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Measuring Infant Memory: Utility of the Visual Paired-Comparison Test Paradigm for Studies in Developmental Neurotoxicology

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Abstract

The assessment of brain function and behavior in young infants is central to understanding the effects of chemical exposure on central nervous system development. One approach to infant cognitive assessment, based on the direct observation of infant eye movements, is known as the Visual Paired-Comparison task. The Visual Paired-Comparison test methodology uses selective visual attention as a vehicle to study emerging recognition memory skills. The utility of this procedure to study visual recognition memory has been well established in both human and nonhuman primate infants. The primary outcome measure produced by this assessment technique is known as the Novelty Preference Score, reflecting the amount of time the infant spends actively looking at novel rather than familiar test stimuli. Visual recognition memory testing has demonstrated a strong sensitivity to conditions that may place infants at risk for poor developmental outcome (e.g. preterm birth, Down syndrome) and in humans; performance is significantly related to later measures of I.Q. and language competency. This assessment methodology has been successfully applied to the study of neurobehavioral effects after fetal neurotoxicant exposure. Field and laboratory studies have used tests of visual recognition memory to better understand the effects of compounds such as lead, methylmercury and polychlorinated biphenyls on emergent cognitive processing. The Visual Paired-Comparison paradigm and its capacity to measure recognition memory in preverbal infants provide a valid and theoretically meaningful approach to neurobehavioral assessment for studies in developmental toxicology and teratology.

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Introduction

For children living in industrialized nations, the world has changed dramatically in the last century. The danger that infectious diseases (e.g. small pox, polio, malaria) pose to children has been drastically reduced through the development of childhood vaccinations and the increased safety of food and water supplies. Although threats of classic infectious disease have diminished in most countries, a new, more subtle threat to children's health has emerged over the last several decades (Landigran *et al.*, 2004). Developmental disorders such as autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) and learning disabilities are impacting greater numbers of children each year. These clinical syndromes have complex etiologies and are associated with abnormalities of the developing nervous system, exerting an enduring impact on school achievement, adaptive behavior and social competence (Goldman *et al.*, 2004, Pallapies, 2006).

There is a growing public health awareness that exposure to environmental chemicals may be contributing to the increased number of children with certain chronic childhood illnesses or disabilities (Woodruff *et al.* 2004, Landigran and Goldman, 2011, Landigran and Miodovnik, 2011). Pregnant women and children are exposed to a vast array of synthetic chemicals in air, water, soil, and food. Exposure-related effects on physical and mental growth in children have been documented for a range of environmental pollutants including lead, methylmercury, arsenic, solvents, pesticides and polychlorinated biphenyls (PCBs) (Grandjean and Landrigan, 2006). Chemical exposures pose unique risks to infants and children and chemically-induced injury can take many forms (Faustman *et al.*, 2000). In the absence of congenital malformations, prenatal exposure to low-dose neurotoxicants can be expressed as functional changes in postnatal neurobehavioral competence or losses in sensory acuity (e.g. vision, hearing, touch). Although the clinical significance of chemically-related effects on neurodevelopment are sometimes minimized, a recent analysis found that the contributions of methylmercury, organophosphate pesticides and lead to lost IQ points in children exceeded nonchemical risk factors such as preterm birth, traumatic brain injury and congenital heart disease (Bellinger, 2011).

Assessment of Cognitive Development During Infancy

Within the field of developmental neurotoxicology, the assessment of brain function and behavior is central to understanding the effects of chemical exposure on central nervous system development (Paule *et al.*, 2012). The meaningful measurement of behavior in infants is psychometrically challenging as infants lack spoken language, sleep a great deal and are unable to engage in coordinated, directed movement. The young infant is however, responsive to a rich variety of sensory stimulation and spends most waking hours engaged in visual explorations of the environment. Given the real-world limitations of the infant behavioral repertoire, adverse changes in cognition that are related to neurotoxicant exposure can be difficult to detect. The measurement of subtle changes in behavior is limited by the sensitivity of available measurement tools and observational acumen.

Early studies of infant cognition, between the 1930's and the 1960's, concentrated heavily on developing standardized tests for assessing age-related changes in developmental

functioning (Bayley, 1969, Cattell, 1940; Gesell and Amatruda, 1954). Using an interactive platform to administer simple play tasks, trained examiners were able to quantitatively measure aspects of mental and physical development. The Bayley Scales of Infant and Toddler Development (current version BSID-III) is a standardized series of measurements used primarily to assess the motor (fine and gross), language (receptive and expressive), and cognitive development of infants and toddlers between birth and 42 months of age (Bayley, 1969, 2006). This well-established, time-honored instrument has been used in studies investigating the developmental effects of neurotoxicants such as lead (Hu *et al.*, 2006), PCBs (Verner *et al.*, 2010) and organophosphate pesticides (Eskenazi *et al.*, 2010) as well as therapeutics such as antiretroviral treatment (Williams *et al.*, 2010). One important weakness of this assessment tool is the lack of predictive validity associated with performance outcomes. Over time, longitudinal analyses using Bayley data collected during infancy have not revealed strong associations with later intellectual outcome.

The Mullen Scales of Early Learning, a relative newcomer to the psychometric scene, is also based on an interactive test platform where examiners engage the infant in a series of simple games and play activities (Mullen, 1995). This standardized assessment is designed to evaluate cognitive and motor functioning in children from birth to 68 months in five domains of neurobehavioral development: receptive language, expressive language, visual reception, fine motor and gross motor. The Mullen was originally designed to identify children with special education needs but has been increasingly utilized as a research tool to identify infants and children at risk for poor developmental outcome (e.g. biliary atresia, autism spectrum disorders, Fragile X syndrome) (Eigsti *et al.*, 2010, Akshoomoof, 2006, Zingerevich *et al.*, 2009). This test was recently used in an epidemiology study to evaluate neurobehavioral changes in development in infants exposed to polychlorinated biphenyls, dichlorodiphenyltrichloroethane, and dichlorodiphenyldichloroethylene (Pan *et al.*, 2009). The predictive validity of the Mullen has not been established to date.

A different approach to infant cognitive assessment, based on the direct observation of infant eye movements, is known as the **Visual Paired-Comparison (VPC)** task. The VPC test methodology uses selective visual attention as a vehicle to study emerging perceptual-cognitive skills in preverbal infants (Fagan, 1990). In this manuscript, the utility of the VPC as a test methodology will be examined within two scientific frameworks, 1) infant perceptual-cognitive development and 2) psychometrics for developmental neurotoxicology. As this manuscript will demonstrate, laboratory and field investigations have utilized the VPC test paradigm to probe early memory processing in both human and monkey infants exposed to neurotoxicants during prenatal development.

Origins of the Visual Paired-Comparison Test Methodology

Originally conceived in 1956, Robert L. Fantz developed an innovative approach to the evaluation of perception in infants based on the principle of visual selectivity (Fantz, 1956). He surmised that if the infant looked longer at one stimulus than another, they must be able to perceive a difference between the two. Using a technique originally called the “visual interest test”, Fantz presented an infant chimpanzee with pairs of stimuli varying in attributes such as color, form and size in a controlled environment (Fantz, 1958). The infant

demonstrated strong preferences for certain stimuli across testing sessions. For example, the color blue was consistently preferred to red and a checkerboard pattern was preferred over a solid square image. These findings were interpreted as the first empirical demonstration of visual responsiveness, form perception and basic discrimination in an infant primate shortly after birth.

After the publication of Fantz's original findings with the chimpanzee infant, laboratory studies were quickly initiated to study similar processes in humans. Shown in Figure 1, the original Fantz apparatus used to test human infants consisted of a heavy metal box on four legs that was placed over a specially constructed crib.

The interior of the looking box was covered in light blue felt to contrast with the visual test stimuli and a sliding door was located on the ceiling of the looking chamber. Two cards displaying images were placed in the sliding doors and presented to the infant laying supine in the crib. The data collector recorded gaze patterns to each stimulus (duration and frequencies of individual visual fixations) by looking through a small peep hole. The accurate recording of eye movements is difficult and Fantz increased the reliability of the method by cleverly positioning the chamber lighting source so that reflections of the test stimuli were mirrored in the infant's eyes. Using corneal reflections, data collectors were able to more accurately measure direction of gaze in young infants. Using this general test methodology, researchers found that human infants have strong visual preferences that include patterned over plain visual surfaces (e.g. bull's-eye preferred over solid colored disk), curvilinear contours over straight edges and face-like images over abstract geometric forms (Fantz, 1958, 1961, 1963, 1965). These robust, reliably elicited preferences provide evidence of form perception shortly after birth and suggested that infants do not live in "one great blooming, buzzing confusion" (William James, 1890) but instead, selectively move their eyes in distinct and meaningful ways.

Using the Visual Paired-Comparison Test Paradigm to Study Recognition Memory

In 1964, Fantz adapted the VPC paradigm to study memory in infants. The authors observed that visual attention directed toward stimuli that were presented repeatedly declined across test trials. The decrease in visual responsiveness/attention toward previously seen images was interpreted as evidence that the familiar image was "remembered" and therefore, of diminished or limited interest to the infant. Scientists quickly corroborated this finding and firmly established the human infant's strong proclivity to direct more visual attention to novel rather than previously seen (i.e. familiar) visual targets (Fantz, 1964, Fagan, 1970, 1971). This behavioral phenomenon has been interpreted as evidence of basic recognition memory as some aspects of the familiar stimulus must be encoded in memory for the novelty response to occur. Recognition memory is considered a core intellectual process, encompassing a set of retrieval processes through which we know a piece of information, an event or fact has been encountered before (Rose *et al.*, 2003, Mishkin and Murray, 1994).

To measure recognition memory with the VPC test methodology, the infant is seated in a caregiver's lap behind a rotating stage where visual targets are presented. The visual

fixations of the infant are recorded by a trained data collector. A test trial begins with the presentation of two identical copies of a visual image to the infant for inspection. Figure 2 displays an example of a visual recognition memory test where the circle is being used as the familiarization stimulus.

The trained tester, looking through a peephole centered between the two targets, records the amount of time the infant spends looking at the familiarization stimulus. Measurement of gaze is primarily accomplished through the use of corneal reflections, directed eye movements and cues such as eye widening. Individual looks are recorded in real time to provide frequency and duration data. After infant looking time to the familiarization stimulus has reached a predetermined criterion (e.g. 60 seconds of cumulative looking time), the two retention test trials are presented where the familiar stimulus (circle) is paired with a novel stimulus (triangle) and visual inspection time to each is recorded. In this example problem, the amount of looking time directed at the triangle (novel stimulus) during the retention trials would be used to infer recognition memory abilities. To increase the difficulty of the problem, a delay period can be introduced between familiarization and the subsequent retention trials. The left-right position of the novel stimulus is reversed between the retention trials to minimize the influence of side biases in the infant's visual response pattern.

The most commonly derived outcome measure from visual recognition memory testing is the overall percent time looking at the novel stimuli across recognition problems. The increased visual attention directed at novel stimuli, termed the "novelty response" is present in humans as early as three or four days after birth with limited or no delay periods and is robust by 3–5 months of postnatal age (Pascalis and de Schonen, 1994). The age however, at which infants demonstrate immediate recognition is dependent upon on the nature of the previously-exposed and novel targets and the amount of study time they are allowed during the familiarization period (Fagan, 1973). In a well-designed study of preterm and full-term infants, investigators found that total maturational level (gestational age at birth plus postnatal age) rather than length of experience in the visual world (postnatal age) plays the more important role in determining when preferences for novelty will appear (Fagan, 1971).

In a review of several studies and over twenty groups of infants, Fagan found that in healthy, full-term infants, the overall mean novelty preference was 64.4% (range of 58.9 to 74.6). The average standard deviation was 18.47 (range 8.3 to 27.6) (Fagan, 1990). To calculate a novelty preference for a recognition problem, the duration of time spent looking at the novel targets is divided by total looking time on the two retention trials. This value, the mean percent differential fixation to novel targets, is then tested against the hypothetical value of 50% (representing a pattern of random looking behavior). Memory is inferred if the novelty score is significantly higher than 50%, suggesting recognition of the familiar stimulus. This behavioral phenomenon is thought to represent intelligent behavior on the part of the infant (Fagan, 1990). Consider that to display a novelty preference, infants must encode, store, consolidate and retrieve representations of the target stimulus. As conceptualized, the novelty response is a behavioral phenomenon that is fundamentally driven by the infants' recognition of the familiar stimulus during the retention phase. Another important aspect of performance is related to how infants deploy attention during the test (Rose *et al.*, 2009).

Shorter looks and more frequent shifts of gaze are thought to reflect more rapid encoding, more active comparison of the test stimuli and possibly, greater facility at disengaging attention.

Perinatal Risk and Effects on Visual Recognition Memory

As the VPC approach to memory assessment was used with increasingly diverse groups of subjects that varied in neurobehavioral risk, an intriguing pattern of results emerged from the data that suggested infants at high-risk for future cognitive deficits (Down syndrome, preterm birth) exhibited diminished novelty preferences (Miranda and Fantz, 1974, Rose, 1980). The lack of a robust response to visual novelty in these groups raised provocative questions about the meaning of early perceptual-cognitive changes and their possible relationship with long-term intelligence and academic success (Rose *et al.*, 1988). While it is difficult to predict the meaning of early differences in selective visual attention, infant novelty preference scores are related to later performance on standardized tests of intelligence, (Fagan *et al.*, 1986, Thompson *et al.*, 1991, Fagan *et al.*, 2007, Rose *et al.*, 1988, Rose, *et al.*, 2005). In addition, better infant visual recognition memory scores have been associated with enhanced comprehension and gestural communication in toddlers (Heimann *et al.*, 2006) and improved expressive and receptive language skills during preschool and beyond (Fagan and McGrath, 1981, Rose *et al.*, 1991, Thompson *et al.*, 1991).

The moderate predictive validity of infant visual recognition memory scores lends support to the idea that some of the cognitive properties measured with this test during the first year of life are also important to later childhood cognition. A diminished or poor novelty response in infancy may signal recognition memory deficits but it may also forecast longer-term effects on core cognitive abilities during childhood.

Collectively, the VPC data suggested that the absence of selective visual attention to novelty was an early indicator of risk for poor or suboptimal outcome and that early assessment of recognition memory may be an important developmental metric for studies designed to capture individual differences in cognitive development. Tests of recognition memory, using the VPC test methodology, have provided a means to study the consequences of biological and environmental risk that include prenatal cocaine and alcohol exposure, premature birth, Down syndrome and iron deficiency anemia in human infants (Singer *et al.*, 2005, Chiriboga *et al.*, 2007, Gaultney *et al.*, 2005, Jacobson *et al.*, 1985, 2002, Guzzeta *et al.*, 2006, Nygaard *et al.*, 2001, Rose *et al.*, 2001, Carter *et al.*, 2010).

Individual differences in performance on tests of visual recognition memory, including those associated with neurotoxicant exposure, are likely due to a number of factors but information processing speed has been identified as one of the most important. Processing speed is often considered to be a central, limiting factor that accounts for individual differences on a variety of cognitive tasks in childhood and adolescence (Hail, 1990, Kail, 1991). In a study of visual recognition memory in preterm and full-term infants, novelty preference scores were significantly improved in high-risk preterm infants when the time to study the familiarization stimuli was increased (Rose, 1980). This finding suggests that preterm infants may process information more slowly than full-term infants and that

performance can be bolstered by allowing more time to process the test stimuli. The concept of speed as an important component of mental operations is not new and theoretical models of human intelligence have identified processing speed as a core attribute of human intelligence (Fagan, 1990, 2000). Tests of infant recognition memory that rely on the measurement of selective visual attention provide a potential vehicle to measure speed of processing at an early age. As conceptualized, infants who process information more slowly will acquire less information about their world and over time, this deficit in processing may translate to lower I.Q. scores or reduced success in school. Whether processing speed or another attribute of cognitive processing underlies the basis of individual differences in infant novelty scores, the predictive validity of these scores, although limited, raises provocative questions about the meaning of early perceptual-cognitive changes and long-term intellectual outcome.

The sensitivity of visual recognition memory scores to intellectual impairment led investigators at Case Western University to develop the Fagan Test of Infant Intelligence, a commercially-available test that is used in research and clinical settings (Fagan and Detterman, Technical Report, 1992). Figure 3 displays an infant visually exploring two test stimuli during a retention trial on a Fagan Test problem. The Fagan Test uses the faces of infants and adults as test stimuli and systematically varies the age, sex and orientation of the faces in the recognition trials. Familiarization times are linked to the difficulty of the problem. The Fagan Test is designed to detect subtle neurological dysfunction and changes in visual information processing in infants from 5 to 12 months. Like other tests of visual recognition memory, the Fagan Test relies on the overall novelty preference as the primary data outcome measure although average durations of individual looks have also proven to be sensitive to clinical risk.

Effects of Fetal Neurotoxicant Exposure on Recognition Memory in Human Infants

The utility of the VPC task to detect early changes in biobehavioral development has been actively explored in the context of developmental neurotoxicology and environmental epidemiology. A review of the use of the Fagan Test in evaluating the impact of environmental contaminants on infant cognitive development is provided and discussed below (see Table 1):

Methylmercury (MeHg)

In two longitudinal studies, visual recognition memory was measured in methylmercury-exposed and control infants to evaluate the effects of low-dose prenatal exposure on early mental processing. Meyers and colleagues used the Fagan Test to evaluate the relationship between total maternal hair mercury and infant novelty preference in their large maternal-infant cohort in the Seychelles Islands (n=740) (Meyers *et al.*, 1995). This population was selected for study because of the high maternal consumption of fish during pregnancy. Maternal total hair mercury values ranged from 0.5ppm to 26.7 ppm with a median of 5.9 ppm. Infant novelty scores were not related to maternal mercury hair values and test performance across exposure groups was within the normal range (mean novelty score 60.5%). The results of the Fagan Test were consistent with results from other neurobehavioral test measures in this group, providing evidence that at the hair levels

studied, methylmercury exposure was not related to the disruption of early cognitive development and not subject to effect modification from social or environmental factors (Davidson *et al.*, 2006).

In the second study to evaluate the effects of methylmercury on early memory processing, Oken and colleagues used visual recognition memory problems to specifically address the benefits and risks associated with maternal fish consumption in an upper, middle class group of women and their infants ($n=135$) (Oken *et al.*, 2005). In this prospective, cohort study, a food frequency questionnaire used to evaluate long-chain polyunsaturated fatty acid exposure was administered to pregnant women around 26–28 weeks of gestation. The survey instrument quantified the average frequency of consumption of alcohol and over 140 specific foods during the last 3 months, including tuna, shellfish, dark meat fish such as mackerel, salmon or sardines and other fish such as halibut and cod. Hair samples were collected at or near delivery for mercury analysis. Mean maternal hair mercury was 0.55 ppm, with 10% of samples greater than 1.2 ppm. When infants reached approximately 6.5 months, subjects were screened for visual acuity and then tested using a visual recognition memory paradigm to measure novelty preferences. Results indicated that the mean visual recognition memory score was 59.8% (range of 10.8–92.5%) and did not differ by participant characteristics. After adjusting for participant characteristics using linear regression, higher fish intake was associated with better infant cognition. This association strengthened after adjustment for hair mercury level: for each additional weekly fish serving, offspring visual recognition memory scores were 4.0 points higher [95% confidence interval (CI), 1.3 to 6.7]. However, an increase of 1 ppm in mercury was associated with a decrement in visual recognition memory scores of 7.5 points (95% CI, –13.7 to –1.2). Visual recognition memory scores were highest among infants of women who consumed > 2 weekly fish servings and had mercury levels < 1.2 ppm. Novelty scores were the lowest among women who ate fish < 2 times a week and had mercury levels above 1.2 ppm.

Lead

Using the Fagan Test, the neurocognitive status of 452 six-month-old infants whose mothers were exposed to low but varying amounts of lead during pregnancy was evaluated in the Krakow inner city study (Jedrychowski *et al.*, 2008). The overall mean lead level in the cord blood was 1.42 $\mu\text{g}/\text{dl}$ (95% CI: 1.35–1.48). Visual recognition memory scores were inversely related to cord blood lead levels (Spearman correlation coefficient –0.16, $p=0.007$). Exposed infants scored lower by 1.5 points with every one unit increase (1 $\mu\text{g}/\text{dl}$) of lead concentration in cord blood. In infants exposed to lower levels of lead (<1.67 $\mu\text{g}/\text{dl}$), the mean novelty preference score was 61.0% (95% CI: 60.3–61.7). In the higher exposed infants, the mean novelty preference was 58.4 % (95% CI: 57.3–59.7). The difference of 2.5 points was significant at the $p=0.0005$ level. In a separate study of prenatal lead exposure by Emory (2003), 7-month old infants with maternal blood lead levels less than 5 $\mu\text{g}/\text{dL}$ were assessed with the Fagan Test. Significant effects of low-level lead on visual recognition memory were observed; infants who scored in the upper 5th to 15th percentile of novelty preference scores had mothers with lower blood lead levels than those scoring in the lowest 5th to 15th percentile. No infants who scored in the upper percentile range on the Fagan Test were born to mothers with the highest maternal blood lead levels.

Polychlorinated biphenyls (PCBs)

In the first study to use the Fagan test in a population of PCB-exposed infants, Jacobson and colleagues tested 123 infants at approximately 7 months of age in a Michigan cohort (Jacobson *et al.*, 1985). Results indicated that the mean visual recognition memory score was 57.3% (sd= 11.4, range 28.3–77.5%). Two measures of prenatal PCB exposure, cord serum PCB and maternal report of fish consumption were significantly associated with infant novelty preference. Higher levels of PCB exposure were related to reduced novelty scores; providing evidence of central nervous system effects in exposed infants. There was a dose-dependent relationship between visual recognition memory and cord serum PCB level, after adjusting for potential confounders such as birth weight, gestation, maternal age, maternal education and socioeconomic status. The most highly exposed infants failed to provide evidence of intact recognition memory skills (3.6–7.9 ng/mL cord serum PCB) and had scores over ten points lower than the infants with the lowest levels of cord serum PCB (0.2–1.1 ng/mL) on the Fagan Test. Similar results were obtained by Darvill *et al.* (2000) who used the Fagan Test at 6 (n=230) and 12 (n=216) months of age to examine the relationship between umbilical cord-blood PCB levels and infant memory. Analysis of the results revealed a dose-dependent relationship between total umbilical cord-blood PCB levels and poorer Fagan Test performance at both ages. Infants exposed to PCB congeners associated with Lake Ontario fish consumption (septa-, octa-, and nonachlorinated biphenyls) showed visual recognition memory deficits at 12 months but not at the 6-month test. These data support a dose-dependent relationship between prenatal PCB exposure and novelty preference scores.

In a German study of PCB exposure and infant development, 171 mother-infant pairs from the Dusseldorf area were recruited into a multicenter research investigation (Winneke *et al.*, 1998). The sum of PCB congeners 138, 153 and 180 (sigma PCB) in cord plasma and maternal milk was selected to characterize neonatal PCB exposure. Mean sigma PCB-concentrations were 0.55 ng/ml in cord plasma and 427 ng/g fat in breast milk. Both the Fagan Test and the Bayley II Scales of Infant Development were used to evaluate neurobehavioral functioning in infants at 7 months of age. Results from the Fagan Test were not associated with PCB exposure levels at birth or with levels in breast milk, suggesting that the lower blood levels included in this study did not result in adverse changes in the development of infant memory. A significant negative association was found however between the mental development index (MDI) from the Bayley scales of Infant Development and PCB in milk ($p < 0.05$), leading the authors to speculate that in the case of PCBs, postnatal exposure may pose a greater risk to the developing brain than gestational exposure.

Visual Recognition Memory in Neurotoxicant-Exposed Infant Macaque Monkeys

The VPC test methodology can also be used to study the development of recognition memory in nonhuman primates. Infant macaques (e.g. *Macaca nemestrina*, *Macaca mulatta*, *Macaca fascicularis*) show a significant novelty preference by four to six weeks of postnatal age and the strength of this response increases over the first several months of life (Gunderson and Sackett, 1984, Bachevalier *et al.*, 1993, Zeamer *et al.*, 2010). Specific

parameters of visual recognition memory are similar between macaque monkey and human infants; both species are capable of demonstrating recognition after familiarization study times as brief as 5 seconds and after delay periods as long as 24 hours (Fagan, 1973, 1974, Gunderson and Swartz, 1985). The striking inter-species similarities between humans and macaque monkeys in basic memory processing have been well-documented (Elmore *et al.*, 2011, Zola-Morgan and Squire, 1990). Core similarities such as these contribute to the value of the primate model for comparative studies designed to examine the effects of prenatal neurotoxicant exposure on infant development (Grant and Rice, 2008). Comparative studies of high-risk monkey infants have demonstrated the sensitivity of this test paradigm to naturally-occurring perinatal risk factors such as low-birth-weight or failure to thrive in the nonhuman primate animal model (Gunderson *et al.*, 1987, 1989). A summary of infant monkey studies using tests of visual recognition memory in the context of developmental neurotoxicology and perinatal risk is provided in Table 2 and discussed below.

Using an adaptation of the Fagan Test (i.e. human faces removed and replaced with appropriate macaque monkey faces), tests of visual recognition have proven to be sensitive to subtle changes in memory functioning in infant macaques exposed to environmental neurotoxicants during gestation. Figure 4 shows an infant monkey, gently swaddled in a cloth diaper, being presented with a visual recognition memory problem.

In a study of prenatal exposure to methylmercury, infants were tested within the first month after birth on a series of recognition memory problems using both geometric patterns and social stimuli. Prenatal exposure to methylmercury was associated with a diminished novelty response in exposed infants (Gunderson *et al.*, 1986, 1988). To rule out sensory-based performance deficits, infants were screened for visual deficits with Teller Acuity Cards prior to visual recognition memory testing. There were no differences between exposed and control infants in early visual acuity (demonstration of 20/800 Snellen required to resolve the visual elements in the test stimuli). Using a similar longitudinal study design, Burbacher and colleagues examined the infant neurobehavioral consequences of fetal exposure to methanol through maternal inhalation (Burbacher *et al.*, 1999, 2004). Methanol exposed monkey infants, also screened for visual deficits, were able to solve recognition problems with simple test stimuli (bold, geometric patterns) but failed to provide evidence of memory on more difficult test problems (social stimuli) when compared to controls. In a separate study of early weekly ethanol exposure for the first 3, 6, or the entire 24 weeks of pregnancy (Clarren *et al.*, 1992), the cognitive profile of alcohol-exposed animals included the absence of significant novelty scores in the 6 and 24 week exposure group. In this cohort of animals, treatment-related changes in early cognitive development were observed in the absence of craniofacial anomalies that would be characteristic of fetal alcohol exposure (e.g. thin upper lip and smooth philtrum) (Astley *et al.*, 1999).

Over several decades, the neuroanatomical pathways that serve the ability to recognize a previously encountered stimulus have been mapped in the primate brain (Brown *et al.*, 2010, Bachevalier, 2008, Winters *et al.*, 2010). In adult animals, studies of recognition memory have demonstrated that the hippocampus as well as the related entorhinal, perirhinal and parahippocampal cortices function within a “medial temporal lobe memory system” to serve recognition memory (Squire and Zola-Morgan, 1991). The developmental origins of this

memory system and the underlying brain regions have also been explored in young animals. Using the Visual Paired-Comparison paradigm to study recognition memory, Bachevalier and colleagues have demonstrated that the primate hippocampus appears to mature progressively during the first few years of life and damage, including perinatal damage, can produce profound recognition memory losses with little recovery of function (Bachevalier and Vharga-khadem, 2005). More recent laboratory findings have shown however, that young animals with selective neonatal hippocampal lesions show a relative sparing of visual recognition memory abilities (Heuer and Bachevalier, 2011). This finding suggests that the hippocampus, while important, is not the only brain area capable of supporting recognition processes during infancy. The key role of the medial temporal cortical areas in early recognition memory was highlighted in a recent nonhuman primate study where monkeys with sham operations or neurotoxic hippocampal lesions were tested over the first two years of life on the VPC task using various delay periods (Zeamer *et al.*, 2010). Despite hippocampal insult, strong novelty scores on tests of visual recognition memory were seen in operated animals. The authors theorize that the medial temporal cortical areas provide important support to recognition processes in early infancy but with increasing postnatal age and maturity, the hippocampus begins to provide increasing support for these core intellectual processes.

In summary, the Visual Paired-Comparison test methodology and its ability to measure selective visual attention to novelty should be considered a viable and theoretically meaningful approach to studying the effects of prenatal neurotoxicant exposure on infant memory development. The Visual-Paired Comparison test procedure, based on natural visual responses present soon after birth, can be effectively used to study emerging recognition memory in both human and nonhuman primate infants. This theoretically-rich approach to neurobehavioral assessment provides researchers with a creative, psychometric tool that does not rely on spoken language or coordinated motor responses. The assessment of recognition memory during infancy provides a snapshot of abilities that are important to developmental outcome. The brain systems that serve these early intellectual processes have, and are, being defined at an anatomical and processing level that allows the discussion of brain-behavioral correlates. Finally, the literature detailing recognition memory testing in infant populations exposed to neurotoxicants such as lead, methylmercury and polychlorinated biphenyls supports the utility of this measure in successfully detecting exposure-related changes in cognition in subjects less than one year of age.

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Highlights

1. Accurate and sensitive methods are critical to behavioral assessment during infancy.
2. Review of methods to evaluate memory processing in infants.
3. Detailed discussion of the origin of the Visual Paired-Comparison paradigm and its capacity to measure emerging cognition in young infants.
4. Method has been successfully used in both human and nonhuman primate infants exposed to neurotoxicants to evaluate visual recognition memory.
5. The use of the Visual Paired-Comparison test paradigm to study memory is a valid and theoretically meaningful approach to neurobehavioral assessment in preverbal infants.

Figure 1.

This figure displays the early Fantz looking chamber and examples of visual preference test stimuli. Infants were placed in the looking chamber which had two visual displays on the ceiling above the infant's head. The experimenter viewed the infant's eyes by looking through a peephole and recorded individual looks to the two test stimuli. Fantz found that soon after birth, infants strongly prefer to look at patterned stimuli versus plain colored fields, curvilinear versus straight edges and face-like stimuli vs. abstract patterns. The plus mark under one member of the stimulus pairs indicates the preferred image.

Figure 2.

Example of a Visual Recognition Memory test problem as presented to subjects with the Visual Paired-Comparison Test Procedure. Two identical copies of the familiar stimulus (circle) are presented for viewing (Familiarization period). After accruing the required time looking, the familiar stimulus (circle) is paired with a new/novel stimulus (triangle) and looking time to each is recorded by a trained observer (Retention trial #1). The position of the novel stimulus is reversed for the second retention trial and looking time to each is recorded again (Retention trail #2).

Figure 3.

This figure (used with permission from J.F. Fagan) displays an infant being administered a recognition memory problem on the Fagan Test of Infant Intelligence (FTII). Note the infant is looking at two different stimuli (human faces) that are displayed on the testing stage. The data collector sits behind the stage and looking through a peephole, closely observes infant eye moments to record individual fixations to the test stimuli. A sample recognition memory problem is shown on the right.

Figure 4.

Using the VPC test paradigm, infant monkeys are tested on visual recognition memory problems in much the same way as human infants. Infant monkeys are hand-held in front of a viewing stage where two computer generated images are generated. A camera that is mounted behind the viewing stage allows the data collector to record individual looks to test stimuli with foot pedals. A sample recognition memory test problem is provided for review on the right.

Summary of Infant Studies Using Tests of Visual Recognition Memory in the Context of Developmental Neurotoxicology

Table 1

Developmental Neurotoxicant	Sample size	Country	Age(s) at test	Exposure Effect on Novelty Score	Authors
Lead	452	Poland	6 mos..	Yes	Jedrychowski et al., 2008
Lead	79	USA	7 mos.	Yes	Emory et al., 2003
PCBs	171	Germany	7 mos.	No	Winneke et al., 1998
PCBs	200	USA	6 and 12 mos.	Yes at both ages	Darvill et al., 2000
PCBs	123	USA	7 mos.	Yes	Jacobson et al., 1985
Methylmercury	740	Seychelles Islands	6 mos.	No	Meyers et al., 1995
Methylmercury	135	USA	6 mos.	Yes	Oken et al., 2005
Methylmercury/Persistent Organic Pollutants (Tohoku)	687	Japan	7 mos.	Dataset not published	Nakai et al., 2004

Summary of Infant Monkey Studies Using Tests of Visual Recognition Memory in the Context of Developmental Neurotoxicology and Perinatal Risk

Table 2

Environmental Chemical or Perinatal Risk Condition	Sample size	Species	Approximate Age at test	Exposure Effect on Novelty Score	Authors
Methylmercury	20a 17b	Macaca Fascicularis	1 month	Yes	Gunderson, et al., 1986a, 1988b
Methanol	34	Macaca Fascicularis	1 month	Yes	Burbacher et al., 1999
Ethanol	35	Macaca Nemestrina	1 month	Yes	Claren et al., 1992
Low-birth-weight	30	Macaca Nemestrina	1 month	Yes	Gunderson et al., 1989
Failure-to-thrive, perinatal asphyxia	28	Macaca Nemestrina	1 month	Yes	Gunderson et al., 1987