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A Meta-Analysis of Animal Studies on Disruption of Spatial Navigation by Prenatal Cocaine Exposure

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Abstract

Water-maze testing has been used to assess prenatal cocaine (PCOC)- induced deficits in behavioral studies of spatial navigation and memory abilities. Effects of PCOC in acquisition or in probe trials over water-maze testing days were rarely detected. Despite an absence of effects of PCOC when data were collapsed over multiple days, there was a potential difference when examined during the first day of acquisition training, characterized by a PCOC-associated decrease in learning efficiency but not capacity. Here, we review studies of PCOC-related changes in day-1 water-maze acquisition training and examine the relationship between experimental methodologies and PCOC treatment procedures and the variability in effect size estimates across studies. The results revealed a significant increase in latencies to goal platform on acquisition training day-1 in PCOC-exposed offspring vs. controls (effect size: $r = 0.44$). Significant effects attributable to variations in the PCOC treatment procedures across studies were also identified. The moderating variable of PCOC “dose” was significant as lower doses of PCOC exposure yielded larger treatment effects. “Duration” of PCOC exposure was not significant, although a trend for greater effects was observed in studies that employed longer daily treatment schedules or schedules administered in later gestational periods. This analysis identified a consistent difference in acquisition training day-1 of water-maze testing in PCOC-exposed offspring indicating a PCOC-induced deficiency in spatial learning. These findings of impaired spatial learning efficiency are of particular interest given clinical scenarios involving acutely impaired spatial memory and related learning in PCOC-exposed children that highlight the potential consequences in classroom learning.

Keywords

Prenatal cocaine; Morris water-maze; Meta-analysis; Behavior

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1. Introduction

Since initial reports of increased prevalence of *in utero* exposure to cocaine in the early 1980's [15,16,23], clinicians and researchers have attempted to identify and characterize resultant motor and cognitive deficits in prenatal cocaine (PCOC)-exposed children [1,2,9,10,35,45, 52,61,73]. Although early reports of gross physical abnormalities [15,16,23] were contradicted by later reports of more subtle changes associated with PCOC exposure [1,61,62,73,88], based upon numerous reports of motor abnormalities in PCOC-exposed children many researchers have classified the behavioral outcome as a distinct motor syndrome [1,61]. Additionally, some investigations have identified deficiencies in various measures of cognitive ability in these subjects [14,45,62,67,84,88,89,100]. Overall, many of these studies have uncovered disturbances in attention, impulsivity, and learning in PCOC-exposed children from elementary years [5,10,52] throughout adolescence [4,30,39,62,68,84,89].

To learn more regarding the detrimental effects of PCOC exposure on brain function and behavior in humans, the effects of this drug have been explored in animal models [18,24,25, 29,33,76,110,111]. Studies emanating from this work have revealed PCOC-related abnormalities in motor behaviors including baseline differences in habituation and in response to acute drug administration in open-field testing [24,26,33,43,76,93]. Other work has examined the effects of PCOC exposure on spatial memory and spatial navigation types of cognitive performance that are commonly measured using a Morris water-maze, a radial arm maze, or spontaneous alternation tasks [22,42,47,54,60,77,90,96,100]. Water-maze experimentation has been employed most frequently, despite a modest total number of studies that contain limited sample sizes. The Morris water-maze and other variations of the paradigm are aimed at assessing spatial navigation abilities in rodents and are most commonly comprised of two phases of testing. The first is an assessment of acquisition that is generated during water-maze training and the second is performance on the probe transfer-testing phases [12,65,66, 109]. The swim-maze acquisition training often consists of multiple exposures to or trials in the water-maze apparatus over a few days. In this phase, the animal is thought to be utilizing cognitive learning processes or strategies, such as learned sequencing of motor movements (praxis), use of proximal cues (taxis), and/or the spatial configuration of the water-maze in order to navigate to a submerged goal platform position with coordinated swimming while swim distances and/or latencies to the goal platform are recorded. In the probe phase, a trained animal is exposed over multiple trials to the water-maze with the goal platform removed, and times spent in the goal or target quadrants are recorded. This assesses what can be referred to as "spatial accuracy".

A cursory review of studies examining the effects of PCOC exposure on water-maze performance indicates that although these findings are difficult to interpret due to differences in study variables such as prenatal treatment dosing and regimens, most studies of PCOC exposure did not report overall deficiencies in water-maze performance. Results from the water-maze probe testing revealed a consistent absence of differences in PCOC-exposed offspring in probe trial time spent in the goal quadrant of the water-maze compared to control offspring. For example, Heyser et al. [42] examining male and female adult rats did not reveal effects of PCOC exposure in probe trial testing of the Morris water-maze. Riley and Foss [77] found a difference between untreated control and PCOC-exposed rat offspring in probe testing trials, but this effect was marginalized by a lack of effect when comparing either group to pair-fed controls. Inman-Wood et al. [44] did not reveal any differences in latency to platform in PCOC-exposed mice in probe trial testing, except when examined for swim distance. Interestingly, the two most recent reports did reveal effects of PCOC exposure on probe trial testing in juvenile PCOC-exposed rat offspring. Meunier et al. [63] demonstrated that juvenile male and female PCOC-exposed offspring exhibited marked place learning impairment as assessed in probe trials, which was also demonstrated by Bashkatova et al. [6] in juvenile

PCOC-exposed males. Overall, except for these two most recent studies probe trial testing did not reveal an effect of PCOC exposure when compared to controls.

There is also a general consensus that PCOC exposure does not result in differences in water-maze acquisition when collapsed over study trials by day [6,22,42,44,63,77,90], as only one study reported significantly greater latencies to platform across training trials by day in early PCOC-exposed female rat offspring when compared to controls [106]. Additionally, Johns et al. [47] did not find effects of PCOC exposure in latency measures of the Win-Stay water maze during acquisition or performance. Despite a consistent lack of effects due to PCOC exposure across water-maze acquisition training days, several studies have noted that PCOC exposure resulted in disturbances of the initial response to water-maze training characterized in the day-1 acquisition training output as PCOC-exposed offspring exhibited greater latencies to platform on the first day of water-maze acquisition training [18,22,42,44,90]. This first day acquisition effect seems to be masked by the convergence of acquisition performance with control groups over the course of the total training days. Several of these studies have noted that this first day acquisition training effect of PCOC exposure may be an important aspect of water maze results [18,22,42,44,90], while others have stated that the effect was not likely due to a learning deficit, but dispositional factors such as timidity or distractibility [77]. Despite this interpretation, other studies have demonstrated that PCOC-exposed rats display deficits in PCOC-exposed rat offspring in learning conditioning tasks [93,40,41].

The lack of significant effects of PCOC exposure in overall acquisition and probe trial testing in water-maze studies may lead to a tendency to conclude that PCOC-exposure does not lead to changes in spatial navigation abilities. With notable differences in experimental procedures across studies, it becomes difficult to deduce an overall effect of PCOC treatment on spatial navigation or task acquisition learning processes. Statistical meta-analysis can prove to be a useful tool in clarifying an overall effect from these various animal studies using water-maze testing to assess spatial navigation abilities. Results from individual reports can be collectively assessed with meta-analytic procedures to reveal both a more reliable estimate of the true effect size and to quantify the potential contribution of moderating variables such as differences in prenatal treatment methodologies (e.g. variations in drug dosing or exposure duration regimens).

Given the difficulty in interpreting the existing behavioral literature described above and the need for detailed statistical reviews of PCOC research findings, we performed a meta-analytic review of literature on animal models of PCOC exposure that assessed spatial navigation abilities in reports using water-maze testing. The major goal of this study was to reveal an overall effect of PCOC-exposure on day-1 water-maze acquisition, in order to both clarify the existence of a significant effect of PCOC exposure, present a more accurate representation of the true effect size, as well as determine the contribution of moderating variables particularly those pertaining to differences in prenatal treatment procedures. The meta-analysis was performed in such a way that an overall effect of PCOC exposure on the acquisition learning of spatial navigation water-maze tasks could be determined. In addition, the effects of PCOC exposure across all levels of potential moderator variables, including experimental variables related to the PCOC-treatment regimen (e.g. exposure dose and duration) and subject variables (e.g. age, sex), could be determined as well. Concurrently, the findings of this meta-analysis validate the measurability of cognitive variables in animal models of PCOC exposure through the identification of parallel or corresponding behavioral profiles to those observed in the human condition. More importantly this meta-analysis will provide researchers with a computational review of the findings obtained in previous studies in order to properly assess and characterize the profile of spatial navigation abilities in PCOC-exposed animal offspring.

2. Methods

2.1 Literature search and inclusion criteria

In order to obtain studies examining one or more of the dependent variables that describe spatial navigation ability in the Morris Water-Maze, or an adapted version, computer-based literature searches and searches through reference sections of related journal publications, were performed on the literature from 1978 to 2006. Computer-based searches were performed on the National Library of Medicine's MEDLINE bibliographic database and through a personal research database held by the authors. In addition, the references of relevant identified studies were examined for articles that may not have been indexed by MEDLINE. For computer database searches, the keywords "prenatal cocaine" were used in combination with "cognitive abilities", "cognition", "spatial", "spatial memory", "navigation", "spatial navigation", "maze", and "behavior". The referenced abstracts were used to acquire published reports examining spatial abilities in animal models of PCOC exposure and these were assessed for inclusion into the meta-analysis.

Studies had to meet the following criteria to be included into the meta-analysis: 1) be published in a book or a peer-reviewed journal, 2) be written in English, 3) present original data, 4) contain one or more spatial memory measures using latency to the goal platform as the dependent measure, 5) utilize at least one proper control group, and 6) provide a measure of effect size or enough information to estimate an effect size. The search resulted in eleven studies examining the effects of PCOC exposure as measured in a water-maze paradigm, ten of which were included into the meta-analysis. One study did not report measures of latency to reach the water-maze platform and was subsequently not included in the current analysis [100].

2.2 Study Coding

The ten studies were coded for various experimental characteristics in order to determine possible influences of moderating variables, as follows: 1) Natural divisions of "male", "female", or "both" were used to code the "sex" variable. 2) "Age" was coded at three levels, "juvenile", "periadolescent", and "adult", based upon developmental identifications from previous studies examining age ranges. "Juveniles" were coded as postnatal day (PD) 20-35, "periadolescents" as PD 36-59, and "adults" as PD 60 or greater [49,53]. 3) "Species" was coded as either "rat" or "mouse" in order to determine whether species-specific differences occurred in response to PCOC exposure. 4) The "dose" of cocaine delivered in the prenatal exposure regimen was coded using subjective descriptions of dose ranges, including "low", "intermediate", and "high", expressing dosages utilized in published works based upon blood plasma cocaine levels [26,94,106]. The peak plasma cocaine levels associated with each moderator level were "low" (<0.8 ug/ml, 10 mg/kg s.c.), "intermediate" (1.1-1.7 ug/ml, 20-30 mg/kg s.c.), and "high" (>2.1 ug/ml, 40 mg/kg s.c.). 5) The "duration" of the prenatal exposure was coded and separated into four subjective categories of "short", "moderate", "long", and "combined". "Short", "moderate", and "long" correspond in relative duration to gestational trimesters of the rat and mouse, as "short" refers to exposure beginning in middle gestation (5-9 days of exposure during the second trimester), "moderate" refers to exposure beginning in the second trimester and continuing until at least three days before birth, and "long" refers to exposure beginning in the first trimester and continuing until at least three days before birth. "Combined" was coded as the use of more than one treatment duration groupings in the PCOC treated group.

2.3 Statistics

From the ten studies [6,18,22,42,44,47,63,77,90,106] included in the meta-analysis, effect sizes were extracted from independent comparisons of a control group to a PCOC-exposed group on day-1 acquisition testing of spatial navigation in the Morris Water-Maze task as

measured by the mean swim latency or time elapsed to reach the goal platform. Other measures evaluated in water-maze testing, such as day-2 or -3 acquisition training or probe-testing day, were not included in the meta-analysis due to the consistency of reports of statistically insignificant findings in PCOC-treated groups on these water-maze measures. The 10 independent experiments were coded and analyzed separately.

The data from each experiment were utilized to calculate a Pearson's product-moment correlation coefficient, measured as r , which served as a common measure of effect size. Based upon a direct comparison of a PCOC-exposed group to a control group, each effect size included in the meta-analysis was extracted using the mean, sample size, and the standard error of the mean (SEM) converted to standard deviation (SD) to formulate a t -value which was converted to r [81]. Statistical significance was set as $p < 0.05$. Despite the arbitrary nature of standardizing effect sizes, there are accepted guidelines to evaluate the magnitude of effects such that an absolute value of $r=0.1$ denotes a "small" effect, $r=0.3$ denotes a "medium" effect, and a value of $r=0.5$ denotes a large effect [20]. The calculated Pearson's r values were then converted to Fisher's r_z in order to perform meta-analytic comparisons using parametric statistics of effects of PCOC exposure. Weighted and unweighted mean averages were calculated using Fisher's r_z and converted back to Pearson's r [82] for summary purposes. A combined "Z" and corresponding combined " p " were calculated for the 10 effect sizes to examine overall statistical significance of the combined effect size. A χ^2 test of homogeneity was used to determine if significant heterogeneity existed among the observed effect sizes. Statistical analysis of potential moderating variables was performed with planned contrasts utilizing a Z-test to determine significance. Analysis was performed for all pair-wise comparisons of a PCOC-exposed group vs. a control group indexing differences in effect sizes at alternate levels of the moderating variable.

3. Results

3.1 Overall Effect Size of PCOC-Exposure

The obtained effect sizes from ten studies examining the day-1 mean swim latencies during the acquisition stage of water-maze testing ranged from -0.166 to 0.847 (Figure 1). Table 1 displays the calculated effect sizes of each study as Pearson's r and Fishers r_z , as well as the sample size (N) and associated Z-score for each study. A weighted mean average of 0.445 and an unweighted mean average of 0.454 were observed for the ten effect sizes. The effect of PCOC exposure collapsed over all moderating variables was determined to be statistically significant [combined $Z = 3.58$, $p < 0.001$], but was demonstrated to be taken from a heterogeneous group of effect sizes ($\chi^2_{(9)} = 31.05$, $p < 0.01$).

3.2 Analysis of Moderating Variables

The analysis of potential moderating variables of the observed effect sizes was performed for each pair-wise comparison of a PCOC-exposed group compared to an adequate control group in an attempt to explain the observed heterogeneity in the overall analysis. Sex was not a significant moderating influence on observed effect size [$Z = -0.606$] as a statistical difference was not observed in the effects sizes between studies reporting data separately for males ($k=6$), females ($k=3$), or a combined male and female group ($k=4$). Age was not a significant moderator of effect size [$Z = 0.675$] when grouped into "juvenile" ($k=4$), "periadolescent" ($k=1$), "adult" ($k=5$), and "combined" ($k=1$). There was only one effect size extracted for mice ($r=0.829$), while the remaining nine extractions were from studies conducted with rats. Nevertheless, a contrast examining a moderator for "species" revealed a statistically significant increase in effect size in mice when compared to rats [$Z = 2.50$, $p < 0.01$]. Analysis of "cocaine dosage" did reveal statistically significant differences, as effect sizes extracted from studies using "low" ($k=3$) or "intermediate" ($k=5$) PCOC doses were significantly larger

than studies using a “high” ($k=2$) dose of PCOC exposure [$Z=2.69, p<0.01$]. Prenatal exposure duration did not reveal statistically significant differences, but a trend did exist for greater effects of PCOC exposure in studies using “moderate” ($k=4$) and “combined” ($k=1$) durations of PCOC exposure, when compared to studies using a “short” ($n=5$) PCOC exposure duration [$Z=1.31$].

3.3 File-Drawer Analysis

The significant pooled effect size was also subjected to a “file-drawer” analysis. This statistic provides a measure that accounts for research that may have been conducted and never published or not made available for analysis due to statistically non-significant findings. It derives a measure of the number of studies whose unpublished null findings would be necessary to reduce the significant observed effect size to statistical non-significance. The analysis of the file-drawer statistic revealed that 37 studies with an average effect size of zero would be necessary to nullify the significance of the pooled result (weighted mean average = 0.45) that was obtained in this meta-analysis.

4. Discussion

Behavioral studies of children exposed to cocaine *in utero* have reported various abnormalities in measures of cognitive function including spatial memory [39,52,89,98]. The current meta-analysis was performed in order to examine the sequential responsiveness of animals exposed to PCOC in the Morris water-maze, a spatial navigation device [22,42,44,47,77,90,106]. Studies that have examined the effects of PCOC exposure on spatial navigation and memory performance in behavioral paradigms have yielded somewhat conflicting results and have used various non-uniform methodologies, making it difficult to discern the true effects of PCOC exposure [42,47,60,100]. Treatment differences have generally not been observed in the acquisition of water-maze performance in overall analyses across training days [6,22,42,44,63,77,90]. Similarly, differences have not been found on probe trial test days of the water-maze paradigms in time spent in the goal area, distance traveled, or latency to reach the goal area. Despite fairly consistent findings that PCOC-exposure does not result in differences compared to controls in performance on probe test trials [42,77,44], data from individual day acquisition trials supported a potential effect of PCOC exposure [18,22,42,44,90]. The significant difference seemed to be masked by nonsignificant results when the acquisition data were collapsed over all acquisition trials [6,22,42,44,63,77,90].

The current meta-analytic review of day-by-day performance during Morris water-maze acquisition was performed to further examine reports on alterations on mean latency to reach platform [77,93,105] and provide a more definitive statistical account of an overall effect of PCOC exposure on day-1 trials for the acquisition phase of the water-maze paradigm. The existence of PCOC-induced deficiencies in specific or nonspecific acquisition learning in the domain of spatial memory or navigation may be of great interest, and these seemingly null Morris water-maze findings may reveal a PCOC-related deficiency of high relevance to learning behaviors of children exposed to cocaine *in utero*. Several studies examining PCOC-exposed children highlight notable disturbances in acquisition learning [9,5,38,61,71] possibly stemming from various observed cognitive abnormalities. While investigation of such disturbances has not revealed grand-scale deficits, there have been reports of smaller-scale PCOC-related cognitive impairments in PCOC-exposed children [52,62,67,75,84,88]. Related work has uncovered PCOC-induced changes in sensory systems including visual and/or visual-motor processing and attention alterations as contributing to cognitive behavioral changes that may possibly manifest as learning deficiencies [2,10,21,35,39,86]. These clinical studies have been modeled in animal studies where behavioral support and verification of cognitive disturbances in PCOC-exposed offspring have been observed [30,41,79,86,92,99] amidst

studies focused on identifying underlying neural substrates for altered cognitive function post drug treatment [27,28,37,57,68,69,72,107].

This meta-analysis examined effect sizes obtained from ten studies [6,18,22,42,44,47,63,77,90,106] that reported mean latencies to reach a goal platform during an acquisition phase of the Morris water-maze test. A mean effect size of these studies was determined to be 0.44 and the weighted mean average to be 0.45, indicating a statistically significant and medium to large effect size of PCOC treatment. This effect highlights the existence of a generalizable PCOC treatment difference across ten experimental findings that verifies deficiencies in PCOC-exposed offspring on their initial acquisition of the spatial navigation task. The meta-analysis also revealed other striking treatment differences in PCOC-exposed offspring as determined in the analysis of moderating variables of the effect of treatment in the day-1 acquisition in water-maze testing. Meta-analytic review allows examination of the influence of differences in experimental methodologies on the observed effect [81,82]. The present meta-analysis examined the influences of potentially relevant moderating variables, such as “dose” and “species”, on the overall effect of prenatal treatment, which were found to be statistically significant. Larger effects found for specific levels of moderating variables provided additional information as to the specificity of effects of PCOC exposure differentially driven by incongruent experimental methodologies. There were experimental differences in the treatment doses utilized, ranging from a daily PCOC dose of 10 mg/kg to 80 mg/kg, in studies using s.c. administration. Interestingly, the moderating variable of PCOC treatment “dose” revealed that studies that used either “low” or “intermediate” PCOC doses yielded larger effects than studies using “high” PCOC dosage. This is an interesting finding as clinically there have been numerous studies noting dose-dependent abnormalities in PCOC-exposed children such as disruptions of fetal brain development in processes of neuronal proliferation, differentiation, and migration, often leading to subsequent neurobehavioral deficits [7,17,85,87]. Despite these findings there have been several studies noting effects of PCOC exposure with lower prenatal treatment doses [8,13,50,51,56,90,112]. This may reflect the and support reports noting a delicate balance of elucidating the direct effects of cocaine and the effects of significant tetratologic developmental factors potentially stemming from fetal hypoxia, oxidative stress, and ischemic injury [3,57,58,74,97,108].

Examination of the moderator variable PCOC treatment “duration”, although not statistically significant did indicate larger treatment effects using either “moderate” prenatal treatment durations or a “combined” group of both “long” and short treatment durations. This highlights that treatment differences may be moderated by fetal exposure to cocaine during critical periods of gestational development or from a cumulative effect of PCOC dosing. Thus, it appears that the duration of the PCOC treatment regimen significantly moderates the size of treatment-group differences observed in studies of the Morris water-maze suggesting that studies employing longer durations of PCOC exposure and exposures administered during later periods of fetal development yield larger effects. Although various studies of PCOC exposure have yielded interesting developmental effects in PCOC-exposed offspring [32,36,46,53,60,95], the moderator of “age” did not reveal a statistically significant effect on measures of the water-maze acquisition. This may reflect the existence of reports of significant effects of PCOC exposure at varying offspring ages at the time of testing. For example, several studies have reported PCOC-induced effects in behavioral, anatomical, and neurochemical measures in juvenile offspring [43,113], while there has also been numerous reports of PCOC-induced changes in these measures which are long-lasting and persist into adulthood [11,25,64,70,80]. Relevant to animal models of PCOC exposure, the lone study with mice [44] displayed a more intense effect of prenatal treatment when compared to studies using rat models, finding increased latencies in the acquisition training in PCOC-exposed offspring. This finding may also reflect a species-specific difference in physical adaptation in mice compared to rats in the MWM task [101,102]. Although this and all the moderator analyses should be interpreted with

caution given the small sample size, it may indicate that use of mouse models of PCOC exposure may be more successful in elucidating effects of PCOC exposure on cognitive variables.

In summary, the current findings delineate consistent deficiencies in PCOC-exposed offspring in day-1 trials of the acquisition phase of Morris water-maze training. PCOC-exposed offspring display differences in day-1 acquisition training, but their responding converges with control groups on the overall training for the acquisition phase of the Morris water-maze as well as in subsequent probe trial testing phases [42,44,47,90]. Although PCOC-induced differences in probe trial performance or overall differences across daily trials in the acquisition training of the water-maze might be more revealing or indicate more robust abnormalities in spatial memory or spatial navigation abilities, the difference observed on day-1 of maze acquisition trials may be indicative of actual underlying deficiencies in spatial learning specifically, or it may potentially indicate a more general deficit in learning resulting from PCOC exposure.

This treatment difference in the first day of training may have serious implications for the human condition of PCOC exposure if the treatment effect observed here with an animal model is reflective of the effect in PCOC-exposed children. Learning disturbances driven by an altered habituation to novel environments may interfere with a child's ability to acquire new tasks, as suggested by several studies with rats and mice, and such a deficiency might have a strong effect on performance in a multitude of arenas. A convergence of performance for drug-exposed children through repeated training may be problematic in situations of classroom learning where repeated training may not be possible. Indeed, some early studies have begun to report PCOC-related deficits lasting into school age and possibly beyond [1,9,4,5,14]. Therefore, deficiencies in water-maze acquisition training may highlight PCOC-associated changes that have serious clinical implications. Future meta-analytic review of other behavioral paradigms and findings examining cognitive function in PCOC-exposed offspring may provide additional information as to the generalizability of results obtained from animal models. These investigations may further clarify the appropriateness of the comparison of animal models of PCOC exposure to the comparable human condition and subsequently detect parallels in behavioral profiles. It will also provide basic researchers with a stronger framework of PCOC-induced changes in behavioral expression to both design and interpret neurochemical and neuroanatomical studies.

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Table 1**Summary of PCOC-Treatment Effect Size Statistics for Latencies to Platform for Acquisition Day-1 Water-Maze Training**

Summary statistics (*N*, *r*, *Z*) of the main effect of prenatal cocaine exposure on swim latencies to platform on day-1 acquisition of studies included in the meta-analysis

First Author	Year	<i>N</i>	<i>r</i>	<i>Z</i>
Bashkatova	2005	12	0.701	1.144
Meunier	2004	40	0.847	2.466
Inman-Wood	2000	46	0.830	2.598
Choi	1998	24	0.300	0.727
Cutler	1996	16	0.451	0.880
Heyser	1995	32	0.582	1.581
Vorhees	1995	40	0.016	0.051
Johns	1992	56	0.300	1.112
Riley	1991	20	-0.166	-0.370
Smith	1989	16	0.589	1.130

Table 2

Summary of Moderating Variables: First Day Water-Maze Acquisition Training
Summary statistics (N, r, weighted r, Z) of moderating variables on the effect of prenatal cocaine exposure on swim latencies to platform on day-1 acquisition.

Variable	Level	Number of independent effect sizes	Total N	Mean effect size (r)	Weighted mean effect size (r)	Combined Z
Overall	-	10	302	0.445	0.454	3.579
	Sex	6	136	0.501	0.422	2.464
	Female	3	52	0.329	0.394	1.192
Age	Both	4	114	0.424	0.532	2.344
	Juvenile	4	108	0.568	0.619	2.786
	Periadolescent	1	40	0.847	0.847	2.466
	Adult	5	164	0.236	0.209	1.333
Species	Combined	1	16	0.451	0.451	0.880
	Rat	9	256	0.402	0.386	2.906
	Mice	1	46	0.829	0.829	2.598
Dose	Low	3	68	0.712	0.760	2.737
	Intermediate	5	174	0.493	0.506	2.926
	High	2	60	-0.150	-0.045	-0.226
	Short	5	128	0.397	0.383	1.977
Exposure duration	Moderate	4	118	0.540	0.603	2.893
	Combined	1	56	0.301	0.301	1.112