

### NIH Public Access

**Author Manuscript** 

Behav Processes. Author manuscript; available in PMC 2012 January 1

Published in final edited form as: *Behav Processes.* 2011 January ; 86(1): 1–6. doi:10.1016/j.beproc.2010.07.010.

# Two-item discrimination and Hamilton search learning in infant pigtailed macaque monkeys

James C. Ha<sup>a,b,c,\*</sup>, Dorothy J. Mandell<sup>d</sup>, and Jonathan Gray<sup>a</sup>

<sup>a</sup>Psychology Department, University of Washington, Seattle WA <sup>b</sup>UW Infant Primate Research Laboratory, University of Washington, Seattle WA <sup>c</sup>Washington National Primate Research Center, University of Washington, Seattle WA <sup>d</sup>Psychology Department, University of Amsterdam, the Netherlands

### Abstract

This study investigated how infant pigtailed macaque monkeys performed on two separate learning assessments, Two-object discrimination/reversal and Hamilton search learning. Although the learning tasks have been tested on several species, including non-human primates, there have been no normative results reported for young macaque monkeys. The present study provides normative results for these learning tasks in very young captive pigtailed macaques and investigates the degree to which performance on these assessments are related. In addition, an error analysis was conducted to understand the choice patterns of the animals on each task. It was found that males took longer to reach criterion than females on the two-object reversal task. Performance and latency on the discrimination task predicted performance and latency on the reversal task. Performance on Hamilton Search Set-Breaking negatively predicted performance on the later Hamilton Search Forced Set-Breaking task. These data provide strong evidence of a relationship between performance on discrimination and reversal. This study shows that, otherwise, each task assesses a different cognitive function.

#### Keywords

cognition; learning; macaque

### Introduction

The present study summarizes the performance on two-object discrimination and Hamilton Search assessments by nursery-reared infant pigtailed macaque monkeys (*Macaca nemestrina*) collected on over 200 animals. A description of each task and performance on each assessment grouped by sex, birth weight, and birth weight percentile is provided as a summary of normative values for the sample. An inter-task path analysis was also performed to determine the degree to which earlier administered tasks predict performance on later

<sup>© 2010</sup> Elsevier B.V. All rights reserved.

<sup>&</sup>lt;sup>\*</sup>Correspondence to: James C. Ha, Psychology Department, University of Washington, Box 351525, Seattle, WA 98195. **Publisher's Disclaimer:** This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Two-object discrimination (2OD) has a long and storied history as a measure of visual learning ability. An animal learns to associate a stimulus feature with reward in this task: e.g. a black or white block signaling the location of a hidden reward (Harlow, 1959). The two-object reversal task (2ORev) is a test of how quickly an animal can reverse the stimulus-reward association that it had previously formed. Many species of primates (see Deaner et al., 2006 for a review), Long-Evans rats (McDaniel & Thomas, 1978), malamutes and wolves (Frank, 1989), and rock squirrels (King, 1965) have been tested on modified versions of 2OD and 2ORev. The fact that the tasks can be used in many species has also made it the subject of a large body of neurological and psychological research.

It has been shown that non-human primates of higher cognitive order perform better on reversal-discrimination tests, as evaluated by Rumbaugh's reversal or transfer-of-learning index (Rumbaugh, 1970; Rumbaugh & Pate, 1984; Deaner et al., 2006). The reversal index is the ratio of correct performance on reversal trials to correct performance on discrimination. It was originally created in order to compare performance on reversal learning tasks between species in a way that controls confounding factors such as perceptual and motivational diversity among species. We provide a similar measure in our path analysis between 2OD and 2ORev tasks, as discussed below.

The Hamilton Search (HS) tasks were developed in the early part of the 20<sup>th</sup> century by Hamilton as a test of spatial learning and memory (Hamilton, 1911). The basic task requires an animal to choose among several options until a reward is found. In order to succeed on the task, the animal must remember the previous unsuccessful choices and not repeat them. Animals tend to develop response-sets or choice strategies after performing several search problems. A commonly used sub-test of HS utilizes this strategy. In set-breaking, the animal's preferred and non-preferred choice are determined, then only the non-preferred location or choice is rewarded. This sub-task requires the animal to flexibly adjust its response-set to become more efficient at finding the reward. If an animal adjusts appropriately, it can find the reward in one trial because unlike in HS, the location of the reward can be predicted. Errors in HS are caused by repeated or preseverative choices. These types of errors in search tasks are often interpreted as working memory or inhibitory control failure (i.e. Diamond et al., 1997; Weed, et al., 1999). In set-breaking, errors are also caused by failure to adjust response-set and are general thought to be related to a lack of cognitive flexibility.

The HS task and its sub-assessments have not been used as widely as the 2OD and 2ORev tasks; however its usefulness has been shown in nonhuman and human studies (Diamond, et al., 1997; Harlow, 1959; Espy, et al, 1999). Researchers have used HS in order to evaluate the effects of environmental exposure to different toxins on cognitive ability. Infant pigtailed macaques exposed to various levels of ethanol during gestation (Clarren et al., 1988) and other drugs (Ha et al., 1998), as well as rhesus monkeys exposed to lead (Levin & Bowman, 1983, 1986a) and scopolamine have been tested using the HS tasks (Levin & Bowman, 1986b;). However, none of these studies have had success with finding significant performance differences between experimental and control conditions.

Due to the uniquely large sample of animals used within this study it was possible to assess the types of errors animals were making during these tasks. Harlow (1959) argued that learning problems are a culmination of multiple factors operating independently of each other during a trial. For example, errors can be caused by motivational factors, memory

errors, lack of flexibility in responding and incorrect associations with reward. Harlow identified four classes of errors that were made during learning problem sets that could reveal the factors contributing to errors. These error factors included stimulus-perseveration, differential cue, response shift, and position-habit errors. For the purposes of this study, we focused on position-habit errors, or side preference, and another error factor known as 'following the reward' or the win/stay strategy, where the animal's first response after receiving the reward is the location that was previously rewarded.

Finally, very little work has investigated how performance on one task might be predictive of performance between the tasks (for exceptions with other species see: Rumbaugh, 1970; Diamond et al, 1997; Espy et al, 1999; Mandell, under review). The relation between 2OD and 2ORev has been well investigated, especially by Rumbaugh. In Rumbaugh's transfer-of-learning index (the difference between the reversal indices for lower acquisition rate trials and higher acquisition rate trials), negative values suggested that animals were better able to reverse their learning when the initial acquisition was weak and positive scores the opposite, that reversal was better when the initial acquisition was strong. The implication is that positive scores suggested that an animal relied on abstract rules while negative scores implied a reliance on response-outcome associations. This would transfer over to our path analysis in the form of positive and negative path loadings: a positive path loading would imply that animal that does well on acquisition also does well on reversal. If the animal was simply associating outcomes, we would expect a negative path loading score for this relationship.

The relation between the HS tasks and 2OD and 2ORev, however, is less well worked out. There are 2 possible routes through which these tasks can be related and reflect common psychological processing. One of these routes is through the inhibitory demands of the HS tasks and 2ORev. It is a debate whether or not inhibition is a unitary psychological process or whether it can be divided into multiple forms of inhibition (see Nigg, 2000 for a discussion). Both 2ORev and HS require inhibiting a response, either to a previously learned contingency or to a previous searched box, in order to perform well (Diamond et al., 1997). Finding a relation between these two task would support the idea that a common inhibitory process is supported by both tasks. The other route through which these task may be related is with cognitive flexibility. 2ORev and set-breaking require cognitive flexibility to move away from a previously learned contingency or search strategy to develop a new one. Finding a relationship between the set-breaking sub-test and 2ORev would also support the notion that there are shared cognitive processes between these tasks.

Our first objective was to clearly explain the methodology utilized by the University of Washington's Infant Primate Research Laboratory (IPRL) over the past several decades in administering these tasks and their sub-assessments. We then provide a description of what should be expected when these tests are administered to a normative sample of young pigtailed macaques, and descriptive statistics are provided for each task. Nondirectional hypotheses of sex and birth weight effects are tested. We provide an analysis of position-habit and reward-following errors. Finally, we examine whether these tasks are independent measures of cognitive ability or whether performance on any of these tasks can be used to predict ability on later tasks. To achieve this, we use path analysis to examine the relationships among the sub-assessments of each task.

#### Materials and methods

#### Subjects and Housing

Each animal used in the current study experienced the same feeding, housing and testing routine on a set schedule described in the Infant Primate Research Laboratory Protocol

(Ruppenthal and Sackett, 1992). In summary, animals are fed formula on a 4hr-on, 4hr-off schedule until weaned to a totally solid diet at 4 months of age. Animals are individually housed with an extensive socialization program that included age-appropriate socialization in a stable peer-group. Assessments occur periodically during the day; more information about the assessment schedule is provided below. Infants who were chosen for this normative analysis were either non-experimental animals routinely housed in the IPRL nursery for non-medical reasons, or were control subjects assigned to experimental studies. All procedures used here were approved by the institutional review board for animal testing.

After birth, the infant was separated from its dam and placed into individual cages within the infant housing area. A full-time veterinary staff monitored their development and maintained computerized medical records for each infant. The infants were given similar visual, auditory, olfactory, and tactile stimulation in their home cages, including surrogates (cloth diapers) until 140 days of age.

#### Procedures

All tasks were administered in Wisconsin General Testing Apparatus (WGTA), which has been described extensively (e.g., Harlow & Bromer, 1938; Harlow, 1957). It will be briefly described here, however. Animals are placed into a test cage that sits flush against the stimulus display apparatus. The stimulus display apparatus has a guillotine door that, when lowered, occludes the animal's view and ability to reach through the test cage bars. When this door is raised, the animal has access to a stimulus display board that contains wells in which rewards may be placed. When a stimulus is placed over the well, it occludes the contents of the well and sits flush on the display board.

The tester sits behind the stimulus display apparatus and monitors the animal's performance through a one-way window in the back of the apparatus. During a task, the tester baits the wells and places stimuli appropriate for the task over the wells. Upon initiation of the trial, the tester slides the stimulus display board forward so that it is within arm's reach of the animal. When the board is in position, the tester raises the guillotine door and begins timing the task. When the animal makes a response, defined by displacing the stimulus enough so that the animal can see inside the well, the trial terminates and the tester lowers the guillotine door. The tester also records the animal's response, latency to respond and resets the stimulus display board for the next trial. Latency was electronically recorded by the experimenter via a foot pedal. The trial began when the experimented raised the door and terminated when the animal touched a stimulus.

Animals were first adapted to the WGTA at 120 days of age. They were taught to displace a single object in order to gain a reward from one of the wells. The location was pseudo-randomly determined so that no single side was rewarded for more than three trials in a row. No correction trials were used in this procedure. Following this adaptation procedure, animals were tested on the following tasks in the order presented here.

#### **Two-item Discrimination and Reversal**

Animals were presented with two easily discrimable objects: a black or white block. One of the objects signaled the location of the reward. Animals were given 60s to make a choice between the objects. Animals were tested on 24 trials in a session and were tested until they were correct on 23 or 25 trials. The session after the animal reached criterion, the reward contingency was reversed. Animals were again tested until they reached 23 out of 25 trials correct in a single test session.

#### **Hamilton Search Tasks**

Following 2OREV, animals were first habituated to the HS boxes by presenting the animal with a single box containing a reward. Once an animal learned to open the box and retrieve the reward, it began HS testing. The animal was presented with four identical boxes arranged in a row and spaced appoximantly 2.5cm apart. Each trial was set by the experimenter placing a reward in a randomly chose box. The animal was then presented with the boxes and given 60s to search through the boxes to find a reward. Once the reward was found or the 60s had elapsed, the experimented withdrew the boxes and lowered the opaque screen. The number of searches made by the animal as well as the sequence the boxes were opened and the latency to find the reward were recorded. An animal was tested on 25 search problems per session for five test days. In order to test how well the animal learned the task, the animal's efficiency on the fifth day was analyzed.

Following the HS procedure, Hamilton Search Set-Breaking (HSSB) was administered. For this procedure, the animal's least preferred box was determined based on its search sequences in HS. The reward was placed in that box for the duration of the procedure. The task was administered for five consecutive days with 25 search problems in a session. As with HS, the animal's performance on the fifth day of testing was analyzed.

Finally, in Hamilton Search Forced Set-Breaking Task (HSFSB), the reward was again placed in the same well as in HSSB, but the animal was only allowed to chose one box per search problem. This procedure was also administered for 5 test days with 25 search problems per session.

#### Results

Data were used only for those animals that completed the tasks to criterion, therefore, data were not available for every animal on every task. There were data for 220 subjects on 2OD, 185 subjects on 2ORev, and 56 subjects for the measures of Hamilton Search ability.

Sex and birth weight category were placed into an analysis of variance as independent variables for descriptive statistics. Birth weight categories were defined as High: top ten percent of birth weights, Low: bottom ten percent, and Middle: the remaining central eighty percent of birth weights. These categories were used, rather than a continuous covariate, for two reasons: we were interested in differences in low-birth-weight infants to later relate to effects seen in human developmental studies, and secondly, because we were concerned about a lack of a linear relationship between birth weight and the outcome variables. In fact, we have observed significant effects of high birth weight in some of our data for many years (Sackett, pers. comm.). Effect sizes for these analyses are reported as Cohen's f<sup>2</sup>.

Table 1 gives descriptive statistics on overall performance for each task by sex and birth weight category. Similar descriptive statistics for latency are shown in Table 2. There were no significant effects of sex or birth weight category in performance except for a significant difference in the number of boxes opened across birth weight category in Hamilton Search Set-Breaking (p = 0.03;  $f^2 = 0.10$ ): high birth weight animals opened significantly fewer boxes.

In latency to perform a task, there were no significant sex or birth weight effects for 2OD but sex, birth weight, and their interaction were significant in 2ORev (sex: p = 0.008,  $f^2 = 0.03$ ; birth weight: p = 0.03,  $f^2 = 0.03$ ; interaction: p = 0.009,  $f^2 = 0.04$ ). Males had significantly longer latencies on this task, low birth weight subjects had longer latencies, and low birth weight males were the most affected, with significantly greater latencies than any weight of females and normal birth weight males. No effects were found in Hamilton Search

or Hamilton Search Set-Breaking. In Hamilton Search Forced Set-Breaking, high birth weight females had significantly longer latencies than all but normal birth weight males.

The error factor analysis was performed using individual two-tailed unequal variance t-tests. The primary error factors that were investigated included the side preference choice pattern and the reward following patterns between males and females. In addition, similar tests were done to discriminate performance differences between animals in the top ten percentile weight category and animals in the bottom ten percent.

In the error analysis, side preference was not found to be significant on 2OD or on 2ORev, with the exception of a significant (p = 0.018) left food well side preference for animals in the bottom 10% birth weight category on 2OD. However, a significant side preference pattern was found for food wells on the right during the Hamilton Search Set Breaking task (p = 0.001) and Hamilton Search Forced Set Breaking task (p = 0.015). Insofar as reward following patterns, the only significant finding was with 2ORev where males followed the reward more often than females (p = 0.0003). Additionally, there was a significant (p = 0.046) reward following preference for animals in the bottom 10% birth weight category on the Hamilton Search Forced Set Breaking task.

Path analysis was used to determine whether there were significant correlations between tasks. Path analysis is an extension of regression models and calculates the strength of the relationships among two or more variables (Pedhazur and Kerlinger, 1982; Shipley, 1997, 1999). Specifically, path analysis describes the relative strength of direct and indirect relationships, or paths, within a set of variables. Unlike the related structural equation modeling, path analysis deals only with the relationships among a set of measured variables. In our work, path analysis was used to assess the relative ability of earlier tasks, or combination of tasks, to predict later task outcomes. Two path analyses were conducted: one for task performance and one for task latency. Effect sizes were again reported as Cohen's  $f^2$ .

Results of the path analyses indicated that performance on 2OD was significantly predictive of performance on 2ORev ( $R^2 = 0.43$ , p < 0.001,  $f^2 = 0.75$ , Fig. 1). Furthermore, higher performance on Hamilton Search Set-Breaking predicted low performance on Hamilton Search Forced Set-breaking ( $R^2 = -0.37$ , p = 0.030,  $f^2 = 0.59$ , Fig. 1). This results indicates that monkeys that did not form a search strategy during HS had an easy time adjusting their performance to search their least preferred box. Those that did form a search strategy had difficulty breaking it to search their least preferred box.

A similar "intra-WGTA" path analysis was conducted utilizing latency as a predictive factor for latency on later tasks. Latency on 2OD significantly predicted latency on 2ORev ( $R^2 = 0.33$ , p < 0.001,  $f^2 = 0.49$ , Fig. 2), and latency on the 2ORev task significantly predicted latency on the Hamilton Search task ( $R^2 = 0.31$ , p = 0.003,  $f^2 = 0.45$ , Fig. 2), but not on any other task. The predictive value of latency in Hamilton Search Set-breaking on Hamilton Search Forced Set-breaking did not approach significance ( $R^2 = 0.03$ , p = 0.85,  $f^2 = 0.03$ , Fig. 2).

#### Discussion

The purpose of this study was to evaluate the 2OD, 2ORev and Hamilton Search Tasks as independent measures of cognitive ability while providing normative descriptive statistics for each task. Two specific questions were asked in addressing this goal. First, what are the results when testing a large sample of nonhuman primates on the 2OD, 2ORev and Hamilton Search learning tasks? Secondly, are these measures testing independent cognitive functions, and if not, what predictive relationships in performance and latency exist among these tasks?

On average, there were few effects of sex or birth weight on performance (number of days to criterion for Two-item and Reversal and number of boxes opened on Hamilton Search). Only in the one case did high birth weight animals perform significantly better than normal or low birth weight subjects. Latencies to complete these tasks were more strongly effected by a combination of sex and birth weight: low birth weight males took much longer to complete the Reversal task. The lack of a performance difference between normal birth weight males and females is surprising as 2ORev has been shown to be sensitive to developmental sex differences in rhesus macaques and in humans (Goldman et al., 1974; Overman et al., 1996), with males developing quicker than females. However, two results do suggest that there is a developmental sex difference in performance between males and females. Males engaged in reward following to a higher extent than females on the reversal task and low-birth weight males had longer latencies on 2ORev. Reward following can be an adaptive strategy for determining reward contingencies (Harlow, 1949), therefore it may be that males had a more mature response to the reversal contingency than did females. Additionally, low-birth weight males but not females were affected on 2ORev in terms of their latency. This finding supports the notion that males develop faster on this task than do females and the groundwork for this development is laid prenatally (Goldman et al., 1974).

High birth weight females had very long latencies on Hamilton Search Forced Set-Breaking. There is no clear explanation for these results. But given the high drop out rate and that there were very few high-birth weight females animals, it is very likely that this result is spurious.

Within the past two decades, researchers have increasingly used the HS task with nonhuman primates to examine cognitive differences between groups of normal controls and those exposed to various toxins or drugs (Levin and Bowman, 1986a, 1986b; Clarren et al., 1988; Ha et al., 1998) in macaque monkeys. However, there have been very few studies that have shown differential effects on this task. The results of this analysis may shed light on why these null findings persist. One result of this analysis is that animals of this age performed rather poorly on HS. Optimal performance on this task would be to open an average of 2.5 boxes per search. However, animals were opening closer to 3, indicating poor performance and substantial number of repeat searches. Additionally, the negative relation between HS and set breaking indicates that the animals that do develop a search strategy have a difficult time breaking it to form another. Taken together, these normative results suggest that the lack of findings in the toxicology and teratology literature may be because the animals were administered the task too young. Therefore, effects of the toxins on development could not be determined because the control animals had not yet reached a level of developmental maturity to perform well on the task either.

The WGTA path analyses showed that both performance and latency on 2OD predicted both performance and latency on 2ORev. This finding can be interpreted with Rumbaugh's (1970) suggestion that animals with positive relations between 2OD and 2ORev are using abstract rules of learning rather than simply associated outcomes. In his review, he found that prosimians and New World primates were more likely to use associated outcomes while Old World monkeys and great apes were more likely to use abstract rules. This continues to be supported by broader taxonomic analyses, using a wider range of learning task (Deaner et al., 2006).

There was little evidence for a direct relation between 2ORev and any HS task, which may suggest little continuity in the cognitive processes underlying these two tasks. Interestingly, however, the error analysis revealed a lack of side bias in 2OD but significant side biases in the Hamilton Search tasks. Whereas, side biases in discrimination are maladaptive, they can be adaptive in HS. The side bias in HS may possibly reveal formation of a spatial search strategy, whereas the lack of one in 2OD suggests the use of an object-oriented strategy. The

ability to adapt responses and response strategies to task demands, which is a component of cognitive flexibility, may be at the heart of the underlying process between the two tasks. Another possible explanation for the development of side-bias, handedness, is not well supported in the literature or in these data. Generally, while specific animals may exhibit handedness preferences, consistent, population-wide handedness in macaques has not been found (Schmitt et al., 2008). Westergaard and colleagues have found that individual handedness in rhesus macaques may reflect immune functioning and behavioral reactivity (see Westergaard, et al., 2004 for review), but we do not have data on handedness in this specific assessment.

The path analysis also revealed that strong performance on Hamilton Search set-breaking predicted poor performance on Hamilton Search forced set-breaking. This finding shows that animals that formed search strategies had a difficulty breaking them, suggesting that they have not developed another aspect of cognitive flexibility, the ability to switch from previous learn response patterns. Similarly, latency was not similarly predictive between the two tasks. But given that administration of set breaking and forced set breaking is quite different, it is not surprising that latencies on the tasks are not significantly related. The only other significant finding within the path analyses was that latency on the 2ORev task predicted latency on the HS task. However, no relationship was found in terms of performance on these two tasks suggesting that the latency relationship may be related to continuity in global processing rather than a specific relation in cognitive processing. Inhibition failure has been cited as a reason for animals to perform poorly on search based tasks as well as reversal tasks. The idea of inhibition as a unified concept is being debated within the human literature (see Nigg, 2000). The results from this study shows that there is little evidence for a relation between HS and reversal behavior, suggesting that multiple forms of inhibition can be differentiated in nonhuman primates. However, these null results must be viewed with caution as performance on HS was also quite low. It may be that there is a predictive relation between these tasks, but that we did not assess HS at an appropriate age to detect the relationship.

Each of these cognitive behavioral tasks provides insight into unique and specific areas of animal performance. The present study provides descriptive data and evidence of relatively few predictive relationships for performance and latency among these tasks. These results suggests to us that these tasks are independent and assess different cognitive functions of the brain. This work will provide a baseline for understanding the normative performance on these tasks, especially for animals of such a young age, while presenting a standard methodology in administering each task.

#### **Research Highlights**

Normative values for infant pigtailed macaque monkeys

Males delayed relative to females on two-object reversal learning

Performance and latency on the discrimination task predicted performance and latency on the reversal task

Two-object discrimination performance unrelated to Hamilton Search task performance

#### Acknowledgments

We would like to thank Gene (Jim) Sackett for helpful comments on earlier drafts of this paper. Support for this research was provided by NIH grant RR00166 to the Washington National Primate Research Center. All procedures have been approved by the Institutional Animal Care and Use Committee at the University of Washington, and the principles of laboratory animal care (NIH publication No. 86-23, 1985) were followed.

#### References

- Clarren SK, Astley SJ, Bowden DM. Physical anomalies and developmental delays in nonhuman primate infants exposed to weekly doses of ethanol during gestation. Teratology 1988;37:561–569. [PubMed: 3400071]
- Deaner RO, van Schaik CP, Johnson V. Do some taxa have better domain-general cognition than others? A meta-analysis of nonhuman primate studies. Evolutionary Psychology 2006;4:149–196.
- Diamond A, Prevor MB, Callender G, Druin DP. Prefrontal cortex cognitive deficits in children teasted early and continuously for PKU. Monographs of the Society for Research in Child Development 1997;62:1–206. [PubMed: 9353949]
- Espy KA, Kaufmann PM, McDiarmid MD, Glisky ML. Executive functioning in preschool children: Performance on A-not-B and other delayed response format tasks. Brain and Cognition 1999;41:178–199. [PubMed: 10590818]
- Frank H, Frank MG, Hasselbach LM, Littleton DM. Motivation and insight in wolf (*Canis lupus*) and Alaskan malamute (*Canis familiaris*): Visual discrimination learning. Bulletin of Psychonomic Society 1989;27(5):455–458.
- Goldman PS, Crawford HT, Stokes LP, Galkin TW, Rosvold HE. Sex-dependent behavioral effects of cerebral cortical lesions in the developing rhesus monkey. Science 1974;186:540–542. [PubMed: 4219963]
- Ha JC, Nosbisch C, Abkowitz JL, Conrad SH, Mottet NK, Ruppenthal GC, Robinette R, Sackett GP, Unadkat JD. Fetal, infant, and maternal toxicity of Zidovudine (Azidothymidine) administered throughout pregnancy in *Macaca nemestrina*. J. Acquir. Immune Defic. Syndr. Hum. Retrovirol 1998;18(1):27–38. [PubMed: 9593455]
- Hamilton GV. A study of trial and error reactions in mammals. Journal of Animal Behavior 1911;1:33–66.

Harlow HF. The development of learning in the rhesus monkey. Am. Sci 1959;47:459-479.

- King JE. Discrimination and Reversal Learning in the Rock Squirrel. Perceptual and Motor Skills 1965;20:271–276. [PubMed: 14286535]
- Levin ED, Bowman RE. The effect of pre- or postnatal lead exposure on hamilton search task in monkeys. Neurobehavioral Toxicology and Teratology 1983;5:391–394. [PubMed: 6877479]
- Levin ED, Bowman RE. Long-term lead effects on the hamilton search task and delayed alternation in monkeys. Neurobehavioral Toxicology and Teratology 1986a;8:219–224. [PubMed: 3736749]
- Levin ED, Bowman RE. Scopolamine effects on hamilton search task performance in monkeys. Pharmacology BioChemistry and Behavior 1986b;24:819–821.
- Mandell DJ. Building the blocks of executive functioning: A neuropsychological approach for differentiating early emerging processes underlying executive functioning skills. (under review).
- McDaniel WF, Thomas RK. Temporal and parietal association cortex lesions and spatial and two-item reversal learning in the rat. Physiological Psychology 1978;6(3):300–305.
- Nigg JT. On inhibition/disinhibition in developmental psychopathology: Views from cognitive and personality psychology and a working inhibition taxonomy. Psychological Bulletin 2000;126(2): 220–246. [PubMed: 10748641]
- Overman WH, Bachevalier J, Schuhmann E, Ryan P. Cognitive gender differences in very young children parallel biological based cognitive gender differences in monkeys. Behavioral Neuroscience 1996;110:673–684. [PubMed: 8864260]
- Pedhazur, EJ.; Kerlinger, FN. Explanation and Prediction. New York: Holt, Rinehart and Winston; 1982. Multiple Regression in Behavioral Research; p. 784
- Rumbaugh, DM. Learning skills of anthropoids. In: Rosenblum, LA., editor. Primate Behavior: Developments in Field and Laboratory Research. New York: Academic Press; 1970. p. 1-70.
- Rumbaugh, DM.; Pate, J. The evolution of primate cognition: A comparative primate perspective. In: Roitblat, HL.; Bever, TG.; Terrace, HS., editors. Animal Cognition. New Jersey: Lawrence Erlbaum Associates; 1984. p. 569-587.
- Ruppenthal, G.; Sackett, GP. Infant Primate Research Laboratory Research Protocols. Seattle, Washington: University of Washington Child Development and Mental Retardation Center; 1986.

Page 9

- Schmitt V, Melchisedech S, Hammerschmidt K, Fischer J. Hand preferences in Barbary macaques (Macaca sylvanus). Laterality: Asymmetries of Body, Brain and Cognition 2008;13(2):143–157.
- Shipley B. Exploratory path analysis with applications in ecology and evolution. The American Naturalist 1997;149(6):1113–1138.
- Shipley B. Testing causal explanations in organismal biology: Causation, correlation and structural equation modeling. Oikos 1999;86(2):374–382.
- Weed MR, Taffe MA, Polis I, Roberts AC, Robbins TW, Koob GF. Performance norms for a rhesus monkey neuropsychological testing battery: Aquisition and long-term performance. Cognitive Brain Research 1999;8:185–201. [PubMed: 10556598]
- Westergaard GC, Chavanne TJ, Houser L, Cleveland A, Snoy PJ, Suomi SJ, Higley JD. Biobehavioural correlates of hand preference in free-ranging female primates. Laterality: Asymmetries of Body, Brain and Cognition 2004;9(3):267–285.



#### Fig. 1.

Path analysis of "intra-WGTA" predictive strength in performance. Numbers are statistical p values for strength of indicated relationship.



#### Fig. 2.

Path analysis of "intra-WGTA" predictive strength in latency. Numbers are statistical p values for strength of indicated relationship.

**NIH-PA Author Manuscript** 

# Table 1

Number of days to reach criterion on the Two-item and Two-item Reversal tasks, number of boxes opened on day 5 for Hamilton Search and Hamilton Search Set-Breaking task, by sex and birth weight category.

Performance	Two-item	Two-item Reversal	Hamilton Search	HS-Set Breaking	HS-Forced Set Breaking
Low BW, Female					
Z	13	13	9	9	9
Mean	3.69	8.08	3.48	2.03	13.00
Stdev	1.60	3.71	0.48	0.47	8.51
Normal BW, Female					
Z	74	60	31	13	11
Mean	4.13	7.05	2.91	2.36	11.18
Stdev	2.38	3.25	0.61	0.55	6.306
High BW, Female					
N	20	17	10	9	7
Mean	3.55	5.88	2.94	1.97	5.14
Stdev	2.09	2.29	0.30	0.26	5.43
Low BW, Male					
Z	13	13	5	9	9
Mean	3.15	5.77	2.89	2.28	7.67
Stdev	1.62	2.71	0.48	0.50	8.07
Normal BW, Male					
Z	84	72	45	21	22
Mean	3.75	6.22	2.96	2.33	9.59
Stdev	1.85	2.89	0.52	0.50	9.05
High BW, Male					
N	16	10	7	4	4
Mean	3.75	6.50	2.83	2.10	12.00
Stdev	2.11	3.03	0.26	0.58	9.76

Performance	Two-item	Two-item Reversal	Hamilton Search	HS-Set Breaking	HS-Forced Set Breaking
Overall					
Z	220	185	104	56	56
Mean	3.82	6.57	2.96	2.25	9.68
Stdev	2.06	3.04	0.52	0.50	8.03

Behav Processes. Author manuscript; available in PMC 2012 January 1.

## Table 2

Latency of response on the Two-item and Two-item Reversal, Hamilton Search, Hamilton Search Set-Breaking, and Hamilton Search Forced Set-Breaking tasks, by sex and birth weight category.

Latency	Two-item	Two-item Reversal	Hamilton Search	HS-Set Breaking	HS-Forced Set Breaking
Low BW, Female					
Z	13	13	6	6	9
Mean	5.086	4.342	7.387	4.973	6.240
Stdev	4.363	3.074	2.388	2.041	2.512
Normal BW, Female					
Z	74	60	32	13	11
Mean	8.132	4.617	10.252	4.083	3.458
Stdev	7.712	4.541	7.871	2.469	2.176
High BW, Female					
Z	20	17	10	6	7
Mean	5.859	3.575	7.352	10.353	53.511
Stdev	3.124	2.897	3.194	4.987	78.785
Low BW, Male					
Z	13	13	5	6	9
Mean	4.878	9.738	11.352	7.093	7.100
Stdev	2.835	11.758	11.003	4.090	5.166
Normal BW, Male					
Z	84	72	45	21	22
Mean	5.679	4.021	8.236	6.973	21.785
Stdev	5.235	2.770	8.167	8.538	43.649
High BW, Male					
Z	16	10	7	4	4
Mean	9.103	6.292	5.286	4.110	1.752
Stdev	11.351	7.499	2.425	1.309	0.995

Latency	Two-item	Two-item Reversal	Hamilton Search	HS-Set Breaking	HS-Forced Set Breaking
Overall					
Z	220	185	105	56	56
Mean	6.687	4.720	8.669	6.259	17.481
Stdev	6.580	4.993	7.421	5.985	40.792

Behav Processes. Author manuscript; available in PMC 2012 January 1.

Page 16

**NIH-PA** Author Manuscript