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Emotion-related learning in individuals prenatally exposed to alcohol: an investigation of the relation between set shifting, extinction of responses, and behavior

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Abstract

The association between deficits in emotion-related learning, conceptual set shifting, and behavioral problems was investigated in individuals with substantial prenatal alcohol exposure. Twenty subjects with confirmed prenatal alcohol exposure (10 of whom were diagnosed as having Fetal Alcohol Syndrome) and 20 normal controls matched for age, gender, and ethnic background participated. The two groups were administered a battery of tests including two tests of emotion-related learning (visual discrimination reversal and extinction of reward–response associations), tests of conceptual set shifting and intellectual ability, and behavioral measures. The alcohol-exposed group made fewer reversals than the control group in visual discrimination reversal and exhibited more variability in extinction. These group differences remained significant after controlling for intellectual ability and conceptual set shifting. Variability in extinction and two measures of set shifting, perseverative errors on the Wisconsin Card Sorting Test and omission errors on reversal learning, were found to be robust predictors of parent-rated behavioral problems.
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1. Introduction

It is now established that excessive maternal consumption of alcohol during pregnancy can produce a constellation of anomalies known as fetal alcohol syndrome (FAS) in offspring. Depending on a host of moderating factors, such as maternal age [14], frequency, quantity, and timing of exposure [22], the deleterious effects of alcohol on the fetus are known to vary widely. The full-blown syndrome is characterized by a unique pattern of facial dysmorphia (e.g. short palpebral fissures and abnormalities in premaxillary zone), prenatal and postnatal growth retardation, and abnormal brain function reflected in cognitive dysfunction [16]. In lesser manifestations of the disorder, some physical anomalies and neurodevelopmental problems can be seen without facial dysmorphia [30].

Neurodevelopmental studies of FAS over the past 3 decades have revealed specific patterns of cognitive deficits in affected individuals. There is converging evidence that alcohol-affected individuals show difficulty with complex tasks that involve holding and manipulating information in working memory. Tests measuring executive control functioning typify such complex tasks. Several researchers have reported that children exposed to alcohol prenatally perform less competently than controls on the Wisconsin Card Sorting Test, a classic test of executive control functioning [4,17]. Alcohol-affected children tend to make more perseverative errors and consequently complete fewer categories on this test. Alcohol-exposed children also tend to exhibit marked deficits in planning ability, as indicated by poorer performance on look-ahead puzzles [17]. Kodituwakku et al. [17] also found that alcohol-affected

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children performed less proficiently than controls on letter fluency, non-verbal analogic reasoning and complex tests of attention. There is evidence that alcohol-affected children exhibit deficient skills in hypothesis testing, as reflected by impaired performance on tests such as the 20-questions Test (A.M. Goodman, S.N. Mattson, A.R. Lang, & E.P Riley, 1999, unpublished data).

The foregoing tests of executive control functioning can be characterized as involving complex cognitive skills. Both animal and human research justifies drawing a distinction between cognitive and emotional aspects of executive control functioning [6]. While cognition-related executive skills involve holding, updating, and manipulation of non-emotional, complex information in working memory (e.g. solving a novel math problem), emotion-related abilities involve establishment and modification of behavioral sets based on emotionally significant information. Establishment of a reward–response association in a flexible manner represents this latter set of skills. There is increasing evidence that the dorsolateral sector of the prefrontal cortex plays a critical role in cognition-related executive skills, whereas the orbitofrontal cortex is preferentially involved in emotion-related executive skills. Damasio and his colleagues [2,6] have demonstrated that patients with orbitofrontal damage exhibited marked difficulty in an experimental gambling task, which was designed to measure reward–response decision making, despite their relatively preserved cognition-related executive control skills. Rolls and colleagues [29] have reported that patients with orbitofrontal damage are markedly deficient in emotion-related learning. The patients with orbitofrontal damage failed to modify behavior in response to changing reinforcement conditions on a test of reversal learning. Bechara et al. [2] and Rolls et al. [29] have both reported that deficient performance of orbitofrontal patients on tests of emotion-related executive functioning predicted these patients' dysfunctional behaviors of daily living.

Pertinent to the dissociation between cognitive and emotional aspects of executive functioning is the increasing evidence for a distinction between attentional and affective shifts [7,8,27]. An attentional shift occurs when the subject switches attention from one dimension of a stimulus to another dimension when it is necessary. The Wisconsin Card Sorting Test (WCST) typifies a method designed to assess attentional shift, as this test requires the subject to switch attention from one stimulus dimension to another, e.g. color, shape, and number (we used the term, conceptual set shifting, in this paper to denote attentional shifts in the WCST). In contrast, affective shifts involve reversal of a stimulus–reward association, which is measured by reversal learning tasks. In a typical reversal learning task, the subject is presented with two stimuli, with one of them being rewarding and the other non-rewarding. When the subject has learned to respond to the rewarding stimulus and to withhold responses to the non-rewarding stimulus, the reinforcement contingency changes without warning, requiring the subject to reverse responses. Using a primate analogue of the WCST, Dias et al. [8] have demonstrated a double dissociation between attentional and affective shifts in the prefrontal cortex. These researchers found that lateral, but not orbitofrontal cortex, played a critical role in attentional shift and that orbitofrontal, but not lateral frontal cortex was the critical locus for affective shift.

While individuals with Fetal Alcohol Syndrome are known to display a range of behavioral and emotional difficulties, no studies of emotion-related aspects of executive control functioning in alcohol-affected humans have yet been published. There exist, however, animal models in which impairments of emotion-related learning have been demonstrated in association with prenatal alcohol exposure. Riley and colleagues [25] found that alcohol-exposed rats were deficient in reversal learning in a T-maze shock escape paradigm. Liquid diets containing either 35%, 17%, or 0% ethanol derived calories (EDC) were administered to mothers on days 5–20 of pregnancy and offspring were tested on postnatal days 20–21. In the acquisition phase, the animals were trained to run to their non-preferred side of the T-maze to escape a mild shock. After reaching a learning criterion, reversal training began during which the animals had to run to the previously incorrect side to escape shock. Despite a lack of significant group difference in the acquisition phase, alcohol-exposed offspring made more errors than controls in reversal learning. Furthermore, this deficit was found to have a linear association with the amount of EDC consumed by the mother. Subsequently, a number of other researchers have demonstrated deficient reversal learning in alcohol-exposed animals [1,18,34].

Lilliquist et al. [19] have reported that rats exposed to alcohol in the early postnatal period, which corresponds to the third trimester in humans [9], display a resistance to extinction of a learned response. It is known that a partially reinforced response is more resistant to extinction than a continuously reinforced response, an effect termed the partial reinforcement extinction effect (PREE). Lilliquist et al. [19] found that rats with high peak exposure to alcohol during early infancy exhibited a disruption of PREE, with alcohol-affected animals that were on a continuous reinforcement schedule displaying an abnormal persistence during extinction trials.

The present study extended to humans the above animal models of the adverse effects of ethanol exposure on emotion-related learning. It utilized tests of visual discrimination reversal and extinction developed by Rolls et al. [29]. Some modifications to test instructions and procedures were made in order to make these

tests suitable for children with cognitive dysfunction. It was hypothesized that alcohol-affected individuals would be deficient in visual discrimination reversal and extinction of learned responses. It was also hypothesized that deficient performance of alcohol affected individuals on reversal learning would be independent of that on a measure of attentional or conceptual set shifting. Furthermore, it was expected that deficient performance on emotional set shifting tasks would predict behavioral problems in these individuals as reported by their caregivers.

2. Methods

2.1. Participants

The participants in this study were 20 children and young adults with a confirmed history of prenatal alcohol exposure and 20 controls. As shown in Table 1, the alcohol-affected group ranged in age from 7.67 to 19.42 years with a mean of 11.12 years. This group, which included 13 males and 7 females, was recruited almost exclusively from ethnic minority populations in the Southwestern US (i.e. American Indian = 13; Hispanic = 6; Caucasian = 1). Parents/caregivers of 32 potential subjects were invited to participate in the study by means of a letter that described the purpose of the project. A research assistant identified these subjects through a register in the Genetics and Dysmorphology Clinic at the University of New Mexico. In order to assure optimal performance on the primary tests employed in the study, only those who were in the age range 7–20 were included. The following exclusionary criteria were applied in the selection of subjects: moderate to severe mental retardation, lack of fluency in English, and a history of head trauma with loss of consciousness or major neurological/psychiatric illness that required medication (e.g. seizure disorder). There were 24 replies and five undelivered letters due to change of address. One of the subjects was excluded because of mental retardation, and three were excluded because of being younger than the above minimum age.

Ten of the 20 who met the study criteria were previously diagnosed by two dymorphologists/geneticists at the University of New Mexico (Jon Aase, M.D. and Carol Clericuzio, M.D.) as having Fetal Alcohol Syndrome (FAS) and the others as having prenatal alcohol exposure without FAS. While 3 of the 10 alcohol-exposed participants without FAS displayed isolated dysmorphic features often associated with the syndrome (e.g. smooth philtrum) 5 of them showed random minor anomalies (e.g. strabism). As is shown in Table 2, these two alcohol-exposed groups were comparable with respect to age, intellectual ability (Raven Standard Matrices), conceptual set shifting (Wisconsin Card Sorting Test), reversal learning, and behavioral measures (Personal Behavior Checklist-36 and Children's Executive Functioning Scale).

The control group was recruited through advertisement in libraries, schools, and community colleges in selected communities in New Mexico. Those parents who consented to allow their child to participate in the study were interviewed by telephone to determine if the child met the study criteria. The control group was comparable to the alcohol-exposed group with respect to age (mean age = 11.01), gender, ethnic background, and socioeconomic status (Table 1), as measured by the Occupational Scale of the Hollingshead Four Factor Index [12]. The control subjects did not have a history of neurodevelopmental problems or special education.

3. Measures

3.1. Reversal learning

As noted above, the reversal learning task adapted by Rolls and colleagues [29] for use with humans was utilized with some modifications in the present study. Given that most participants were children, the test was introduced as a game in which they could win points. After the subject was seated in front of a laptop computer, the experimenter gave the following instructions: "I am going to show you two designs on this computer screen, one at a time. One of those designs is the

Table 1
Means, standard deviations, and ranges for demographic and comparison variables

Variable	Alcohol-exposed			Control			*P*
	M	SD	Range	M	SD	Range	
Age	11.12	2.62	7.67–19.42	11.01	2.41	7.83–18.7	n.s.
Socioeconomic status (SES)	4.90	2.73	1.0–9.0	4.85	2.01	1.0–9.0	n.s.
Raven standard matrices (IQ)	82.25	10.35	65.00–98.00	101.45	12.89	78.00–130.00	<0.0001
WCST categories	3.90	2.31	0.00–6.00	5.50	0.95	3.00–6.00	<0.01
WCST perseverative errors	23.75	15.46	6.00–56.00	12.75	7.18	3.00–26.00	<0.01
WCST response sets lost	1.15	1.13	0.00–4.00	1.05	1.05	0.00–4.00	n.s.

Table 2
Group comparisons between alcohol-exposed subjects with and without fetal alcohol syndrome

Variable	FAS		Without FAS		t	P
	M	SD	M	SD		
Age	12.20	2.90	10.03	1.85	1.99	n.s.
Raven standard matrices (IQ)	79.60	11.57	84.90	8.76	−1.16	n.s.
WCST perseverative errors	25.30	16.65	22.20	14.91	0.44	n.s.
Number of reversals	1.10	0.99	1.00	0.94	0.23	n.s.
Last error (reversal)	20.00	17.00	27.00	30.77	−0.68	n.s.
Trials to extinction	20.70	7.80	16.40	5.40	1.43	n.s.
Last Error (Extinction)	12.30	19.84	3.60	5.74	1.33	n.s.
PBCL-36	18.30	7.66	14.50	7.15	1.15	n.s.
CEFS	98.10	25.52	92.52	36.43	0.43	n.s.

'winning' one and the other one is the 'losing' one. If you click this mouse button (pointing to the left mouse button) when the winning one is on, you will hear a nice sound and the screen will say you have won a point. If you click on the losing one you will hear a crashing noise and the screen will say you have lost a point. Also remember, if you don't click when the winning design is on, you will lose a point. If you don't click when the losing one is on, you will win a point, also. So, when the winning one is on, always click quickly. When the losing one is on, don't click; just wait for a few seconds. Do you have any questions?'' In order to ensure that the subject understood the task, the experimenter then administered a few practice trials. Two fractal images were presented in a random order, each one for a maximum duration of 7 s. A trial was terminated upon the subject clicking the mouse button or following the 7-s duration, if he or she had not responded. With the termination of a trial, the image that was displayed disappeared and pleasant or unpleasant consequence followed (a pleasant consequence consisted of a pleasant sound and a message on the computer screen, ''Congratulations, you have won a point'' along with a running total of points. A negative consequence comprised an unpleasant sound and a message, ''Sorry you have lost a point'', together with a running total of points). When the subject was judged to have understood instructions, as indicated by accurate responding on rewarding and non-rewarding trials, the experimenter presented the reversal learning test saying, '' try to win as many points as possible by clicking on the winning one and not clicking on the losing one''. Two new fractal images were used in the reversal learning test, and the subject was not given further assistance or clarification during the administration. Upon the subject reaching a learning criterion — 9 correct in a block of ten trials — the reinforcement contingencies changed without warning. That is, the rewarding stimulus became non-rewarding and vice versa. After the subject reached the learning criterion in the reversed condition, the reinforcement contingencies changed without warning to those in the previous condition. This procedure continued until the subject completed three reversals following the attainment of the learning criterion or until the subject completed a maximum of 100 trials.

The trial number on which the last error was made before reaching the learning criterion was used as a measure of learning efficiency [29]. If the subject did not reach the learning criterion, the last error made before the 100th trial was used. The number of reversals made over the next 30 trials after reaching the learning criterion constituted the measure of reversal learning (Errorless performance yielded three reversals). Furthermore, proportions of commission errors (i.e. number of times the non-rewarding stimulus was clicked) and omission errors (i.e. number of times the rewarding stimulus was not clicked) were computed.

3.2. Extinction

The extinction test was administered immediately after the reversal learning test. It was expected that carry-over from reversal learning would build a resistance to extinction, specifically in alcohol-affected subjects. A different pair of fractal images was used in the extinction test, which was introduced as an extension of the reversal learning test: ''This is the last part of the game. Again, I would like you to earn as many points as possible''. In the extinction test, it became incorrect to click on either image after reaching the learning criterion. Nine correct responses in a block of 10 trials were used as the extinction criterion. If the subject failed to reach the extinction criterion, the test was discontinued after 35 trials following the attainment of the learning criterion. If the subject failed to reach the learning criterion, the test was terminated after the 100th trial. The trial number on which the last error was made before reaching the learning criterion and the number of trials needed to reach the extinction criterion were used as dependent measures.

3.3. Comparison tests

The Raven Standard Progressive Matrices (RSPM) and the Wisconsin Card Sorting Test (WCST) were administered to measure general intellectual ability and set-shifting ability respectively. The expectation was to determine if abilities tapped by reversal learning and extinction tests were related to those measured by the RSPM and WCST.

3.3.1. Raven Standard Progressive Matrices

This test includes 60 items designed to measure a number of related competencies ranging from simple visual matching to complex analogic reasoning [24]. Each item consists of a visual pattern with a part removed and an array of pictured inserts, one of which contained the removed part. The subject is required to select the insert that completes the pattern. Given that the RSPM requires minimal verbal instructions [37] it was considered suitable for the participants of the present study, the majority of whom were from disadvantaged backgrounds.

3.3.2. Wisconsin Card Sorting Test

Designed to assess abstraction ability and the ability to shift response sets [3,10], the WCST is one of most commonly used neuropsychological tests. In this test, the subject is required to learn to sort cards by one perceptual dimension (e.g. color) and then to shift attention to sort by a different perceptual dimension (e.g. shape) utilizing the examiner's feedback. The standard version of the test was used in the current study.

3.4. Behavioral assessment

The Personal Behavior Checklist–36 [33] and the Children's Executive Functioning Scale (C.H. Silver, S. Kolitz-Russell, F. Bordini, & J. Fairbanks, 1993, unpublished test) were used to assess behavioral problems in the participants.

3.4.1. Personal Behavior Checklist–36 (PBCL-36)

Developed to assess behavioral problems specifically in individuals prenatally exposed to alcohol, the PBCL-36 comprises of 36 items pertaining to the following areas of functioning: academic/work performance, social skills and interactions, bodily or physiological functions, communication and speech, personal manner, emotions, and motor skills and activities. This checklist was filled out by a caregiver, who was familiar with the subject's current behavior.

3.4.2. Children's Executive Functioning Scale (CEFS)

An experimental version of this 99-item questionnaire was utilized to obtain additional information on behavioral deficits. The CEFS consists of 5 sub-scales that purport to measure social appropriateness, inhibition, problem solving, initiative, and motor planning. This questionnaire, too, was filled out by a caregiver. The test battery also included the Florida Affect Battery, the results of which will be presented in a separate paper.

3.5. Data transformation and analysis

As normal controls achieved a ceiling on reversal learning and extinction tests, the data from these tests were markedly skewed. An inspection of the data also revealed a significant heterogeneity of variance. Accordingly, we utilized a method of data analysis recommended by Connover and Iman [5], which involves application of the usual parametric procedures to the ranks of data rather than to the data themselves. Within each set, data were ranked from the smallest to largest, with smallest being assigned rank 1, the next smallest rank 2 and so on. Average ranks were assigned in case of ties (see note 1 in Appendix). Skewed distributions of proportions were subjected to arcsin transformation [36]. Subsequent analyses revealed that these transformations resulted in data distributions that met the assumptions of parametric statistical tests (e.g. normal distribution and homogeneity of variance). If a group difference in variability was deemed clinically significant, a test of variance effects recommended by O'Brien [23] was employed. This test involves conducting a regular analysis of variance following a transformation of the dependent measure, a transformation termed 'r' transformation. The merits of this test include its robustness to departures from normality and its relative power [21]. Given that the two alcohol-exposed groups were comparable on all variables (Table 2), we compared the combined alcohol group with the control group in the analyses described below.

4. Results

As is shown in Table 1, the two groups were comparable in age [t (38) = 0.135, $P = 0.89$]. Because there was a wide age range (7.67–19.42 years), associations between age and the measures of reversal learning and extinction were also examined. Correlations between age and these measures were not statistically significant. Pearson correlations between age and the two measures of reversal learning (last error before reaching the learning criterion and number of reversals) and those of extinction (last error before reaching the learning criterion and trials to extinction were -0.14, 0.20, -0.11, 0.10 respectively. However, the alcohol-exposed group performed worse than controls on the Wisconsin Card Sorting Test, as reflected by a greater number of perseverative errors committed [t (38) = 2.89, $P < 0.01$], and

a fewer number of categories completed [t (38) = 2.87, $P < 0.01$]. There was no significant group difference in the number of response sets lost, suggesting that the alcohol-exposed group had greater difficulty in the shifting aspect of attention than in the sustaining aspect (see Table 1). It is also shown that the alcohol- exposed subjects performed worse than controls on the Raven Standard Progressive Matrices Test [t (38) = 5.20, $P <$ 0.0001], indicating relative impairments of non-verbal intellectual ability.

4.1. Reversal learning

Despite having received prior training through a practice test, the alcohol-exposed group demonstrated more difficulty in visual discrimination learning than the control group. Even though both groups achieved the learning criterion, the alcohol-exposed group required more learning trials (median = 21.5) than the control group (median = 10). A statistical comparison of rank-transformed data indicated that this group difference was significant [t (38) = 3.898, $P < 0.0001$]. There was also greater variability in performance of the alcohol group during the learning phase, as indicated by a statistical comparison of the measure of learning to criterion following the 'r' transformation explained above [F (1,38) = 8.94, $P < 0.01$].

As mentioned above, the number of reversals were scored on a 0 to 3 scale, with 3 indicating a perfect performance. As Table 3 shows, the alcohol-exposed group made fewer reversals than the control group. Eight of the 20 alcohol-exposed subjects failed to make any reversals, 3 made 1, 9 made 2 and none of them earned a perfect score of 3. In contrast, all the subjects in the normal control group succeeded in making at least one reversal (4 made 1, 9 made 2, and 7 made 3 reversals). A statistical comparison of the two groups on rank-transformed number of reversals showed a significant mean difference [t (38) = 3.947, $P < 0.0001$).

In light of the finding that animals with prenatal alcohol exposure show response inhibition deficits [26], we reasoned that a higher number of commission errors made by the alcohol-exposed subjects would account for their greater difficulty in reversal learning. A commission error results from responding on a trial that requires withholding response, whereas failure to respond on a trial that requires responding constitutes an omission error. Proportions of commission and omission errors (errors per trial) made by each subject were subjected to arcsin transformation because of non-normality of distributions (Proportions were not subjected to rank transformation). To statistically test if the alcohol-exposed group made more commission than omission errors, a 2 (group) by 2 (error type) repeated measures ANOVA was performed. This analysis did not reveal a significant group by error type interaction [F (1,38) = 0.80, $P = 0.375$]. There were, however, highly significant main effects of group [F (1,38) = 23.41, $P < 0.0001$] and error type [F (1,38) = 50.46, $P < 0.0001$]. Inspection of marginal means showed that the alcohol-exposed group made both commission and omission errors more often than the control group. Overall, both groups made more commission than omission errors. Both commission and omission errors were associated with the number of reversals, Pearson correlations being -0.72 and -0.44 respectively.

Given that intellectual ability and the categories completed on the Wisconsin Card Sorting Test were correlated with the number of reversals, we conducted an analysis of covariance (ANCOVA) to determine if the two groups differed in reversal learning after adjusting for Raven scores and the number of WCST categories. The ANCOVA showed a significant group difference in reversal learning [F (3,36) = 5.81, $P < 0.05$] after adjusting for these variables. Thus, the results suggested that emotional set shifting is relatively independent of nonverbal intellectual ability and conceptual set shifting. A follow-up analysis was performed to answer the question of whether the alcohol-exposed group was more impaired in emotional than in conceptual set shifting. In order to determine the relative magnitude of the effects we transformed the number of reversals and WCST categories in to a common scale (z-scores) and conducted a 2 (reversals and WCST categories) by 2 (group) repeated measures analysis. If the group effect in emotional set shifting was larger than that in concep-

Table 3
Means, standard deviations, and ranges for primary dependent variables

Variable	Alcohol-exposed			Control		
	M	SD	Range	M	SD	Range
Number of reversals	1.05	0.94	0.00–2.00	2.15	0.74	1.00–3.00
Last error (reversal)	23.80	24.50	0.00–80.00	3.55	3.12	0.00–10.00
Trials to extinction	18.55	6.80	12.00–31.00	15.65	2.39	12.00–20.00
Last error (extinction)	7.95	14.89	0.00–64.00	3.90	3.90	0.00–11.00
PBCL-36	16.40	7.47	1.00–30.00	4.60	5.39	0.00–17.00
CEFS	95.30	30.75	31.00–144.00	31.25	28.44	1.00–97.00

tual set shifting, a significant group by repeated measures interaction was expected. While this analysis did not show a significant interaction [F (1,38) = 0.77], it revealed a highly significant overall group effect [F (1,38) = 18.36, $P < 0.0001$]. Profiles of FAS and control group means indicated comparable magnitudes of effects in both WCST categories (means −0.41 and 0.41) and the number of reversals (means −0.53 and 0.53) respectively.

4.2. Extinction

The primary hypothesis related to extinction was that the alcohol-exposed group would be slower to extinguish learned behavior than the control group. Before testing this hypothesis, a group comparison in learning to criterion in the extinction test was performed. As is shown in Table 3, the median trial numbers on which the last error was made before reaching the learning criterion were comparable. The comparability of the two groups in learning to criterion was confirmed by a statistical analysis of rank-transformed data [t (38) = 0.10]. Thus, the alcohol-exposed group had a marked improvement in learning to criterion, as indicated by a significant difference in the trial number on which the last error was made in the two tests [Paired Samples t (19) = 2.62, $P < 0.05$].

The number of trials to reach the extinction criterion significantly varied between the two groups, despite a lack of significant difference in central tendency (median trials, alcohol-exposed group = 16; median trials, control group = 15). The number of trials to extinction in the alcohol-exposed group varied from 12 to 31 and in the control group from 12 to 20. As variability in extinction was considered of clinical significance, variability was further analyzed following an 'r' transformation of the raw data [23]. A statistical comparison of r-transformed data indicated that there was a greater variability in extinction in the alcohol-exposed group [t (38) = 3.53, $P < 0.001$] than in the control group.

4.3. Behavioral problems

The alcohol-exposed group had significantly higher mean scores than the control group on the Personal Behavior Checklist-36 [t (38) = 5.73, $P < 0.0001$] and on the Children's Executive Control Functioning Inventory [t (38) = 6.30, $P < 0.0001$) respectively. Even though the PBCL-36 and the CECF contain items referring to different areas of functioning, the scores of the two instruments were highly correlated ($r = 0.82$, $P < 0.001$), suggesting that they probably measure a common construct. In view of small sample size, the groups were not compared on sub-scales of the above behavioral scales. The purpose of the last two analyses was to determine the relative utility of the measures of conceptual and emotional set shifting in predicting behavioral problems exhibited by the two groups. In the first analysis, PBCL scores were used as the dependent variable and the following set of variables as predictors: Raven, WCST categories, WCST perseverative errors, number of reversals, omission errors, commission errors, and variability in extinction. The stepwise method of variable selection showed that a combination of 3 variables, namely WCST perseverative errors, omission errors in reversal learning, and variability in extinction, accounted for about 50% of the variance in PBCL-36 scores. In this analysis, WCST perseverative errors were entered first, variability in extinction next and omission errors in reversal learning last (see Table 4). In the second analysis, CEFS scores were regressed on the same set of predictors and comparable results were obtained. The stepwise procedure selected WCST perseverative errors and omission errors, which accounted for about 40% of the variance in CEFS scores.

Table 4
Hierarchical regression analysis predicting PBCL scores

Step	Variable	R^2	F-change
1	Raven matrices	0.13	5.80[a]
2	Perseverative errors (WCST)	0.37	14.07[c]
3	Omission errors (reversal)	0.45	4.82[a]
4	Variability in extinction (reversal)	0.59	11.72[b]

[a] $P < 0.05$.
[b] $P < 0.01$.
[c] $P < 0.001$.

5. Discussion

As predicted, the combined alcohol-exposed group exhibited more difficulty than the normal control group in visual discrimination reversal. That is, the alcohol-exposed subjects made fewer reversals and demonstrated more variability in extinction of reward–response association than the control group. Furthermore, both groups made more commission than omission errors. Commission errors in reversal learning have also been called perseverative errors, as they result from responding to the previously correct stimulus. The hypothesis that the group effect of emotional set shifting would be relatively independent of that of conceptual set shifting was also confirmed. The results showed both effects were highly significant and were of comparable magnitude. Selected measures of conceptual and emotional set shifting were highly associated with parent-rated behavioral problems of the participants. It should be underscored that there was no significant association between the degree of dysmorphia and cognitive dysfunction within the alcohol-exposed group.

Mattson and colleagues [20] also failed to find group differences in neuropsychological test performance of alcohol-exposed subjects with and without fetal alcohol syndrome. This finding is not surprising because cognitive and behavioral disabilities in alcohol-exposed individuals are presumed to vary as a function of a host of variables (e.g. postnatal environment) in addition to direct effects of ethanol [32].

The design of the present study did not allow a detailed examination of the cognitive processes underlying perseverative responses in reversal learning. Our observations of performance by patients with focal brain damage on the visual discrimination reversal test suggest two types of perseverative errors, which we have tentatively labeled 'processing-related', and 'stimulus-driven'. Processing-related errors refer to those errors committed as a result of forgetfulness or impoverished conceptual skills. This type of perseverative errors can be contrasted with the stimulus-driven errors, which occur as a result of being 'pulled' to a perceptual feature. Notwithstanding his ability to repeat test instructions, for example, a patient with massive frontal damage continued to click on a feature that looked like a target on the fractal image, irrespective of whether it was rewarding or not. He often laughed while responding to this feature suggesting an affective and impulsive basis of his behavior. Therefore, the stimulus-driven perseverations overlap with what Hauser [11] has called affective perseverations- perseverations resulting from a failure to inhibit prepotent emotions. A third type of perseverative errors in reversal learning has been described by Rolls et al. [29] in patients with orbitofrontal damage and these errors are analogous to 'stuck-in-set' perseverations in the Sandson and Albert taxonomy [31] or what Hauser [11] has called paradigmatic perseverations. Failure to reverse response sets in the reversal condition because of the inability to inhibit previously learned response pattern is an example of stuck-in-set or paradigmatic perseveration.

There is indirect evidence to suggest that commission errors made by the alcohol-exposed group were primarily related to deficient processing skills rather than to paradigmatic or affective disinhibition. We found that individuals prenatally exposed to alcohol made more errors than controls on the Matching Familiar Figures Test, despite a lack of group difference in response latency, a pattern of performance consistent with slow processing (P.W. Kodituwakku, A. Aragon, & P.A. May, 1999, unpublished data). Jacobson [15] has reported that alcohol-exposed infants were slower than controls on information processing measures. The performance of the alcohol-exposed group on tests of reversal learning and extinction was also suggestive of slow processing. Despite receiving practice trials, the alcohol-exposed group took more trials than the control group to reach the learning criterion in reversal learning. In the extinction condition, which followed the reversal learning condition, the former group reached the learning criterion as efficiently as the latter.

Thus, the performance of individuals with prenatal alcohol exposure on tests of reversal learning and extinction resembles, in some respects, that of the patients with orbitofrontal damage, but differ in other respects. Like the patients with orbitofrontal damage, those with prenatal alcohol exposure made more commission errors and achieved fewer reversals than controls on reversal learning. However, the alcohol-exposed group had more difficulty than the control group in achieving the learning criterion in the reversal learning task, a difficulty not exhibited by the frontal patients in Rolls and colleagues' study [29]. While the frontal patients were slower in achieving the extinction criterion, the alcohol-exposed group did not require more trials than controls to achieve it. The alcohol-exposed group exhibited, however, more variability in performance than the controls on the extinction test.

The foregoing comparison was meant to underscore that cognitive deficits associated with a neurodevelopmental disorder may be qualitatively different from those resulting from an acquired brain damage in adulthood. It has been well documented that patients with orbitofrontal damage show marked difficulty in emotion-related learning and decision making, notwithstanding the relative integrity of their general cognitive abilities [2,29]. In contrast, individuals with prenatal alcohol exposure perform poorly on a range of standard neuropsychological tests [20]. The results of the present study showed that alcohol exposed individuals exhibited deficits in both conceptual and emotional set shifting. Autopsy and imaging studies (e.g. MRI) of alcohol exposed subjects have revealed evidence of abnormalities in a number of structures including the basal ganglia, hippocampus, and corpus callosum [28]. However, no structural abnormalities in the prefrontal cortex of these individuals have been reported. Given that the orbitofrontal cortex receives projections from a number of areas in the brain, such as the inferior temporal lobe, amygdala, and thalamus, it is possible that the deficient performance of the alcohol-exposed group on reversal learning reflects an abnormality of cortico-cortical or cortico-subcortical functional connectivity. Such an abnormality of connectivity has been proposed as a possible mechanism of frontal dysfunction in patients with schizophrenia [35].

In addition to failing to directly test the underlying mechanisms of set shifting difficulty, the present study has other shortcomings that may limit the generalizability of the results. First, the sample was relatively small and was drawn from one region in the US. Second, it was a truncated sample, as those alcohol-exposed individuals with mental retardation were excluded.

Despite the above limitations, the present study is the first to demonstrate impairments of emotional set shifting, in addition to those of conceptual set shifting, in humans with a history of prenatal alcohol exposure. The results showed that tests measuring emotional and conceptual set shifting and extinction of reward–response associations were robust predictors of parent-rated behavioral problems in individuals with prenatal alcohol exposure. Two measures of set shifting — perseverative errors on the WCST and omission # errors on reversal learning — and, variability in extinction accounted for about 50% of the variance in the two parent-rated behavioral measures. The finding that omission errors in visual discrimination reversal are more predictive of behavioral problems than commission errors conflicts with a prevalent belief among clinicians that hyperactivity and impulsivity lead to other problems in alcohol exposed individuals. As was mentioned above, there is evidence to suggest that alcohol-exposed children differ from those diagnosed as having Attention Deficit Disorder in neuropsychological test performance [4]. Accordingly, these findings have implications for the characterization of behavioral disturbances in individuals with prenatal alcohol exposure as well as for the development of appropriate interventions for their behavioral problems.

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Appendix. Note 1

There exist two distinct approaches to handling non-normal data: transformation of the data into a form resembling a normal distribution or application of a distribution free method. Connover and Iman [25] have proposed an innovative method of combining these two approaches, which involves applying parametric methods to the ranks of data than to data themselves. Connover and Iman show that the parametric F-test computed on ranks (F_R) is mathematically related to the Kruskal–Wallis H, the t-test computed on ranks (t_R) to the Wilcoxon–Mann–Whitney T and so on. The advantage of the combined approach is that it will allow the researcher to use a powerful analytical tool on non-normal data. For example, when using the parametric F-test on ranked data one compares F_R to a critical F-value, whereas when using the Kruskal–Wallis Test one compares H to a critical χ^2 value. Iman and Davenport [13] have reported that the F approximation is generally superior to the χ^2 approximation.

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