Nutrition Survey. The original survey included more than 3,000 pregnant women in 33 barangays (health units), who answered questions about maternal health and nutrition. Women were surveyed in 1991-92 and again in 1994-95 to explore changes in the reproductive lives.

A modified version was applied to fit our study. The nutrition section includes the following:

- General Information
  - Current Status
  - Spending patterns
  - Support systems: Services agencies
  - Nutrition patterns: Four food groups
  - Children (s) Nutrition patterns.

The questions were design to understand if the women nutrition patterns contributed to the risk factors of producing an FASD child.

Reference:

http://www.fhi.org/en/RH/Pubs/wsp/fctshts/Philippines1.htm

http://www.cpc.unc.edu/projects/cebu/codebook/1991/91quest.pdf

APPENDIX C

Partnership Agreement

Canadian Centre for Behavioural Neuroscience (CCBN)

of

University of Lethbridge

AND

First Steps for Healthy Babies Prevention Program

of

Blood Tribe Dept of Health Inc. (BTDH)

Joint Blood Tribe, Lakeland, and Lethbridge Project

on

Effective FASD Prevention

June 2004 – May 2005

Primary Research Objectives

Blood Tribe Dept Health – First Steps for Health Babies Prevention Program and the Canadian Centre for Behavioural Neuroscience of the University of Lethbridge agrees to work in partnership to mount an interdisciplinary research project that will have three primary objectives:

1. To measure the effectiveness of the prevention program through collecting relevant information and establishing a continuing FASD Database. (See Appendix I: List of categories information to be collected)
2. To collaborate in a comparative study on measuring the three prevention programs.
    a. Blood Tribe Dept of Health – First Steps for Healthy Babies program,
    b. Lethbridge – First Steps program and
    c. Cold Lake – Lakeland Centre for Fetal Alcohol Spectrum Disorder
3. To evaluate neuropsychological functioning in high-risk women, especially in relation to the criteria for the categories of FASD.

Other Objectives

1. To promote networking around FASD and to reinforce on-going funding support through communicating research results. To assist in influencing policies and regulations at a local, provincial, and national level.
2. To assist in training research assistants and First Steps mentors.
3. To provide training in neuropsychological assessment as requested by the Blood Tribe and as is available through CCBN and the University of Lethbridge.
4. To facilitate the creation of independent research programs on the Blood Reserve.
5. To foster collaborative projects involving the Blood Reserve and the University of Lethbridge.
6. To provide constructive feedback that can be used to improve services and effectiveness of First Steps for Healthy Babies.
7. To provide constructive feedback from service providers that can be used to improve future research methodology.

Financial & Supervisory Obligations

The Canadian Centre for Behavioural Neuroscience of the University of Lethbridge agrees to provide funding for one full-time researcher/mentor for the First Steps for Healthy Babies program on the Blood Reserve.

The Canadian Centre for Behavioural Neuroscience agrees to pay for:

- ✓ Researcher/mentor full-time wage
- ✓ Job expenses for researcher/mentor:
    - Training: Research Training & Mentorship Training
    - Workshops, Conferences, Seminars,
    - Travel expenses: mileage, accommodations, food, incidentals.
    - Supplies
    - Rental of 1 office space
- ✓ Research Training for Coordinator and mentors on research methods and operations.
- ✓ One lap-top computer will be provide for researcher/mentor employee

The Coordinator of the First Steps for Healthy Babies program on the Blood Reserve will provide supervision and in service training of the researcher/mentor employee in respect to mentor activities. Thus, CCBN and the Coordinator of the First Steps for Healthy Babies program on the Blood Reserve will serve as co supervisors of this employee. A safe workplace in Standoff for the research assistant/mentor will be provided by First Steps for Healthy Babies.

Intellectual Property Rights

The Partnership Agreement fully states that no royalties or financial benefits will be derived from this research project.

Any material created by the partnership agreement for the purpose of publication will require informed consent by the CEO of the Blood Tribe Department of Health (or its designate) and the Director of CCBN (or designate). The data collected remain the property of the Blood Tribe as represented by the CEO of the Blood Tribe Department of Health (or its designate).

This agreement shall remain in force until the first anniversary of the beginning of the project.

The FASD data refers to *raw data* collected within your organization (Blood Tribe) is for the purpose of informing policy decisions, case management, improving service delivery, financial budgeting, and seeking program funding.

The collaborated data refers to Lethbridge, Blood Tribe and Lakeland FASD raw data held in trustee of CCBN for the sole purpose of producing a final report for Alberta

Centre for Child, Family and Community Research. The final report is for the shared purpose of informing policy decisions, case management, improving service delivery, financial budgeting, and program funding.

The overall purpose is to promote practices that decrease the number of FASD affected individuals and decrease the personal, family, medical, and societal costs of FASD.

Definition of Roles and Responsibilities

See Appendix II

Confidentiality

It is agreed that all information collected as part of this partnership agreement shall not identify any person participating or provide information that could be used to identify any person participating. (See Appendix III for the Informed Consent form and for a list of overarching ethical principles).

Amendments

This agreement can be amended as result of a further agreement between the Director of CCBN and CEO BTDH with consultation with the Research Project Advisory Committee and the First Steps Core Committee.

Signed on behalf of CCBN Inc.	Signed on behalf of Blood Tribe Dept of Health
_____	_____
Robert James Sutherland	Charles Weasel Head
Director, CCBN	Chief Executive Officer
	Blood Tribe Dept of Health Inc.

Signed on this day_____at _____

Appendix I

Research List

Part A: Background Informational Research

This section of questionnaires is included in Part B (see Part B's Questionnaire Forms).

Part B: FASD Positive/Negative Risk Factor Research

Outline of Questionnaire Forms:

1. Addiction Severity Index (ASI)
2. Native American Version (ASI) – Tribal Affiliation
3. Native American Version (ASI) – Spiritual & Ceremonial Practice
4. Cultural/Spiritual Questionnaire
5. Family APGAR
6. Major Depressive Disorder Scale (CES-D)
7. SAQ Self-Administrative Questionnaire

8. Household Questionnaire – Background characteristics, Fertility/pregnancy and Family Planning/sexual experience (contraceptives).
9. Mother's Diet

Note: Questionnaire forms may be modify in the development and implementation stage of research project.

- Attached are the Questionnaire Forms.

Part C: Neuropsychological Assessment Research

- Client information
  - Neuropsychological Assessment CCBN
- Birth Statistics
  - Number of Births
  - Number of FASD Births.
  - Number of probable FASD Births.

This section requires outside assistance i.e. administration, hospitals etc.

Appendix II

Definition of Roles and Responsibilities

TITLE

Joint Blood Tribe, Lakeland, and Lethbridge Project on Effective FASD Prevention

FUNDING AGENCY

Alberta Centre for Child, Family and Community Research

PRINCIPAL INVESTIGATOR

Robert J. Sutherland

Alberta Heritage Medical Scientist

Director, Canadian Centre for Behavioural Neuroscience

Professor, Dept of Psychology and Neuroscience

University of Lethbridge

4401 University Drive

Lethbridge AB Canada

T1K 3M4

Office: 403-394-3987

Admin Assistant: 403-394-3979

Fax: 403-329-2775

E-mail: robert.sutherland@uleth.ca

Responsibilities

- Project design and oversight
- Publication/public relations
- Budget management

CO-INVESTIGATOR

Robert Williams

Faculty of Health Sciences

University of Lethbridge

4401 University Drive

Lethbridge AB Canada

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Office: 403-328-7128

Responsibilities

- Assist principal investigator

ADVISORY COMMITTEE

1. Charlie Weasel Head, CEO Blood Tribe Dept of Health Inc.
2. Audrey McFarlane, Executive Director Lakeland Centre for FASD
3. Sharlene Campbell, Regional Manager Lethbridge First Steps Programme
4. Rebecca Many Grey Horses, Coordinator First Steps for Healthy Babies Programme
5. Lynn Basford, Dean, Faculty of Health Sciences University of Lethbridge

Responsibilities

- Quarterly meetings to review progress
- Advice on overcoming unexpected difficulties
- On-line virtual meetings as advice or updates are needed

PUBLICATION COMMITTEE

1. Robert Sutherland, Director CCBN
2. Charlie Weasel Head , CEO Blood Tribe Dept of Health Inc.
3. Audrey McFarlana, Executive Director, Lakeland Centre for FASD
4. Sharlene Campbell, Regional Manager Lethbridge First Steps Programme

Responsibilities

- Before the fact, requests will be made to communicate results of the project through any media, at meetings, or through publication (in print or on-line).
- The committee will review and respond in writing to such requests in a timely manner. Approval of a research communication will require an affirmative vote of the majority of the committee.

STAFF

1. Research assistant/mentor, Blood Tribe First Steps for Healthy Babies Programme
2. Research assistant/mentor, Lethbridge First Steps Programme
3. Research assistant/mentor, Lakeland Centre for FASD
4. Research assistant/database coordinator, CCBN

All staffing decisions, including committee membership, will be the responsibility of the Principal Investigator who will consult with the Co-Investigator and the relevant constituencies.

CONTACT INFORMATION

Robert J. Sutherland

Principal Investigator

Alberta Heritage Medical Scientist

Director, Canadian Centre for Behavioural Neuroscience

Professor, Dept of Psychology and Neuroscience

University of Lethbridge

4401 University Drive

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Office: 403-394-3987

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Fax: 403-329-2775

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Robert Williams

Assistant Principal Investigator

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Charlie Weasel Head

Chief Executive Officer

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Rebecca Many Grey Horses

Coordinator

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Dean

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Office: 403-317-2810

Appendix III

Informed Consent

&

Ethical Conduct for Research Involving Humans

Insert 1: Consent Form

Insert 2: Neuropsychological Assessment Consent Form

Insert 3: Tri-Council Policy Statement Ethical Conduct for Research Involving Humans

Releases Form

I. _____, consent to be a participant in the research project titled: **Joint Blood Tribe, Lakeland, and Lethbridge Project on Effective FASD Prevention.**

I understand that the purpose of the project is to collect Fetal Alcohol Spectrum Disorder (FASD) data for the purpose of improving service delivery for **First Steps for Healthy Babies Program - Blood Tribe Dept of Health Inc.**

I understand that Canadian Centre of Behavioral Neuroscience is administrating the research service on behalf of the **First Steps for Healthy Babies Program - Blood Tribe Dept of Health Inc.**

I understand that the information collected may be used for scholarly, educational, and other purposes.

I understand that the **First Steps for Healthy Babies Program - Blood Tribe Dept of Health Inc.** will keep my identity and participation anonyms and at no time would the information be used against me.

ACCEPTED AND AGREED

Signature _____Date _____

Printed name _____

Address_____ Postal Code _____

Telephone ( ) _____

Partnership Agreement

Canadian Centre for Behavioural Neuroscience (CCBN)

of

University of Lethbridge

AND

Lakeland Centre for Fetal Alcohol Spectrum Disorder

Joint Blood Tribe, Lakeland, and Lethbridge Project

on

Effective FASD Prevention

June 2004 – May 2005

Primary Research Objectives

Lakeland Centre for Fetal Alcohol Spectrum Disorder prevention program and the Canadian Centre for Behavioural Neuroscience of the University of Lethbridge agrees to work in partnership to mount an interdisciplinary research project that will have three primary objectives:

4. To measure the effectiveness of the prevention program through collecting relevant information and establishing a continuing FASD Database. (See Appendix I: List of categories information to be collected)

5. To collaborate in a comparative study on measuring the three prevention programs.
    a. Blood Tribe Dept of Health – First Steps for Healthy Babies program,
    b. Lethbridge – First Steps program and
    c. Cold Lake – Lakeland Centre for Fetal Alcohol Spectrum Disorder
6. To evaluate neuropsychological functioning in high-risk women, especially in relation to the criteria for the categories of FASD.

Other Objectives

8. To promote networking around FASD and to reinforce on-going funding support through communicating research results. To assist in influencing policies and regulations at a local, provincial, and national level.
9. To assist in training research assistants and First Steps mentors.
10. To provide training in neuropsychological assessment as requested by the Lakeland Centre for Fetal Alcohol Spectrum Disorder and as is available through CCBN and the University of Lethbridge.
11. To facilitate the creation of independent research programs with Lakeland Centre for Fetal Alcohol Spectrum Disorder.
12. To foster collaborative projects involving the Lakeland Centre for Fetal Alcohol Spectrum Disorder and the University of Lethbridge.
13. To provide constructive feedback that can be used to improve services and effectiveness of Lakeland Centre for Fetal Alcohol Spectrum Disorder.
14. To provide constructive feedback from service providers that can be used to improve future research methodology.

Financial & Supervisory Obligations

The Canadian Centre for Behavioural Neuroscience of the University of Lethbridge agrees to provide funding for one full-time researcher/mentor for the Lakeland Centre for Fetal Alcohol Spectrum Disorder program.

The Canadian Centre for Behavioural Neuroscience agrees to pay for:

- ✓ Researcher/mentor full-time wage
- ✓ Job expenses for researcher/mentor:
    - Training: Research Training & Mentorship Training
    - Workshops, Conferences, Seminars,
    - Travel expenses: mileage, accommodations, food, incidentals.
    - Supplies
    - Rental of 1 office space
- ✓ Research Training for Coordinator and mentors on research methods and operations.
- ✓ One lap-top computer will be provide for researcher/mentor employee

The Executive Director of the Lakeland Centre for Fetal Alcohol Spectrum Disorder program will provide supervision and in service training of the researcher/mentor employee in respect to mentor activities. Thus, CCBN and the Executive of the Lakeland Centre for Fetal Alcohol Spectrum Disorder program will serve as co supervisors of this employee. A safe workplace in Cold Lake for the research assistant/mentor will be provided by Lakeland Centre for Fetal Alcohol Spectrum Disorder.

Intellectual Property Rights

The Partnership Agreement fully states that no royalties or financial benefits will be derived from this research project.

Any material created by the partnership agreement for the purpose of publication will require informed consent by the Executive Director of the Lakeland Centre for Fetal Alcohol Spectrum Disorder (or its designate) and the Director of CCBN (or designate). The data collected remain the property of the Lakeland Centre for Fetal Alcohol Spectrum Disorder as represented by the Executive Director of the Lakeland Centre for Fetal Alcohol Spectrum Disorder (or its designate).

This agreement shall remain in force until the first anniversary of the beginning of the project.

The FASD data refers to *raw data* collected within your organization (Lakeland) is for the purpose of informing policy decisions, case management, improving service delivery, financial budgeting, and seeking program funding.

The collaborated data refers to Lethbridge, Blood Tribe and Lakeland FASD raw data held in trustee of CCBN for the sole purpose of producing a final report for Alberta

Centre for Child, Family and Community Research. The final report is for the shared purpose of informing policy decisions, case management, improving service delivery, financial budgeting, and program funding.

The overall purpose is to promote practices that decrease the number of FASD affected individuals and decrease the personal, family, medical, and societal costs of FASD.

Definition of Roles and Responsibilities

See Appendix II

Confidentiality

It is agreed that all information collected as part of this partnership agreement shall not identify any person participating or provide information that could be used to identify any person participating. (See Appendix III for the Informed Consent form and for a list of overarching ethical principles).

Amendments

This agreement can be amended as result of a further agreement between the Director of CCBN and Executive Director of the Lakeland Centre for Fetal Alcohol Spectrum Disorder with consultation with the Research Project Advisory Committee.

Signed	Signed
on behalf of CCBN	on behalf of Lakeland Centre for Fetal Alcohol Spectrum Disorder
_____	_____
Robert James Sutherland	Audrey McFarlane
Director, CCBN	Executive Director
	Lakeland Centre for Fetal Alcohol Spectrum Disorder

Signed on this day_____ at _____

Appendix I

Research List

Part A: Background Informational Research

This section of questionnaires is included in Part B (see Part B's Questionnaire Forms).

Part B: FASD Positive/Negative Risk Factor Research

Outline of Questionnaire Forms:

10. Addiction Severity Index (ASI)
11. Native American Version (ASI) – Tribal Affiliation
12. Native American Version (ASI) – Spiritual & Ceremonial Practice
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16. SAQ Self-Administrative Questionnaire
17. Household Questionnaire – Background characteristics, Fertility/pregnancy and Family Planning/sexual experience (contraceptives).
18. Mother's Diet

Note: Questionnaire forms may be modify in the development and implementation stage of research project.

- Attached are the Questionnaire Forms.

Part C: Neuropsychological Assessment Research

- Client information
  - Neuropsychological Assessment CCBN

- Birth Statistics
    - Number of Births
    - Number of FASD Births.
    - Number of probable FASD Births.

This section requires outside assistance i.e. administration, hospitals etc.

Appendix II

Definition of Roles and Responsibilities

TITLE

Joint Blood Tribe, Lakeland, and Lethbridge Project on Effective FASD Prevention

FUNDING AGENCY

Alberta Centre for Child, Family and Community Research

PRINCIPAL INVESTIGATOR

Robert J. Sutherland

Alberta Heritage Medical Scientist

Director, Canadian Centre for Behavioural Neuroscience

Professor, Dept of Psychology and Neuroscience

University of Lethbridge

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Responsibilities

- Project design and oversight
- Publication/public relations
- Budget management

CO-INVESTIGATOR

Robert Williams

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4401 University Drive

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Office: 403-328-7128

Responsibilities

- Assist principal investigator

ADVISORY COMMITTEE

3. Charlie Weasel Head, CEO Blood Tribe Dept of Health Inc.
4. Audrey McFarlane, Executive Director Lakeland Centre for FASD
6. Sharlene Campbell, Regional Manager Lethbridge First Steps Programme
7. Rebecca Many Grey Horses, Coordinator First Steps for Healthy Babies Programme
8. Lynn Basford, Dean, Faculty of Health Sciences University of Lethbridge

Responsibilities

- Quarterly meetings to review progress
- Advice on overcoming unexpected difficulties
- On-line virtual meetings as advice or updates are needed

PUBLICATION COMMITTEE

5. Robert Sutherland, Director CCBN
6. Charlie Weasel Head , CEO Blood Tribe Dept of Health Inc.
7. Audrey McFarlana, Executive Director, Lakeland Centre for FASD
8. Sharlene Campbell, Regional Manager Lethbridge First Steps Programme

Responsibilities

- Before the fact, requests will be made to communicate results of the project through any media, at meetings, or through publication (in print or on-line).
- The committee will review and respond in writing to such requests in a timely manner. Approval of a research communication will require an affirmative vote of the majority of the committee.

STAFF

5. Research assistant/mentor, Blood Tribe First Steps for Healthy Babies Programme
6. Research assistant/mentor, Lethbridge First Steps Programme
7. Research assistant/mentor, Lakeland Centre for FASD
8. Research assistant/database coordinator, CCBN

All staffing decisions, including committee membership, will be the responsibility of the Principal Investigator who will consult with the Co-Investigator and the relevant constituencies.

CONTACT INFORMATION

Robert J. Sutherland

Principal Investigator

Alberta Heritage Medical Scientist

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Sharlene Campbell

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Appendix III

Informed Consent

&

Ethical Conduct for Research Involving Humans

Insert 1: Consent Form

Insert 2: Neuropsychological Assessment Consent Form

Insert 3: Tri-Council Policy Statement Ethical Conduct for Research Involving Humans

Releases Form

I. _____, consent to be a participant in the research project titled: **Joint Blood Tribe, Lakeland, and Lethbridge Project on Effective FASD Prevention.**

I understand that the purpose of the project is to collect Fetal Alcohol Spectrum Disorder (FASD) data for the purpose of improving service delivery for **Families First and First Steps – Lethbridge.**

I understand that Canadian Centre of Behavioral Neuroscience is administrating the research service on behalf of the **Families First and First Steps – Lethbridge.**

I understand that the information collected may be used for scholarly, educational, and other purposes.

I understand that the **First Families First and First Steps – Lethbridge** will keep my identity and participation anonyms and at no time would the information be used against me.

ACCEPTED AND AGREED

Signature _____Date _____

Printed name _____

Address_____ Postal Code _____

Telephone ( ) _____