RELATIONSHIPS BETWEEN NEONATAL RISK, COGNITIVE DEVELOPMENT AND INHIBITORY CONTROL AT THREE YEARS OF AGE.

By

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Abstract

RELATIONSHIPS BETWEEN NEONATAL RISK, COGNITIVE DEVELOPMENT AND INHIBITORY CONTROL AT THREE YEARS OF AGE.

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Ronny Geva

Advisor: Professor Doreen Berman

This dissertation examined the relationships between different levels of neonatal risk, cognitive development and inhibitory control in three-year-old children. The assignment of subjects to clinical groups was determined by neonatal neurofunctional status, based on auditory brainstem evoked responses (BAER), and neonatal neurostructural status, based on cranial ultrasound (US) data. The sample included 87 children and was comprised of five groups: 35 fullterm controls (the FTN/N group), 20 infants from the Neonatal Intensive Care Unit with normal BAER and normal US (the NICU/N group), 13 infants with only BAER abnormality (the BAER-only group), 14 infants with mild or moderate IVH seen on US (the Mild/Mod group), and eight infants with severe structural damage seen on US (the Severe group).

The subjects were tested with the Griffiths Mental Development Scales and two tasks that were designed to tap inhibitory control (IC): a rapid sequential automated naming task and a graphomotor task. The results indicated that: (1) differential cognitive

development and IC outcomes resulted from different types and magnitude of neonatal insult, (2) males were more likely than females to be in clinical groups the BAER-only and the Severe group that had more cognitive developmental deficiencies and IC difficulties than did other groups, (3) females were more likely than males to be in clinical groups, the NICU/N and the Mild/Mod groups, that showed minimal residual deficits, (4) the NICU/N group showed general cognitive development within the normal range, minimally slowed processing, and discrete deficiencies in tasks requiring motor integration, (5) the Mild/Mod group showed general cognitive development resembling that of the FTN/N group, no IC difficulties, but some minimally slowed processing and discrete but moderate difficulty in tasks requiring eye-hand coordination, (6) the Severe group showed multiple cognitive deficiencies, slowed processing and more IC difficulties than any other group, (7) performance of the BAER-only group resembled most that of the Severe group, though with a lesser magnitude of deficits; their cognitive performance was marked by difficulties in a number of domains and minimal slowed processing. In addition, IC difficulty, on both the verbal and the graphomotor task, was found independent of speech ability, coordination or the ability to perform under time pressure.

This study indicates that brainstem malfunction intrudes upon the development of a number of cognitive functions and the development of IC.

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I. Introduction

This study focuses on the effect of neonatal brain damage on cognitive development and inhibitory control (IC) capacity. While other studies have shown an association between neonatal cerebral structural injury and delayed mental development, developmental trajectories linking particular types of lesion with specific deficiency patterns have received little attention. Furthermore, little is known about the effects of neurofunctional deficits on development, particularly those that may be related to infra-cerebral levels of the central nervous system (CNS) and its effect on specific behavioral functions. This study will concentrate on the effects of damage to infra-cerebral levels of the CNS on mental development and IC.

Brainstem related mechanisms have been implicated in modulation of responses to sensory input, which can be either facilitatory or inhibitory. Neonatal behavioral measures indicated that neonates with brainstem related neurofunctional abnormalities in the absence of identifiable cerebral damage show abnormal responses to stimulation in a manner that resembles that of infants with extensive structural damage to the CNS. The behavior may be interpreted as resulting from poor ability to modulate and handle increased stimulation, thus implicating brainstem related pathology in contributing to IC deficiency. Early maturation in the brainstem may result in a relatively limited plasticity to overcome pathogenic processes. Therefore, early damage to

brainstem structures may have long-term neuropsychological effects.

Technological advances have improved the ability to detect and diagnose relatively mild neonatal brain insult by using techniques such as brain imaging and evoked potentials, thereby offering the opportunity to evaluate and compare outcome from different types and magnitude of insults to the CNS. This, combined with neuropsychological evaluation tools of different areas of functioning, may be valuable in detecting discrete developmental disabilities and IC deficiencies in these children. Thus, integration of structural, functional and neuropsychological data may contribute to the identification of neonatal risk factors for abnormal mental development and IC deficiencies.

A. Neonatal Brain Damage

Studies of brain damaged populations typically are based on heterogenous cohorts. Subjects' injuries differ, among other factors, in etiology, location, magnitude and severity of injury. Part of the variability is a product of the patients' age at injury. In the initial phases of development, diffuse lesions are seen more often than in other developmental phases. The focal-diffuse distinction in neonates is often not a clear cut one. Brain insults may produce focal lesions and/or diffuse effects. Focal lesions may be associated with strokes, trauma that penetrates the skull, or small tumors. Diffuse lesions result from degenerative processes, metabolic disorders, oxygen deficits, drug abuse or

trauma that does not penetrate the skull. These may produce general deterioration in all aspects of functioning.

Serious damage to the CNS, although more frequent in preterm than full-term infants, can occur to both pre-term and full-term infants, with hemorrhage into the ventricles of the brain and/or necrosis around the ventricles (Papile, Bruno, & Shaefer, 1983; Sostek & Magrab, 1992). Trauma or poor oxygenation of the brain as a consequence of asphyxia, acidosis or respiratory distress results in intraventricular hemorrhage (IVH) particularly in preterm infants and also loss of myelin or necrosis, particularly in infants born at term. The major consequences of hemorrhage are direct damage to areas of the brain and/or increase of fluid pressure.

The group at greatest risk for IVH is the very low birth weight (VLBW) group (Sostek, 1988). Sostek's review concluded that 43% - 58% of infants born weighing less than 1500 grams and/or born prior to 32 weeks estimated gestational age (EGA) had some degree of IVH, detected by cranial ultrasound (US).

A 1. Neuropsychological Outcome

Outcome from neonatal brain damage depends on multiple factors such as location, extent and type of injury, and may include highly specific effects in certain locations, or no observable effect at all (Sattler, 1988). Due to plasticity

and reorganization that occurs during early development, direct relationships between locus of neonatal damage and residual deficits require rather complex predictive models (e.g., Dalton & Redrosian ,1989; Joungmans, Henderson, & Dubowitz, 1994; Karmel, Gardner, Brown, Zappulla, Magnano, Goodman & Carr, 1988 a; Golden, Vaughan, Kurzberg & McCarton, 1988; Murray, 1988).

Sostek (1988) pointed out that clinical deterioration does not necessarily accompany evidence of IVH, nor is it known whether IVH is responsible for the increased risk for prematurely born children to show subtle disorders, such as learning disabilities. Sostek, Smith, Katz and Grant (1987) showed that global performance on the Bayley Developmental Scales of two year old children born prematurely but without IVH resembled that of full-term children without IVH. At the same time, studies of school readiness, using questionnaires, parental interviews and behavior check lists, about children who were born prematurely but without IVH, confirmed findings of subtle deficits even in those with normal intelligence (Hunt, Cooper, & Tooley, 1988; Klein, Hack, & Breslau, 1989; Sostek, Katz, Valvano, & Smith, 1988; Stjernqvist, 1992; Williams, Lewandowski, Coplan, & D'Eugenio, 1987). Hence, it seems that detection of IVH is useful, but additional measures might better document the presence or absence of neuronal insult, especially in term infants, and might improve the accuracy of prognosis, particularly in those children in which US was not sensitive enough to detect abnormality (see section A 3 , below). Particularly for those with only suspected or mild injuries, there is a need, as suggested by

McCarton (1988), to improve the initial diagnosis of injury and specify further the inclusion criteria, to develop outcome measures that focus on specific functional skills, and to detect the emergence of distinct behavioral profiles with relation to particular forms of damage.

There are two classical propositions concerning outcome of neonatal brain damage. On the one hand, it has been suggested that early brain damage produces less dramatic behavioral effects and better recovery prospects than damage sustained later in life, due to plasticity in early development (e.g. Kennard & McCulloch, 1943). On the other hand, it has been argued that lesions in the early phases of development affect the system in a particularly profound manner, since immature systems lack compensatory resources (e.g. Hebb, 1942; Kamphaus, 1993).

It appears that multiple recovery processes co-occur, so that the prognosis regarding a particular case of early brain damage depends largely on the interactive effects of variables such as type, location and extent of damage, as well as experiential/environmental variables, both internal and external to the infant, that interact with development, rather than solely on the age of onset (Isaacson, 1990; Rourke, Bakker, Fish, & Strang; 1983; Sattler, 1988; Spinelli, 1990). Cumulative interactions among etiology, recovery period, experiential / environmental influences and the child's personality traits, may weaken the expectation for linear relations between a particular pathophysiological measure and behavioral outcome. Nevertheless, the location and type of brain lesion

influence outcome significantly.

Joungmans, Henderson and Dubowitz (1994) studied six-year-old children who had suffered ischemic or hemorrhagic lesion at birth, as detected with US imagery, and reported that children who had sustained ischemic lesions in the area of the arterial border zones surrounding the lateral ventricles were functioning less well than their peers with hemorrhagic lesions around the germinal matrix. Interestingly, this was observed among children whose scans were classified as revealing either "major" or "minor" lesions. Infants with lesions of any sort were more likely to show subtle perceptuo-motor than generalized cognitive impairments at age 6 years.

A 2 Assessment

Cranial US is a commonly used tool to evaluate infants for certain types of neonatal brain injury, particularly those that involve the ventricles and the surrounding tissue (Dalton, Redrosian, 1989; Karmel et al., 1988 a; Levene, Wigglesworth & Dubowitz, 1981; Sostek, 1988). Cranial US has been valuable in identifying IVH in utero (Chinn & Filly, 1983) as well as peri- and post-natally. There are a number of reasons for its widespread use. Neonatal brain imaging through the anterior fontanelle is non-invasive; it allows for bedside evaluation without undue handling; it lacks ionizing radiation; the costs are relatively low; and, above all, the information is useful in evaluating CNS status.

IVH has been classified by Papile, Burnstein, Burnstein & Koffler (1978) into four severity grades (Figure 1):

Grade I - hemorrhage in the germinal layer.

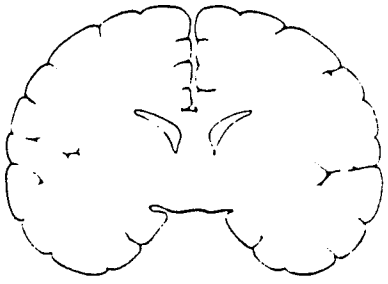
Grade II - hemorrhage extending to the ventricles but without ventricular dilatation.

Grade III- hemorrhage extending to the ventricles and with ventricular dilatation.

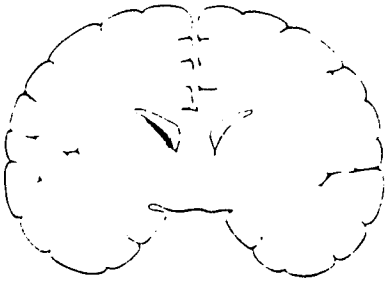
Grade IV- hemorrhage with ventricular dilatation and parenchymal involvement.

Sostek (1988) studied 135 VLBW infants with US on postnatal days 1, 7 and at hospital discharge. The infants were classified into four groups : no-IVH, minor IVH (Grade I, II), Moderate IVH (Grade III) and Severe IVH (Grade IV), according to a modification of the classification based on Papile et al. (1978). The children were then followed periodically until 24 months of age, evaluating their motor and mental development with the Bayley Scales of Infant Development (Bayley, 1969), and their neurologic development with an examination based on that of Amiel-Tison and Grenier (1980). Sostek found relations between motor functioning at 24 months and severity of the neonatal injury, such that the mild and moderate IVH groups scored significantly higher than did the major hemorrhage group. The mean mental scores of those with no-IVH and of children with minor IVH did not differ. However, it was noted that the variability in the no-IVH group (SD=27.5) was significantly greater than the variability in the minor IVH group (SD = 16.9).

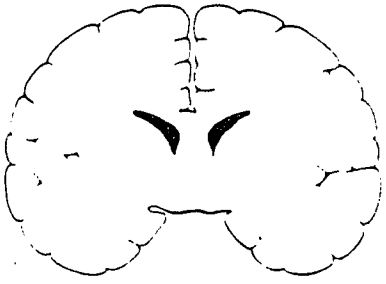
Figure 1. Schematic illustration of IVH grading, based on ultrasound imaging, based on Papile et al (1978), adapted from Strenqvist (1992).



Normal



Grade I



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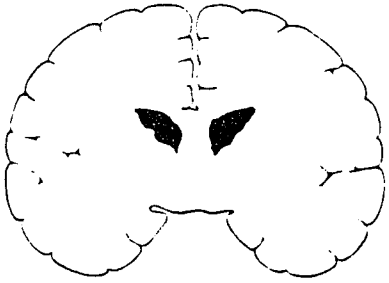
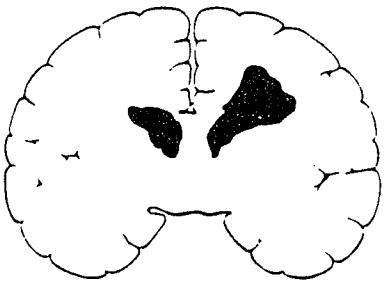


Grade III



Grade IV

These findings concerning the relationship between severity of injury and developmental outcome are interpretable in three ways. First, the motor and mental outcome for the most severely affected children may be qualitatively different than that for all other CNS injury risk groups. Second, the large variability in outcome in the no-IVH group relative to the minor IVH group may be indicative of other pathogenic elements that dilute the differences between these two groups. This hypothesis is supported by the finding that the percentage of infants developmentally delayed at 24 months (corrected Bayley Index < 80) was somewhat greater in the no-IVH group (11% of the children showed mental delay) than in the minor-IVH group (7% mental delay). There was a linear relationship between the percentage of neurological abnormalities, based on muscle tone, range of motion, deep tendon reflexes, equilibrium, protective reactions and maturation of primitive reflexes, and the probability of risk or magnitude of injury. The finding that there was a similar incidence of delay in the no-IVH group and the minor-IVH group supports a third interpretation that minor IVH results in a developmental trajectory that is not different from that estimated for low-risk cohorts.

Functional measures of CNS integrity are possible through the use of brainstem auditory evoked responses (BAER), as a marker of CNS dysfunction. Karmel et al. (1988 a, b) have argued that, since brainstem functions are at the core of the organization of behavior, functional evaluation at the brainstem level provides discrete and significant additional information for evaluation of neonatal

CNS injury. Furthermore, hypoxic injuries to the brain in neonates frequently specifically affect brainstem areas (Leech & Alvord, 1977).

The use of BAERs during the neonatal period has provided reliable and valid information contributing to differential diagnosis of at-risk neonates (see Appendix B). As noted by Salamy and Eldredge (1994), BAERs have been used for several purposes in neonates: to screen for hearing loss, to estimate neurophysiological maturation, and to detect perinatal complications, including anoxic events, intracranial hemorrhage, hyperbilirubinemia, neurological disorders, hydrocephalus and structural abnormalities of the brain (see also Bozynski, Nelson, Rosati-Sketich, Geneze, O'donnell, & Naughton, 1984; Cycowicz, Schmuel, Freeman, Wanszelbaum & Sohmer, 1988; Kraus, Ozdamar, Heydemann, Stein, & Reed, 1984; Nwaesei, Aerde, Boyden, Perlman, 1984; Salamy & Eldredge, 1994; Yashuhara, Kinoshita, Hori, Iwase, Kobayashi, 1986; cited in Salamy & Eldredge, 1994).

The disturbances are manifested in the BAER by decreased amplitude, absence of one or more components, and/or prolonged latency, particularly of the three major components, Wave I, Wave III and Wave V (Eggermont & Schmidt, 1990; Picton, Taylor & Durieux-Smith, 1992; Salamy et al, 1994).

Karmel, Gardner, Zappulla, Magnano, and Brown (1988), Salamy, Mendelson, Tooley, and Chaplin (1980) and others have used the BAER to monitor diffuse CNS dysfunction in high risk infants, arguing that brainstem structures are vulnerable to many of the perinatal conditions that compromise the

high risk infant.

BAER results have also been used to aid in neurologic diagnosis (Despland & Galambos, 1980; Hecox, Cone, & Blau, 1981) and to evaluate the integrity of the brainstem in adults (Zappulla, Karmel & Greenblatt, 1981). Furthermore, BAERs have also been used for detection of damage in children who are at risk for neurobehavioral problems. Murray (1988) used ratings of salient markers of disability, namely, motor dysfunction and general cognitive development, on a large sample of infants who were at risk for developmental disorders (N=1613) and found that the neonatal BAER had a significant mild to moderate predictive value for neurobehavioral status at the age of one year.

Each of these evaluation tools, the US and BAER, provides information concerning the CNS status of the neonate that is reliable and has predictive validity. Karmel et al. (1988 b) studied the correlation between structural and functional measures of CNS integrity in the neonate and the degree to which each evaluation tool added unique information to developmental models.

The analysis indicated that US abnormality was significantly related to a prolonged Wave I and the Wave III- V interval. The authors speculated that a delay in Wave I latency could be associated with acute compromise to the cochlea, auditory nerve or both (this was also suggested by Hecox & Buchard, 1982), or with hemorrhage that affected the inner ear (Spector, Petit, Davis, Strauss, & Rauchbach, 1978). Karmel et al. (1988 a, b) rejected the interpretation that the detected abnormality, specifically when it involves Wave I

latency, represents a significant hearing loss, on the basis that these infants showed adequate orienting responses to auditory stimuli using a corn-rattle stimulus (which is predominantly a low intensity wide-band noise) and maternal voice (which is predominantly a low intensity high frequency distributed tone). Moreover, the BAER abnormality was a transitory phenomenon that resolved with recovery.

The prolonged Wave III-V interval, according to Karmel et al., results from hemorrhage, compression, edema, loss of adequate cerebral blood flow in the brainstem or hydrocephalus with increased intracranial pressure reflected from the third and fourth ventricles. This interpretation was supported by a rat model in which Wave III-V interval prolongation and recovery was demonstrated following mechanical brainstem compression and release (Zappulla, Wang, Malis, & Karmel, 1985). Hence, it appears that the BAER may be affected by some of the conditions that are apparent on cranial US, though probably not by all, and in addition may be affected by conditions, primarily at the brainstem level, that are not demonstrable by using US.

The cross-classification relationship of US and BAER (using discriminant algorithm equation) is higher than 76% (Karmel et al., 1988). An average concordance of 83% was found for a cohort that included infants averaging 34 weeks EGA and a concordance of 76.5% for an independent replication sample that included 213 slightly older infants, averaging 35 weeks EGA. Among those infants without insults detected by US there was a subgroup that could be

differentiated on the basis of the BAER. In fact more than 14% of the at-risk sample had only a BAER abnormality, with no insult apparent by US.

Neurobehavioral evaluation of the BAER-only group before hospital discharge (postnatal day 2 - 21) showed a distinct and unexpected profile of problems (Gardner, Karmel, Magnano, Norton, & Brown, 1990). In this group, the incidence of visual attention problems was as high as for infants with moderate-severe US abnormality; they also showed a higher incidence of head and neck control problems than did infants with moderate US abnormality. Furthermore, their visual preferences were different from those of normal infants and were indicative of poor attention/arousal modulation (Gardner, Karmel, & Magnano, 1992). The neurobehavioral pattern differentiated the BAER-only group from the linear trend seen in other brain injured (BI) groups of increased frequency of problems as the magnitude of damage increased. Hence, an a priori suggestion that regarded the BAER-only group as a group of 'almost' normal infants was rejected. Had these children been classified as normal, they would have diluted differences between the groups of "normal" and brain injured children. Therefore, the findings from various studies support inclusion of measures of both CNS structural status (cranial US) and of CNS functional status (BAER) in determining risk group affiliation. This might be an important step toward resolving inconclusive results concerning long-term effects from mild forms of injury. (For BAER findings with clinical populations with IC deficits, see section B 4).

B. Inhibitory Control

B 1. Neuropsychology

The process of stopping, checking, suppressing or preventing the occurrence of some action, behavior or thought is referred to as inhibition, and its internalized control is called inhibitory control (IC). IC is essential for regulating motor output of multiple behaviors, ranging from the execution of intentional motor acts to interacting socially in an appropriate manner. IC is a prerequisite for planning and developing executive abilities as well as for maintaining and shifting an action or a mental set. Inadequate IC is inferred from behaviors that are characterized by errors due either to impulsiveness or perseverative output and/or by lack of persistence.

Diamond (1990) described normally occurring inhibition and executive control errors as follows:

> All of us, on occasion, make slips of the tongue or slips in our behavior, where we intended to do one thing but did something else instead. Such slips can be considered failures of inhibition or of executive control. A slip in behavior, and occasionally a slip of the tongue, may consist of doing the usual, habitual or most easily elicited action, when it was really something else we intended. On such occasions it is as if we let ourselves run on "automatic pilot" when we should have been paying attention (i.e., when we should have been exerting executive control) ...with effort and concentration we are capable of exercising inhibitory control. Organisms without frontal cortex may be incapable of this. Thus, although fragile, this ability may be one of the things that distinguishes us from lower organisms. The ability to resist

> the strongest response of the moment endows us with extraordinary flexibility and the freedom to choose and control our actions.
> (p. xlix)

Along these lines, Reason and Mycielska (1982) explain that a large proportion of absent minded errors actually take the form of intact, well organized segments of skilled action that are suitable for the environmental context most of the time, but not when changed circumstances require some alteration of normal practice, or when new goals demand the modification of existing routines (pp. 39 - 40). When executive functions are deficient, such "slips" occur too often or repeatedly.

Although instances of poor auto-regulation occur in normally functioning individuals, recurrent or pronounced poor regulation constitutes a diminished quality of functioning, which may serve as poor background for cognitive operations and may disrupt adaptive behavior and learning. Deficient IC is expressed by difficulties in making mental or behavioral shifts that result in perseverative behavior or rigidity, or in impulsivity and distractibility. Difficulties in shifting set may impede shifting attention, changing movement, or flexibility in attitude. Perseveration refers to repetitive prolongation or failure to appropriately discontinue an act or activity sequence, or repetition of the same or a similar response to differing questions, tasks or situations (Lezak, 1983). Premature discontinuation of a mental set, constitutes impersistance and distractibility.

Both problems of the IC continuum obstruct adaptive behavior and have been described for several clinical groups, for instance, attention deficit/ hyperactivity disorder (Rourke & Del Dotto, 1992). The most recent Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; APA, 1994) lists several diagnostic criteria for Attention-Deficit / Hyperactivity Disorder. Among the criteria for hyperactivity and impulsivity, the DSM-IV includes: is often "on the go" or often acts as if "driven by a motor" (Criterion 2 e); often has difficulty awaiting turn (criterion 2 h). This inability to discontinue a sequence depending on changing environmental limitations constitutes deficient IC.

A somewhat similar symptomatology has been described for brain damaged children (Lishman, 1987) and for brain damaged adults (Bond, 1984, 1986), even in cases where no direct prefrontal damage was documented. Bond listed characteristics of head injured victims that are most likely to give rise to adjustment problems for brain injured people and their families. Some of the symptoms that may be closely related to IC deficiencies include impaired self-control characterized by impulsivity, random restlessness and impatience; and behavioral rigidity. There is not enough evidence, however, to support a direct association between neonatal brain damage and the later development of deficient IC. Although some children with brain damage develop symptomatology that may be indicative of deficient IC, many children with deficient IC had no known brain injury.

B 2 Development

B 2 a Neuroanatomical.

Sattler (1988) reported the more common chronic symptoms observed in brain-damaged children. Among these symptoms are possible markers of IC deficits, such as hyperkinesis (constant movement, inability to sit still fingering, touching, and mouthing objects, voluble and uninhibited speech), involuntary movements, awkwardness in skilled movement, repetitive movements, perseveration, poor concentration, attraction to minute details, difficulty in shifting from one activity to another, and interpersonal difficulties. Sattler's data do not permit for analysis of the relationship between different types or severity levels of CNS damage and auto-regulatory or IC deficiencies.

The pathways in the mature brain thought to be responsible for action initiation and for alteration of course of ongoing activities, both motor and mental, involve the striatum and its connections to the frontal lobe (Diamond, 1990; Lezak, 1983, 1989; Luria, 1973). This pathway is directly connected to lower limbic nuclei and it is not myelinated at birth. With increased myelination, the prefrontal cortex becomes richly connected with the upper parts of the brainstem and thalamus and with other cortical zones. Goldman-Rakic (1987) reviewed experimental data on the development of cortical circuitry and cognitive function. The circuitry includes connections of the principle sulcus with

other areas of parital association and limbic cortex and projections to the caudate nucleus, supperior colliculus and other premotor centers. Anatomical tracing in primate fetuses indicated that these various classes of cortical connections begin to form during the second trimester of pregnancy.

Animal models of IC show not only cortical pathway involvement, but also involvement of sub-cortical pathways that project frontally. Many signs of frontal lobe IC-related dysfunction seem to be a consequence of severed subcortical connections. This was suggested by Diamond (1990), who described IC difficulties using barrier tasks in primates with olivary and fronto-limbic pathway lesions, and by Patterson and Newman (1993), who described motor disinhibition after limbic system lesions.

Dopaminergic neurons with cell bodies located in the mesencephalon innervate a number of telencephalon structures including the frontal cortex, the nucleus accumbence and the corpus striatum (Diamond, 1990, 1993; Hoffman & Heller, 1984; Kolb & Whishaw, 1990). In addition, serotonergic projections, which have been thought to act in the CNS to modulate and maintain behavior within certain limits, arise from the dorsal nucleus of the Raphe in the midbrain and project collaterals to both striatum and the substantia nigra, forming an ascending functional relationship with the reticular activating system and the limbic- frontal system (Carpenter, 1993).

B 2 b Neuropsychological.

From early phases of development, children are capable of some levels of IC. Studies conducted by Diamond (1990) have shown various developmental milestones in the child's IC capacities. One of the first instances of inhibition seen in development is the inhibition of neonatal reflexes, such as grasping. When infants begin to reach for objects they sometimes encounter difficulties due to inability to inhibit the reflexes (Twitchell, 1965; 1970). In children of five to seven and a half months of age, an inadvertent touch of a neighboring object en route to an object-goal may trigger a reflexive grasp of the neighboring object (grasp reaction) or a reflexive pull back of the hand (avoidance reaction). After seven and a half months of age, reflex inhibition is achieved, probably through maturation of the supplementary motor area (SMA).

From seven and a half months until the end of the first year, the inhibition of predominant response tendencies (built up through reinforcement experience), and of prepotent responses (behavioral tendencies that are inherently strong), are mastered. Diamond's examples of prepotent behaviors are reaching directly for an unreachable visible goal or being distracted by a compelling stimulus (Diamond, 1990; Diamond, Cruttenman & Neiderman, 1994). The required IC is dependent upon maturation of the dorsolateral region of the prefrontal cortex (Lezak, 1983). These maturational changes begin posteriorly in SMA and progress toward the frontal pole over these months. Diamond (1990)

summarized that "neither SMA nor dorsolateral prefrontal cortex are fully mature by 12 months, nor is IC fully developed, but significant strides are made during the first year". The ability to inhibit predominant responses paves the way for the evolution of executive skills, which involve the prefrontal cortex. These are the abilities to form goals, plan ahead, consider all possible alternate solutions for problems, carry out a plan and persist until goals are reached.

B 2 c. Psychological.

Researchers have investigated IC development past infancy from psychosocial, analytic and Piagetian theoretical. Psychosocial approaches are concerned with socialization processes and the development of social judgement and morality in young children. Researchers have studied children's voluntary control in their natural environment and report that by the second year of life children are responding to social demands for compliance and impulse control (Londerville & Main, 1981; Minton, Kagan & Levin, 1971; Power & Chapienski, 1986). Behaviors, such as momentary reaching for a previously forbidden object and a quick and independent withdrawal of the hand before making contact, are observed, and typically are taken as evidence of IC.

Schneider-Rosen and Wenz- Gross (1990) conceptualized children's compliance as "reflecting the child's ability and willingness to modulate behavior in accordance with the caregiver's expectations and demands for self control."

They studied patterns of compliance in children from 18 to 30 months of age across a variety of naturally occurring situations in the children's home environments. Child-parent interaction around the child's manipulation of breakable or unsafe objects was the focus of these studies. The experimental situation appears to have involved two elements: first, the child's neuropsychological "ability" to exercise IC; and second, an emotional component affecting the child's decision making or "willingness" to act. Emotional components concerning forbidden stimuli are bound to have caused a chain of events that was unique for each subject, that could have affected the exercise of inhibition or lack thereof. Nevertheless, the researchers found, rather than a linear progression of increased IC with age, that the age of twenty-four months signaled an important transition in the emergence of compliant behavior.

Using a different methodology and longitudinally studied cohorts, Kopp (1982) and Gralinski and Kopp (1993) looked at compliance from a social science theory point of view. Self-regulation, they argued, is a complex process linking caregiver's transmission of behavior and young children's developing abilities to engage in family approved and socially approved behaviors and to inhibit undesirable behaviors. Gralinski and Kopp analyzed parental reports concerning the type of restrictions applied in a variety of daily situations. A main effect of age for controlled performance was found in a 13 - 30 months cohort, but there was no main effect of age, nor an interaction of age x situational demand condition, in a 30 - 48 months cohort. A possible limitation

to this study was that no evaluation by a neutral observer was incorporated to provide ratings that would be free of parental expectations, frustrations and biases. In any event, whether IC develops linearly or through transitions, by the age of three years, signs of self regulation of behavior with and without external regulators are seen, and are psychosocially expected. Furthermore, the beginning of the fourth year of life appears to be a time of stability (rather than a transition point) in the evolution of IC and further development of IC occurs more slowly.

Greenspan's (1979) integrative theory of psychoanalytic and Piagetian views concerning intelligence and adaptation dealt, among other issues, with the capacity for internalization of behavior organization and initiative in toddlers. Lack of such internalization, he argued, may result in behavior that is fragmented, and is related to somatic or to external cues. Fragmentation was attributed to the child being overprotected, or lacking sufficient human contact for support when attempting to take the initiative. According to Greenspan, a severe disorder at this phase involves compromises in the internalization, organization, and originality of behavior. These may result in lack of imitation and intentionality, and poorly organized emotional and behavior systems. The resulting profile has direct implications with regard to IC. According to Greenspan, the symptoms of severe fragmentation may include chronic temper tantrums, inability to initiate self control, lack of motor coordination, extreme chronic negativism, delayed language development, and relationships

characterized by chronic aggressive behavior. Greenspan's theory, which analyzes human behavior from a realm supposedly unrelated to neuropsychology, highlights an altogether familiar child, who hosts a constellation of behaviors indicative of poor IC along with emotional difficulties, poor motor coordination and poor verbal skills; a child who presents with symptoms that actually may represent a dysfunction along the limbic-striatal-frontal pathway.

B 3. Assessment

Lezak (1983) described a number of common evaluation tools used with adults and school age children to evaluate self-regulation skills. These are based on the assumption that the ability to self-regulate behavior can be demonstrated on tests of flexibility that require the subject to shift a course of thought or action according to the demands of the situation. Poor regulation may appear as inability to shift perceptual organization, train of thought or ongoing behavior to meet the varying needs of the moment. Inflexibility of responsiveness results in perseverative, stereotyped, nonadaptive behavior and difficulties in regulating and modulating motor acts. Lezak lists three channels to detect IC problems: (a) verbalizing sequences, (b) drawing designs, and (c) manual reaching movements. All require a series of alternating responses to be executed and each involves different modalities and different functional capacities.

B 3 a. Verbal sequencing tasks.

Rapid alternation of verbal as well as manual responses, can be evaluated as indices of mental control. Typically, automated naming tasks are used for this purpose. The original Rapid Sequential Automated Naming tasks (RSANT) were constructed by Eakin and Douglas (1971), Denckla and Rudel (1976) and Wolf (1984) to predict dyslexia in early school age children. Different rapid automated naming tasks are available for children in this age group, including naming of objects, of colors and of animals, and are used, both in research and clinical settings, to detect children who are at risk for reading difficulties (Catts, 1993).

Normative data with average readers revealed that different semantic categories have different patterns of speed, accuracy and consistency. The order of rate of completion time for normal readers, from fastest to slowest was naming of number, letters, colors, animals, random and use objects. A similar order was found for low achieving non-dyslexic children (Denckla & Rudel, 1976). The findings suggest that processing of some categories may be more "automated" than others. Denckla and Rudel also showed that latency measures distinguished among groups, whereby the dyslexic group was slowest and the normal control group the fastest. Thus, both speed and accuracy measures are helpful for differential diagnosis of mental control ability, using this paradigm.

B 3 b. Graphomotor tasks.

Graphomotor perseveration can be evaluated in adults by asking them to copy and maintain patterned sequences of alternating letters in script. e.g., *mnmnmn*, *mnomnomnom*, or alternating simple design series such as ⊓⋀⊓⋀⊓ which are typically drawn along a full row on a legal page. Perseveration in these tasks might be expressed in patterns such as perseveration on intact segments (*mnmmn, mnmo);* or in poor transitions that are perseverative in nature, such as /\/_/\/¯⊔. Repetitive sequential patterns of hand movements, such as simple alternating movements analogous to the above sequences, also have been used for scoring perseverative behavior (Christensen, 1979; Lezak, 1983; Luria, 1966). Most of these tasks, however, are not suitable for use with preschool children, as they require mature graphomotor skills, perception of categories of letters and of geometric forms to facilitate automated production that increases the likelihood of perseverative output; and also a capacity to perceive a non-representational pattern.

Line tracing tasks have been used to elicit perseverative behavior in adults and in school age children (Lezak, 1983). A line tracing task is also used in the MacQuarrie test for mechanical ability, in which the tracing, tapping and dotting components appear to be sensitive to impairment in fine motor regulation. Typically used materials for these tasks are isolated forms or connected

sequences. Scoring systems for copying graphic designs, such as the classic Bender Visual Motor Gestalt test of geometric figures, were also developed to include perseverative behavior (Hutt, 1977). Hutt described 11 kinds of deviations that are particularly associated with brain damage, including perseveration of elements within a design and of elements of one design in another. In this regard, the Bender-Gestalt test, as a whole, has been widely reported to be sensitive to diffuse cortical disease or subcortical lesions (Lyle & Gottesman, 1977; Lyle & Quast, 1976; Riklan & Diller, 1961). Similarly, according to Lezak (1983), copying requires a high level of integrative behavior that is not necessarily specific to visuo-graphic functions but tends to break down with many kinds of cerebral damage.

B 4. BAER and Inhibitory Control

The BAER has been used as a marker to evaluate CNS dysfunction, specifically along the brainstem-frontal axis. Loberg (1986) discussed the role of the brainstem in the modulation and maintenance of activation and the possible use of BAER for real time evaluation of patients in which such dysfunction is observed.

Chu, Squire, and Starr (1982) studied BAERs of chronic alcoholic adult patients who had shown frontal symptomatology. They found a clear relationship between BAER abnormalities, age, and number of alcoholic

neurological complications. Even excluding patients with primary brainstem involvement, those with Wernicke-Korsakoff syndrome and those with cerebellar degeneration, a third of the group still had abnormal BAERs. The study supports the importance of using BAERs in populations where poor regulation of output can be expected.

Hecox, Cone, and Blau (1981) studied children with maple syrup disease and phenylketonuria (PKU) using BAER recordings and showed that the disease course correlated well with alterations in amplitude, latencies of major components and topography of the BAER waveform. This study is of a interest since recent work by Diamond (1993) has demonstrated that children with PKU show IC deficits even when their dietary treatment has been well regulated from an early age and through the preschool period. These data indicate that BAER studies aid in assessment of at-risk populations, since they have been shown to be sensitive to IC abnormalities that result from neural perturbation, even in mild, "transitory" or indirect insults to the relevant pathway.

C. Mental Development

Evaluation of the general developmental status of children who have sustained brain damage around the time of birth is of importance to determine the particular damage characteristics that are likely to result in an attenuated general developmental level vs discrete cognitive deficit vs no detectable deficit.

A composite score may be the best measure for determining the presence or absence of overall cognitive impairment post-brain injury (Kamphaus, 1993), and there is substantial data indicating decreased general developmental scores in children who were neonatally diagnosed with brain damage. However, these reports were not based on a common classification system of the CNS injury nor on similar evaluation tools. In addition, specific descriptions of the CNS injury were often not available. Nevertheless, Kamphaus (1993) analyzed several studies that used the WISC-R mean scores of school aged children diagnosed with brain damage and found that all group means were in the low average range. Kamphous's meta- analysis demonstrated a uniform pattern, whereby brain damaged groups score somewhat lower than normals in the performance domain, although still within the normal range, and have further lowered verbal abilities, on the borderline of the normal range (see Table 1).

Bond (1986) reported similar results and concluded that the most intractable deficits that should impact cognitive performance after brain injury are memory, concentration and mental slowness, with mental slowness being one of the most frequently reported problems in long-term follow up studies of brain damaged cohorts.

Table I

Meta analysis of WISC-R scores for brain damaged populations

Author(s)/ Date	N	WISC-R Mean Scores		
		Verbal	Performance	Full Scale
Paramesh (1982)	140	86.4	90.4	87.2
Vance, Fuller,& Ellis (1983)	135	89.8	90.1	88.8
Phelps & Russo (1984)	60	81.2	92.4	85.3

adapted from Kamphaus (1993)

An appropriate instrument to evaluate mental development after brain damage would provide both an overall general intellectual development score and additional quantification of performance on discrete neurofunctional skills. The Griffiths Mental Development Scales (GMDS-II) provide such measures (Griffiths, 1984). The scales are designed for testing children from birth to eight years of age. They yield a General Quotient score that is equivalent to Mental age * 100 / Chronological age. In addition they provide six separate but inter-related sub quotients, namely: Scale A- Locomotor, Scale B- Personal -Social, Scale C- Hearing & Speech, Scale D- Eye & Hand Coordination, Scale E- Performance, and Scale F- Practical Reasoning, which give individual sub quotients as well as mental age equivalents.

Stjernqvist (1992) evaluated outcome in extremely low birth weight infants (BW $<$ 901 g) during the first four years of life using the GMDS-II. She found that 80% of the children had scores within the normal range, but had lower mean scores than normal full term controls. The children who showed mental delay had neonatal intracranial hemorrhage Grade III or IV.

A long, but still probably non-exhaustive, list of variables has been shown to affect cognitive development after CNS injury. Golden, Vaughan, Kurtzberg, and McCarton (1988) submitted 21 variables, which were potentially predictive of outcome after neonatal brain damage (n = 245), to a multiple regression analysis. Eight of the variables were found to be significantly related to neurologic and cognitive outcome at several ages until 36 months of age.

These were EGA, total number of days on a ventilator, IVH, Apgar scores at 5 minutes, gender, and CT scan (which was missing for 60% of the cases, but aided in detecting some form of abnormality in 31% of the residual sample).

Hack and Breslau (1988) studied biological and social determinants of IQ in 308 VLBW children at three years of age. They found that brain growth, estimated by changes in head circumference, was affected by socioeconomic status (SES) of the children, such that lower SES cases experienced a double hazard. It is important to note that regression analysis on at-risk samples conducted by Rose (1988, 1992) indicated that both SES and infant measures, predominantly visual recognition measures, predict later IQ, but each accounted for different and independent amounts of variance. Similarly, research by Colombo (1993) indicated that the variance in childhood IQ predicted by visual preference measures was not mediated or moderated by SES.

Bendersky and Lewis (1994) conducted a followup study of 175 preterm infants with and without IVH. They found that a family risk factor that is constructed from social support, parent-child interaction, stressful events and organization of the home environment, was as powerful a predictor of overall 2-year outcome for these preterm children as measures of early medical compromise, accounting for 17 and 19 % of the variance in Mental Developmental Index and Psychomotor Developmental Index of the Bayley, respectively. However, the interaction of family risk indicator x IVH severity became weaker the greater the severity of the IVH. The effect was moderate

for mild IVH and not demonstrable for severe IVH group. Similarly, Korner et al (1993) found that neonatal medical risk was significantly associated with developmental outcome through three years of age. They found that environmental factors, such as early intervention, maternal education and race had less relation to outcome at two years in children who had lower BWs or who were more medically compromised neonates.

Low correlations have been reported between intellectual competence measured between birth and 30 months and again at three to eight years of age for normally developing children (range of Pearson coefficients = .01-.59; Goodman, 1990). However, higher correlations were found for children who showed developmental delays. Developmentally delayed young children's intelligence scores were considerably more stable over time than those of normal children. Stability coefficients for children who were developmentally at risk, tested during the second year of life and again between four and five years of age, were in the .7-.9 range. Hence, the likelihood that a diagnosis of developmental delay made during the first two years of life will hold at a later age is very good (Goodman, 1990).

Some qualifiers need to be made concerning Goodman's argument. Even though the range of DQ in mentally delayed children is more restricted than that of normally developing children and the values more stable, factors shown to have an effect on DQ should still affect outcome in mentally delayed children, but to a lesser degree.

Wachs (1993) identified many determinants of childhood intelligence. Determinants of intellectual development, other than biomedical, were: genetic (Loehlin, Willerman, & Horn, 1988; Wachs & Weizman, 1992), nutritional (Grantham, McGregor, 1984; Pollitt, 1980, Sigman, Neumann, Jansen, & Bwibo, 1989), environmental (Gottfried, 1984; Wachs & Grune, 1982; Wachs, 1986; Wohlwill & Heft, 1987), and individual characteristics, such as temperament (Matheny, 1990). Wachs argued that, despite identification of these factors as determinants, for the most part they were studied in isolation. He argued that variability in intellectual development should be more than the sum of individual determinants considered in isolation, but rather that different determinants interface with each other through passive or active covariance and through interaction. However, research in the area of intellectual development mostly tends to focus on single determinants because of the search for main effects rather than determinants of individual differences, and because of sampling and statistical issues associated with research designs that are concerned with covariance and interaction, due to the power reduction of findings that are based on highly specific measures and the significantly increased probability of making Type II errors (Cronbach, 1991; Wachs, 1990).

D. Formulation of the Present Study

In this study the sequelae of neonatal brain damage were explored when children were three years of age by evaluating the cognitive development of discrete neurofunctional domains, and by assessing the development of IC for regulating behavioral output.

Different levels and magnitudes of neonatal damage were expected to result in different neuropsychological profiles. If the damage resulted in decreased slowed information processing capacity, one would anticipate decreased general cognitive developmental status (Dalton, Redrosian, 1989; Fagan, 1990). Such a trajectory might be particularly apparent with great damage to the system. Thus, an evaluation of overall level of functioning as well as discrete domains of functioning and evaluation of processing rate are needed to differentiate discrete dysfunctions from global reduction of processing and performance capacity.

It was anticipated that children who sustained major CNS damage at birth would have least chance of full recovery compared to those with minor damage in comparable areas. They were expected to show reduced mental processing speed that limited overall scores, and resulted in minimal inter-scales variability.

The expectations concerning the effect of mild degrees of structurally detectable damage on development measures such as the GMDS were more complex than was the case for severe brain damage. Studies of populations

where CNS injury was mild or only suspected have shown different results depending upon the particular inclusion criteria and the dependent measures used. There is a need to differentiate the neonatally compromised group of children into those who have a mild cerebral structural aberration and those who have no cerebral structural damage, but have a functional abnormality in lower levels of the system. The mildly injured children, therefore, were classified into two groups: I) a group with mild/moderate structural cerebral abnormality, such as Grade I-II IVH documented by US (Mild/Moderate), and ii) a group whose injury was probably in lower regions as evidenced by abnormal BAER but without demonstrable abnormality on US (BAER-only).

The Mild/Moderate group was not expected to have global reduction in functioning, evident in overall scores as low as those of the most severely damaged children. However, this group may show isolated cognitive deficits and also may have difficulty with processing stimuli presented at a rapid rate. The BAER-only group was expected to show more pronounced residual deficits, with discrete deficits in multiple cognitive domains, particularly verbal, and fine motor coordination. The differential predictions for the Mild/Moderate group and the BAER-only group were derived from the hypothesis that early deviation in any developing or dynamically changing system tends to be amplified as a function of time or distance from the initial effect or deviation. Hence, infants, with injury involving brainstem related loci may have a compromised development and organization of behavior, resulting in multiple discrete

neurofunctional deficits, relative to those with damage that is limited to the cerebral ventricles.

Deep levels of the brain mature earlier than diencephalic-frontal areas. It is therefore plausible to argue that the neural system has relatively few resources to recover from damage to deep structures of the neuraxis, such as brainstem loci that mature early, and such damage would result in compromised limbic- striatal-frontal projections. Therefore, such lesions should impose greater risk for inhibitory deficits to occur, compared to damage in loci whose maturation occurs later in development.

It was hypothesized that primary brainstem involvement, such as a mesencephalic pathogenic process that affects dopaminergic neurons innervating the corpus striatum may affect the BAER adversely, and would result in a neurofunctional deficit along the limbic-striatal-prefrontal pathway, which is thought to mature later than brainstem loci. This hypothesis was supported by findings that BAERs are aberrant in populations who show IC deficiencies, even in the absence of documented structural deficits in brainstem loci. Hence, BAER abnormality may be indicative of risk for IC deficiencies. It was further expected that BAER abnormality would be most predictive when resulting from primary damage to lower levels of the system, rather than in cases where it was abnormal due to secondary pressure from structural damage in higher levels of the CNS.

It was therefore hypothesized that children who had certain damage

involving early brainstem dysfunction would have difficulty modulating their voluntary output, and hence will have difficulties in their ability to control, plan and execute intentional motor acts, relative to their neurologically intact peers. Such children would be expected to have decreased ability to initiate and cease activities according to situational demands, to modulate the motor act in social and educational settings, to delay action upon a desired object or goal and to generate socially approved behavior in the absence of external monitors (Kopp, 1982; Silverman & Ragusa, 1991).

With regard to external factors, maternal education has been reported to be related to quality of prenatal care as well as postnatal parental care and parenting, and to be a good estimator of SES (Caputo, Goldstein & Taub, 1981). Therefore, the effect of maternal education on group inclusion was tested to support the hypothesis that maternal education was not a mediating factor in the resulting classification. This hypothesis concerning an association between maternal education and group membership of the neonates, supported by the recent inclusion of maternal education of high school or more, as part of the Antenatal Optimality score by Amiel-Tison, Cabrol and Shnider (1994), was based upon the thought that maternal education may affect maternal awareness for markers of abnormality during pregnancy, and may affect physicians' responses to maternal notification with regard to such concerns during pregnancy and postpartum, resulting in differential diagnosis of IVH or assignment to inhibitory control risk (ICR) grouping depending on maternal

education.

In addition, it was predicted that maternal education would affect general development, particularly skills that reflect general knowledge or verbal abilities. Maternal education was not expected to affect recovery in cases that were severely affected, even though education may augment effects of intervention through better utilization of information by more educated mothers relative to less educated mothers. It was also not expected to be directly related to IC performance. Maternal education effect on outcome measures thus was analyzed to determine its effect on type or degree of neonatal damage as well as on outcome.

Therefore in the present study, children were classified into one of four groups based on neonatal type and magnitude of CNS abnormality, and their cognitive development and IC were evaluated at three years of age to determine the relationship between neonatal brain injury and specific outcome deficits in performance. It was hypothesized that compromise to the brainstem would result in deficits in multiple cognitive domains that were thought to involve cortical structures (e.g., verbal abilities and motor coordination) as well as in a specific IC deficiency, probably due to perturbation to the limbic/striatal/ prefrontal pathway, while mild/moderate perinatal cerebral damage would result in less perturbations in cognitive development and no IC deficiency. Severe perinatal damage involving loss of parenchymal tissue would result in significant perturbations affecting overall cognitive performance including IC.

II. Methods

In the course of the study, the following predictions were tested: (1) prematurity increases the susceptibility of infants to various types of CNS involvement; specifically, LBW increases the likelihood of IVH and of IVH with a greater Grade, (2) gender affects susceptibility to particular types of CNS and in males these types are related to IC difficulties, (3) developmental outcome in children that had neonatal CNS insult is differentially dependent on the nature of the particular insult, (4) neonatal damage in early maturing brainstem related loci results in more significant effects on cognitive domains and IC than damage in later maturing higher levels of the CNS, (5) neonatal brain damage results in slowed information processing, (6) severe neonatal damage, such as severe IVH, results in decreased performance in multiple areas, (7) primary damage that affects the brainstem also results in decreased performance in multiple areas, (8) mild damage in higher levels of the system, such as mild IVH in premature infants, does not affect the system in a generalized way, other than by slowing processing, (9) transient asphyxia without IVH results in discrete motor difficulties, (10) brainstem malfunctioning results in IC difficulties, characterized by verbal and manual perseverative errors, (11) maternal education does not mediate group inclusion, and does not mediate recovery in cases of severe or diffuse damage, but may affect performance on tasks that tap general knowledge or verbal abilities.

Rational for construction of tasks

No standardized instruments have been developed to evaluate IC behaviors in brain damaged preschool children. Furthermore, according to Lezak (1983), such "standardization is not necessary or especially desired, since once perseveration or inability to shift smoothly through a movement, drawing or speaking sequence shows up, that is evidence enough that the patient is having difficulty in self-regulation" (pp. 519-520). Although this may be true, the task still remains to operationally define perseverative behavior. Because of the lack of appropriate existing tools that could be used to test specific hypothesis with this sample of children, new tools were developed with the hope that they would tap into the underlying process as intended as well as differentiate among different degrees and types of CNS pathology. Therefore, the present study employed tasks that allow for quantitative measurement of perseverative behavior to evaluate both individual behavior and to allow for across group comparisons. Paradigms borrowed from clinical neuropsychology studies with school aged children were adapted and used with brain damaged preschool children to evaluate IC.

Children were studied at 34 months of age, when IC has already developed in intact children and is emotionally and socially relevant. Evaluation at this age is practical, since it could confirm "risk" status, thereby expediting referral for remediation before the child had to function and exert IC

in formal academic settings.

The proposed tasks, constructed to be appropriate for three years of age, required the child to self-regulate motor output in accordance with changing restrictive rules by using visual and auditory cues in experimental situations where multiple stimuli needed to be processed, either verbally or manually. The tasks permitted both within and between subject analysis of the effect of neonatal structural and functional abnormalities, and the effect of response modality on the outcome measures of IC.

Several considerations governed the formation of the particular tasks used, in addition to those universally applied in evaluating three year old children, with or without brain damage. First, special care was invested in designing situations to which children had no prior exposure as to content or as to the particular restrictive demand. This was done, even though IC abilities using motor regulation tasks are multi-determined, and hence, are not necessarily expected to correlate with environmental influences, such as SES, type of formal schooling or child rearing, or with degree of language or motor development. Second, the tasks did not involve complex learning procedures, since learning or the difficulty or ease of establishing a habit might confound measuring IC per se. Third, prerequisites such as broad verbal vocabulary and/or advanced verbal comprehension, memory or complex fine motor coordination were not required, as there might have been specific deficits in these domains. Fourth, the tasks were constructed to carry minimal content that

is potentially arousing, frightening or depressing, since these might differentially affect the children's IC depending on their individual temperament and their particular emotional history, in addition to a specific deficit related to limbic involvement that may play a role in performance. Thus, the tasks involved novel stimuli that are not likely to be bound in an emotionally loaded situation and did not involve "forbidden" actions or "don't"s. Fifth, the child was given the choice to be tested with a family member in the room, but seated outside the child's' view, or to have the family member remain in the waiting room. In any event, the procedure involved no direct social interaction with a family member or any other person with whom the child has preexisting emotional authoritative relations.

The proposed IC battery had two components: (a) a rapid sequential automated naming task (RSANT), which evaluates verbal output, and (b) a graphomotor task (GMT), which evaluates manual output.

(1) RSANT- Several modifications were required to adapt the rapid automated naming paradigm for the purpose of the present study. Almost all three year old children are verbal, at least to the extent of being able to name rapidly a couple of simple illustrations of objects. Their naming capacity with other categories, such as colors and animals, however, are often fluid, and naming of letters and numbers is generally absent. Hence, it appeared that object categories might be most useful for evaluating young preschoolers. Nevertheless, Denckla, and Rudel (1976) indicated that this particular category

was the least "automated", the slowest to be executed in rapid automated naming tasks during the early school years. However, fortunately, they found the same magnitude of automatism for all groups, normals and risk, suggesting that, as long as one used the same material for evaluating all groups, degree of automatism should not affect performance differentially.

The task yielded two qualitatively different measures: (a) rate of output, which reflects mental speed and, (b) number of perseverative errors, which reflects IC. Since the paradigm required speeded processing of multiple stimuli, all brain damaged groups were expected to show reduced mental speed relative to normals. Subjects who sustained severe brain insult were expected to exhibit slower mental processing speed compared to those with milder degrees of damage. At the same time, perseverative behavior was not expected in the mild group, but was expected in groups in which poor regulation of output was suspected, namely the BAER-only group, and also the most severe group who presented with both BAER pathology and moderate/severe CNS pathology.

Due to the wide variability in the breadth of three-years-old children's vocabulary and in their memory limitations, RSANT for this age group included a limited number of selected items that are over learned, or are part of the core vocabulary of younger children. Furthermore, since retention span for discrete items is fairly limited at this age, the number of stimuli in the test pool was as small as possible to secure equal salience for all items and to elicit perseverative behavior regardless of order of presentation. Therefore, in this task the child had

to alternate rapidly in naming two common objects (namely, ' fish' and 'cup'). These items are typically found in vocabularies of children who have a Mean Length of Utterance of 1.0 - 2.0 .

The particular items ' fish' and ' cup' were chosen, since both comply with several important criteria. They are high frequency, one-syllable words to avoid discrimination against language delayed children whose utterances are less than average length. Also, anecdotal data cited by Clark (1993) showed both items in the language production protocols of one-year-old children. At the age of three, verbal children are expected to easily perceive and articulate differentially, even if not correctly, minimal phonemic differences. Nevertheless, the 'fish' - 'cup' pair can be differentiated on a number of phonemic properties ensuring that articulatory slippage from uttering one item to uttering the other would not occur. According to Jakobson's phonological theory (Jakobson & Halle, 1956) phonological features function as 'functional atoms' which have an existence of their own: they may spread over segments. Therefore, consideration was given to selecting items in which minimal consecutive distinctive features are found (Basbøll, 1988). In fact, all the phonemes differ: the initial consonant [f] vs [c]; the final consonants: [ʃ] vs [p] and the vowel: [I] vs [u]. The pairs differ also on an articulatory principle, in addition to locus of articulation, such that [f] vs [c] differ along 2 properties, front vs back of oral cavity; and fricative vs explosive. Similarly, the [ʃ] vs [p] sound differs in muscles involved in place of articulation and length of positioning required, since the [ʃ] is a fricative and

the [p] is an explosive. The vowel [I] in 'fish'- is a not a back vowel, with a high locus of articulation, while the [a] in 'cup' is back and not high. Both differ in voice onset time. In addition, the two words represent common objects that have few common semantic fields. Both differ distinctly on qualities of form, animation, motion, use, habitat and more.

(b) GMT - Performance on GMT was expected to be deficient in those clinical groups who have deficient IC. Since only the simplest patterns were used, impairment of hand-eye coordination was not expected to explain poor regulation in performance. Similarly, mental speed was not expected to interfere with performance. Therefore, since the task was expected to trigger perseverative behavior under a "non pressured" condition (no increased perceptual-motor demand, no increased level of stimulation, no requirement for speeded output), GMT was expected to differentiate subjects who tended to perseverate from subjects whose performance was affected in other ways. As such, it was expected that subjects with BAER-only abnormality and those with severe structural damage would exhibit more deficient regulation of output relative to a mild/moderate IVH group and to the normal groups, even when controlling for the effects of eye-hand coordination ability.

The predictions concerning cognitive functioning were not expected to necessarily parallel specific forms of damage and IC capacities. Nevertheless, it was hypothesized that capacities required for performance on tasks that evaluate IC bear upon those skills, particularly verbal and eye-hand coordination

capacities. The relevant sub quotients were used to estimate the contribution of these capacities to performance on tasks that evaluated IC skills, specifically, verbal, hand-eye coordination, and fine motor skills under time pressure that were evaluated in the Performance scale. These expectations are presented schematically in summary Table II.

Table II:

Summary of hypotheses

Groups	Neonatal core pathology		Risk for outcome			
	Cerebrum	Brainstem	Mental	IC		
			GMDS	GMT	RSANT	
					speed	errors
Severe	+	+	2*	2	2	2
Mild/Mod	+	-	1**	0	1	0
BAER-only	-	+	2**	2	1	2
NICU/N	-	-	1**	0	0	0
FTN/N	-	-	0	0	0	0

Note. + = damage predominantly affecting this level of the CNS, - = this level of the CNS is affected minimally or secondarily to the core pathology, 0 = no risk; 1 = some risk; 2 = significant risk; *= without inter-sub quotient discrepancy; ** = with inter-sub quotient discrepancy.

Subjects

The study was performed on a cohort of 114 children composing of the five study groups (FTN/N, NICU/N, BAER-only, Mild/Mod, and Severe). These children represented a sub-sample of infants born in 1990-1992 who were participating in longitudinal studies conducted by Gardner and Karmel at the Infant Development Department (Neurobehavioral and Neurophysiological Laboratories, respectively), Institute for Basic Research, Staten Island. The studies focused on the effects of brain injury and crack-cocaine on arousal and attention processes. They did not involve any manipulation that would interfere with the children's development or behavior.

Due to a suspected interaction between prenatal cocaine exposure and neurogenesis and a suspected interaction between cocaine exposure and susceptibility to specific neuropsychological outcome, particularly with regard to IC, children with known prenatal crack-cocaine exposure (n =27) determined by maternal report and/or urine or meconium analysis, were omitted from the analysis.

The infants were initially identified, recruited and neonatally evaluated by Gardner and Karmel (see Appendix A and Appendix B for cranial US and BAER procedures, respectively). Demographic data concerning BW, EGA, Apgar scores, HC and length were obtained from the hospital charts by the laboratory's research associates. The effects of these non-categorical variables

scores (e.g., EGA, Apgar scores) on outcome were analyzed as possible sources of variance. US data, concerning Grade of IVH, were not so analyzed as they were an integral part of group assignment.

Three brain damaged groups of children were studied. Group A, the Severe group, was comprised of infants with extensive to severe CNS pathology, recruited from the Neonatal Intensive Care Unit (NICU). Group B, the Mild/Mod group, consisted of infants with cerebral damage, including minor to moderate IVH in the germinal matrix without dilated ventricles and without necrotic tissue in the parenchyma, recruited from the NICU. Group C, the BAER-only group, included infants in whom structural cerebral damage was not documented, but who displayed neurofunctional disruption in deeper brainstem loci, as indicated by abnormal BAERs, recruited from the NICU or from the full-term nursery (FTN).

Two control groups were studied. Group D, the NICU/N group, was composed of subjects from the NICU who had normal neonatal US and BAER or had normal BAERs but were too healthy to warrant evaluation with US for clinical purposes. Group E, the FTN/N group, consisted of full-term healthy infants who had normal BAER, or who are too healthy to warrant such clinical evaluation at birth, recruited from the FTN. This group served as a control group for development status of IC at three years of age. The specific criteria for inclusion into the participating groups are presented in Table III.

Group means and SD values on the GMDS at .05 confidence level, were

calculated from a pilot study to determine cell sizes for the experimental tasks (Dallal, 1988). The analysis yielded the need for 8 subjects per cell for power of .8 and 11 subjects per cell for power of .9. Based on the child's date of birth and EGA, subjects were selected to participate on a first-come first- tested basis, until the experimental design cells were completed.

In order to complete collecting the demographic data, information concerning maternal education and maternal age were gathered during an interview of the mother concerning information about the child, needed for completion of the GMDS-II scoring form. Since external factors may affect development both prenatally and postnatally, in cases of foster care, information concerning maternal age of either maternal figure, were not incorporated into the analysis.

Table III

Criteria for inclusion into groups

Group	Description
A. Severe	IVH/PVH Grade III-IV (seen on US); ventriculomegaly > 5 mm dilatation of IIIrd or IVth ventricle; periventricular LM; cerebral edema >48 hr with IVH or LM; multiple sites of porencephaly; parenchymal hemorrhage, seizures >24 hr; typically abnormal BAER.
B. Mild/ Moderate	IVH Grade I, II (seen on US), or a choroid cyst < 3 mm. lobular or prominent choroid; ventriculomegaly 3- 5 mm; normal or abnormal BAER.
C. BAER-only	Normal US, abnormal BAER.
D. NICU/N	Normal US, normal BAER.
E. FTN/N	Normal US, normal BAER.

Note. US = cranial ultrasound; BAER = brainstem auditory evoked responses; IVH = intraventricular hemorrhage; LM = leukomalacia; PVH = periventricular hemorrhage; Grade I: IVH or germinal layer hemorrhage over less than one half of one or both lateral ventricles; Grade II: IVH over greater than one half of one or both lateral ventricles; Grade III: IVH distending any part of the ventricular system; Grade IV: IVH extending into the substance of the brain; NICU/N = NICU normal; FTN/N = full term normal.

Procedure

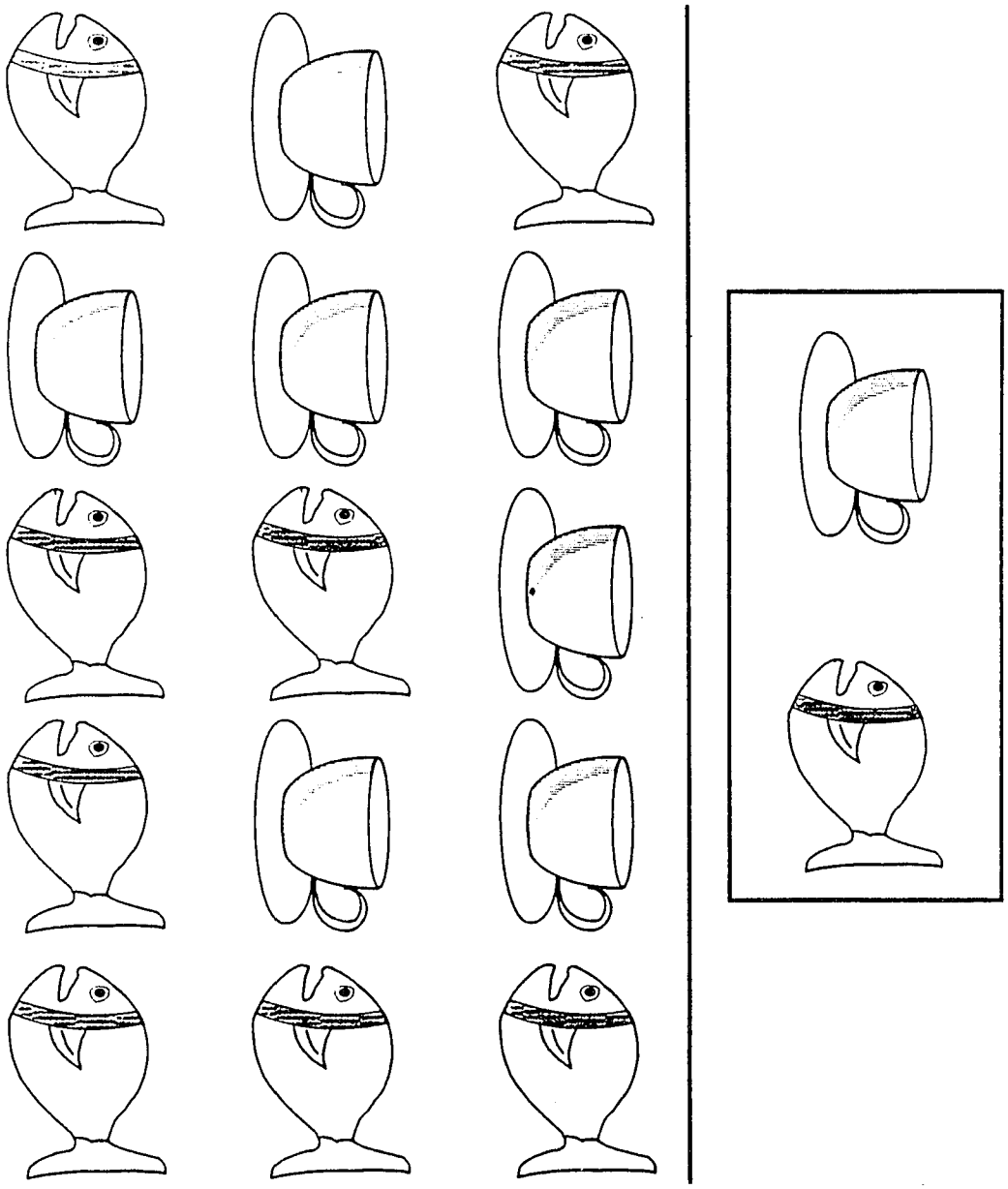
A. Inhibitory Control Procedures

A 1 RSANT.

This task is essentially a non-selective verbal alternation task. The child was presented with a series of pictures of the same two objects and was instructed to name the stimuli as fast as possible. An $8^1/_2$ x 11 in. stimulus board contained 15 fish and cup illustrations, each 30 x 18 mm., presented in a randomized order, and organized in three equal rows (Figure 2). Prior to seeing the board, the child was asked to name each of the two stimuli in isolation to ensure correct naming. When naming was hesitant or wrong, five pair trials were added. This was rare and happened only in 2 cases.

Since young children tend not to scan systematically through the page, a transparent 35 x 25 mm. square pointer with a yellow margin (1 mm. wide) that has a transparent handle guided the child's scanning through the items, with minimal visual obstruction introduced to the field. The child was asked to name the items seen in the pointer's frame as quickly as possible, and the tester shifted the pointer as soon as the child articulated a verbal response to each item. Performance was timed with a stop watch, and the number of perseverative errors were recorded.

Figure 2. Stimulus board for RSANT



Analysis was done by adjusting the scores for the effects of verbal skills (using the Hearing & Speech Sub Quotient of the GMDS) and the ability to perform under time pressure (using the Performance Sub quotient of the GMDS).

A 2. GMT.

A simple graphomotor task was used, wherein the subject was required to form a sequence of spaced dots, which somewhat resembled card numbered 1 b of the Bender- Gestalt geometric figures test. This pattern is the simplest of the Bender - Gestalt figures used to assess perseveration. It is a repetitive sequence that requires an alternation of arm movements (i.e., raising and lowering of the arm, while shifting its position along the page). Producing the dots repeatedly in the same location on the page constitutes a perseverative behavior. To rule out the possibility of the child having fine motor difficulties, a baseline condition was given in which the child was instructed to form a long continuous line along a horizontal plane. Tracing of the continuous line and the dotted line models were observed to evaluate whether the model acted to facilitate or hinder performance.

The GMT was administered after the graphomotor components of the GMDS. The latter items were part of the Eye & Hand Coordination scale, in which the children were asked to form several patterns to models: a horizontal stroke, a vertical stroke, a circle, a cross, and depending on performance with regard to the items mentioned above, a picture of a person and designs of a square

and a ladder. These items served to familiarize the child with the pencil and page, to experiment with pencil and paper, and gave the child the opportunity to view output relative to a model. It enabled evaluation of the child's tendency to perseverate rather than to shift from the GMDS graphomotor tasks to the GMT.

GMT had four components that were presented in a fixed order, based on an a priori notion with regard to increasing levels of control. These components were:

(1) Line formation: The child was asked to imitate a 6-8 inch horizontal pencil stroke.

(2) Line tracing: The child was asked to trace his/her baseline line. A baseline stroke that was between 4-9 inches long on a similar plane but not more than about an inch apart from the baseline line was require.

(3) Dotted line formation: (This condition was the core condition of the four). The child was asked to imitate 4 of 7 intermittent short spaced strokes spaced 15 mm from one another forming a dotted line. Spaces in the range of 5 mm to 30 mm were required.

(4) Dotted line tracing: The child was asked to dot in the vicinity of at least 3 previous dot locations required (at least 2 of which were within 1 in. range from each target on the page).

Performance for each condition was scored as follows:

0 = performance that did not comply with the task where perseveration between components was noted, such as continuing circular scribbling from the GMDS;

1 = perseverative performance within a component, such as repeated marking of the same page location, or failing to cease activity and lift the pencil even beyond the page boundaries; and,

2 = non-perseverative performance.

A count was made of each categorical score. The number of occasions in which perseverative behavior was noted was recorded.

B. Mental Development Evaluation

The children's mental development was evaluated using the GMDS-II. The Scales were used to evaluate the children's functional development in multiple cognitive domains and to estimate the degree of covariation with the IC measures. The particular test was selected from the available tests for this age range for a number of reasons. It provides an overall IQ/ developmental quotient (DQ) and also six discrete quotients for performance in six interrelated domains. It is developed for use with children with CNS injury and developmental delays and is generally not heavily loaded with timed items, which may be particularly difficult with brain damaged groups. The test's broad age range is such that, three-year-old children's performances are not expected to show floor or ceiling effects, except for the Practical - Reasoning scale which is designed for children who are at least two years old.

A possible weakness of the Griffiths test could have arise from the fact that

the test was constructed for and standardized on a sample of British rather than American children. This concern applies particularly to a few items on the Speech and Hearing scale, which are relevant more to the British culture (i.e., a picture of a flag of England to name, an analogy with regard to coal to complete, etc.). However, these items were suitable mostly for children with more developed verbal abilities than those observed for the great majority of the children in the present study and therefore this drawback was probably outweighed by the advantages of the tool. Assessment of the children and scoring was done according to the manual (Griffiths, 1984). The GMDS was administered to the children at the same testing session along with the IC tasks.

C. Order of task's administration

Order of task administration was governed by grouping items and/or tasks that required similar stimuli or skill, also by the overall arousal that each task evoked, and by the type of child-examiner interaction required for the item/task. Tasks that presented the child with a chance for success and involved relatively little interaction with the examiner, such as solving simple puzzles, or building with blocks, were administered at the beginning of the session. Tasks that involved gross motor activity, like the Locomotor Scale were administered toward the end of testing session. The order was kept constant, such that Hand-Eye Coordination Scale items that included graphomotor items, were administered

prior to the administration of the GMT. Hutt (1977) pointed out that perseveration of elements of one design in another is only possible when presenting the subject with a graphomotor task within a framework of other graphomotor behaviors. Therefore, GMT was administered as soon as the children completed the graphomotor components of the GMDS. The Hearing & Speech Scale's items were administered when the child was alert and comfortable in the testing situation. The item of naming of a series of 20 pictures, preceded the administration of RSANT.

III. Results

Group Characteristics

Demographics

The demographic characteristics of the groups that are presented in Table 4 indicated a wide distribution of all measures. Group differences were found for EGA, BW and Apgar scores. Aside from the FTN children, who were significantly more mature than all other groups, ANOVA analyses showed that there were also differences among the risk groups in BW ($F = 3.7$, $p < .06$), EGA ($F = 4.5$, $p < .04$), and Apgar scores at 1 min and at 5 min ($F = 7.8$, $p < .01$; $F = 9.1$, $p < .005$, respectively). These effects resulted from differences between the NICU/N group and the mild risk groups, and the latter groups and the Severe group. NICU/N was relatively more mature and less likely to have been asphyxiated than the Severe group, who were least mature of all groups and had the most depressed Apgar scores at birth. This finding confirms that very premature infants are more susceptible to asphyxia and to the development of severe IVH than are less premature infants.

Orthogonal contrasts among the mildly damaged groups, the Mild/Mod group and the BAER-only group, did not reveal significant differences. No significant differences among the groups were found for head circumference ($F = 1.3$, NS) or crown-heel length ($F = 0.8$, NS), when BW/EGA were treated as covatiates.

Table 4
Demographic characteristic of the groups

Groups	FTN/N	NICU/N	BAER-only	Mild/Mod	Severe
n	32	20	13	14	8
BW (g)					
M	3588	2291	2102	1904	1445
SD	505	904	841	743	988
Range	2580-4678	750-4394	730-3969	992-3829	520-3459
EGA (weeks)					
M	39	36	33	31	30
SD	1.4	4.3	3.9	4.0	5.3
Range	36-42	26-42	27-39	25-40	25-41
Head circumference (cm)					
M	34.1	31.8	28.8	29.2	29.1
SD	1.4	3.5	3.7	2.9	4.1
Range	32.0-35.5	24.5-36.0	24-34	22-33	24-35
Length (cm)					
M	51.0	45.5	42.5	41.3	42.1
SD	2.6	5.5	5.6	5.8	5.7
Range	48.0-54.6	34-51	33-50	30.5-54.7	34-50
Apgar at 1 min					
M	9	7	7	7	4
SD	1	2	2	1	2
Range	6-10	4-9	4-9	4-9	2-9
Apgar at 5 min					
M	9	9	8	8	7
SD	0.5	0.4	0.7	0.7	2.2
Range	9-10	8-9	7-9	7-9	4-9
Maternal education (years)					
M	15	12	13	15	11
SD	4	1	1	3	3
Range	10-23	10-16	12-15	12-18	10-15
Maternal age at giving birth					
M	27	29	31	31	29
SD	5	6	4	7	3
Range	16-31	17-35	25-36	23-38	27-32

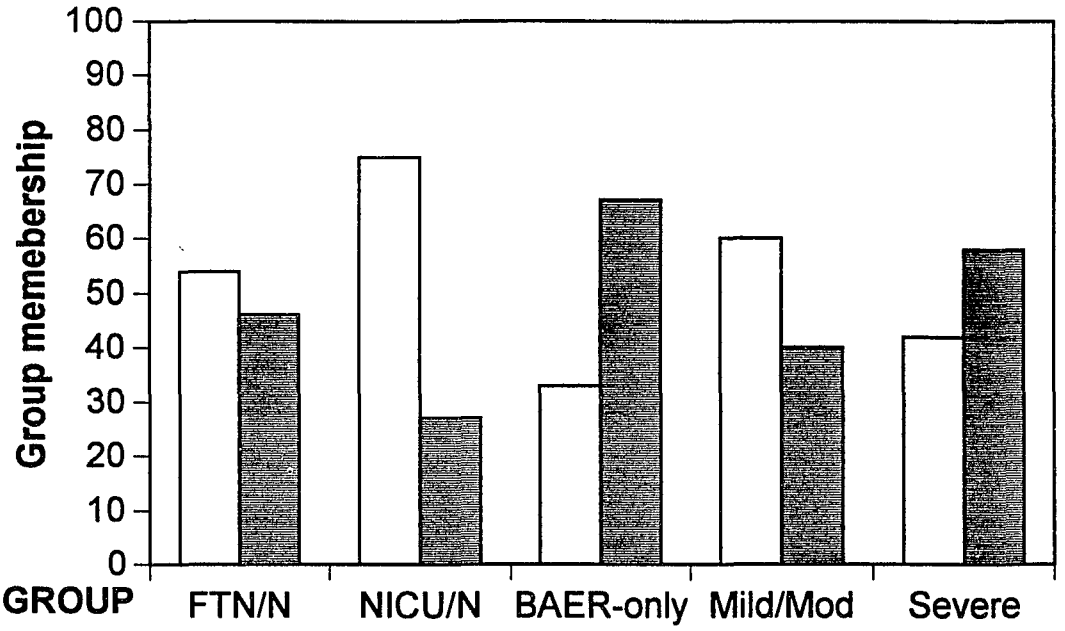
Gender

There was a differential distribution of gender among the groups (Figure 3), even though there was a similar number of females and males in the total cohort (44 : 43). Males were found more often than expected by chance in the BAER-only group and in the Severe group, and females were found more often than expected in the Mild/Mod group and in the normal NICU/N group. The distribution of gender in the FTN control group was not different than chance.

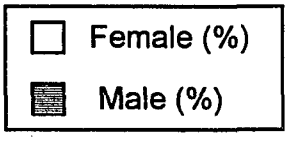
Analysis of the gender distribution among groups was done, concentrating on gender susceptibility to develop IVH and gender susceptibility to be in groups that were expected to have increased risk for IC difficulties. The first analysis was performed by combining the two control groups and the BAER only group (i.e., infants from both the NICU and the FTN) to form a group of subjects without IVH (No-IVH grouping, n = 65, 71% of the sample) and combining the Mild/Mod and Severe groups to form a group of subjects with IVH (Yes-IVH grouping) (n = 22, 20% of the sample). By comparison to the distribution in the total cohort, 40 % of the children had IVH.

A Chi square distribution of gender in the two groups was not different from the distribution expected by chance (analysis for the whole sample: $\chi^2_{(1)} = 1.4$, NS; analysis limited to infants assigned to the NICU: $\chi^2_{(1)} = 1.8$, NS), which also indicated that no one gender was more likely to be diagnosed with IVH.

Figure 3. Sex distribution among groups. In connection to this and to the succeeding figures: US= ultrasound, BAER = brainstem evoked response, FTN = full term nursery; NICU = neonatal intensive care unit, Abn = abnormal, Mod = moderate.



Structure (US)	Normal	Normal	Normal	Mild/Mod	Severe
Function (BAER)	Normal	Normal	Abn	Abn/N	Abn/N
Nursery	FTN	NICU	FTN/NICU	NICU	NICU



The second analysis was based on the study's predictions concerning gender and performance on IC oriented tasks. A combination of the BAER-only and Severe groups formed the high IC risk group (H-ICR), and a combination of the two control groups and the Mild/Mod group formed a low IC risk group (L-ICR). Of the total cohort, 23 % were in the H-ICR grouping and 77 % were in the L-ICR grouping. The male/female ratio in the H-ICR grouping was 2.4 : 1, whereas the ratio in the L-ICR grouping was 0.8 : 1 (Likelihood ratio $\chi^2_{(1)} = 5.7$, $p < .02$), indicating a greater susceptibility for males to be in H-ICR.

Table 5 shows that the subjects in the H-ICR grouping had the most severely affected BAER, and in particular, their discriminant scores for the BAER were worse than those of the other group, followed by that of the Mild/Mod group. A linear progression in the latency of wave I with increased developmental risk, expected from BW/ EGA group distribution in the data set, is evident . The Severe group had the most delayed wave I and the longest wave I - III interval. The BAER-only group had an unexpectedly long wave III - V interval.

Table 5

Mean latencies, standard deviations and range of major BAER measures for the groups

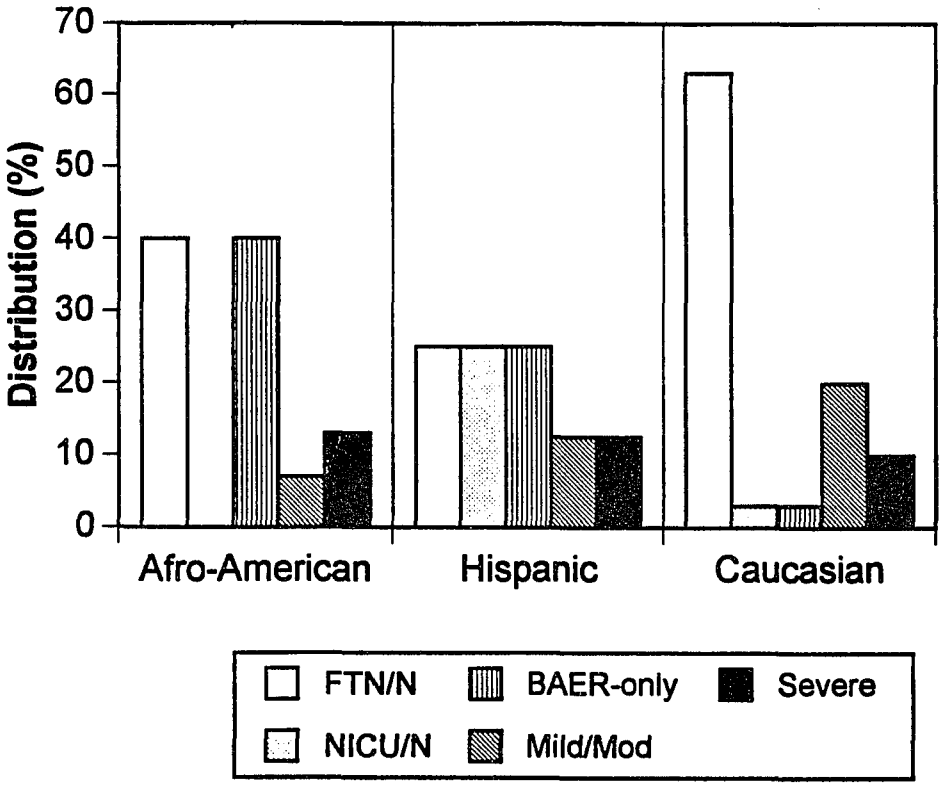
Groups		FTN	NICU-N	BAER- only	Mild/Mod	Severe
Major negative component						
I						
	M	1.5	1.6	1.8	1.8	1.9
	SD	0.1	0.1	0.2	0.2	0.2
	Range	1.4 to 1.6	1.5 to 1.8	1.6 to 2.1	1.6 to 2.1	1.5 to 2.1
III						
	M	4.4	4.4	4.8	4.7	4.9
	SD	0.1	0.3	0.4	0.4	0.5
	Range	4.3 to 4.6	3.9 to 4.9	4.2 to 5.7	4.4 to 5.7	4.4 to 5.8
V						
	M	6.7	6.6	7.5	7.3	7.5
	SD	0.1	0.2	0.5	0.5	0.6
	Range	6.7 to 6.9	6.3 to 6.9	6.7 to 8.6	6.7 to 8.5	6.6 to 8.5
Intervals						
I-III						
	M	2.9	2.8	3.0	2.9	3.1
	SD	0.1	0.3	0.3	0.4	0.5
	Range	2.8 to 3.0	2.3 to 3.2	2.4 to 2.7	2.3 to 3.6	2.6 to 3.8
III-V						
	M	2.3	2.1	2.7	2.5	2.5
	SD	0.1	0.2	0.2	0.2	0.2
	Range	2.2 to 2.4	1.9 to 2.4	2.2 to 2.9	2.3 to 3.0	2.2 to 2.7
Discriminant score						
	M	-1.2	-1.0	0.8	0.5	0.6
	SD	0.3	0.6	0.5	1.1	1.3
	Range	-1.7 to -1.0	-1.8 to -0.4	0.1 to 1.6	-1.3 to 1.9	-1.5 to 2.3

Ethnicity

They were Afro-American (n = 35), Hispanic (n = 11) and Caucasian (n = 41) in the sample (Figure 4). Chi-square analysis revealed no significant effect of ethnicity on group inclusion. The likelihood of being in the IVH-yes group varied between 1:3 and 1:5, regardless of ethnicity ($\chi^2_{(2)} = 0.9$, NS). Among ICR groupings, there was a marginal tendency toward uneven distribution of ethnicity (Likelihood ratio $\chi^2_{(2)} = 5.6$, $p < .07$). The H-ICR grouping included more Hispanics than expected from their distribution in the total cohort (33 % in the H-ICR grouping vs 12 % in the total cohort), as well as more Afro-Americans (58 % in the H-ICR vs 43 % in the total cohort), while there were less Caucasians than expected in the total cohort in this group (13% in the H-ICR grouping vs 46 % in the total cohort).

It is worth noting that recruitment was such that gender was confounded with ethnicity. More Hispanic females than males (8 : 3), and more Caucasian females than males (24 : 17) were recruited. However, the numbers of Afro-American females and males were similar (17 : 18).

Figure 4. Ethnic groups distribution (in percents) among groups.


70
60
50
40
30
20
10
0
Distribution (%)
Afro-American
Hispanic
Caucasian
FTN/N
BAER-only
Severe
NICU/N
Mild/Mod

Maternal education

Analysis indicated that there was no correlation between maternal education and diagnosis of IVH or between maternal education and H-ICR grouping. For the purpose of this analysis, maternal education was classified into two levels: high school education or less (27% of the cohort), and more than high- school education (73 % of the cohort). There was no differential distribution of maternal education between H/L ICR groupings (Likelihood ratio $\chi^2_{(1)} = 0.4$, NS), or between the yes/no IVH groupings (Likelihood ratio $\chi^2_{(1)} = 0.5$, NS).

Cognitive Development

GMDS-II

Developmental Quotient.

Despite the fact that 64 % of the sample were at some level of developmental risk, the groups differed significantly on the developmental quotient (DQ) score ($F(4, 80) = 5.7$, $p < .000$), as well as on most GMDS-II scales scores (Table 6), even though the majority of the children (81%) had DQ within or above the normal range. Differences among groups (clinical groups) accounted for 22.4 % of the variance in DQ (see Figure 6), while ICR grouping ($F(1, 83)=6.4$, $p < .013$) accounted for 7.2 % of the variance. DQ was not affected by yes/no IVH grouping ($F = 0.3$, NS).

Table 6:
GMDS means, standard deviation and ranges for the groups

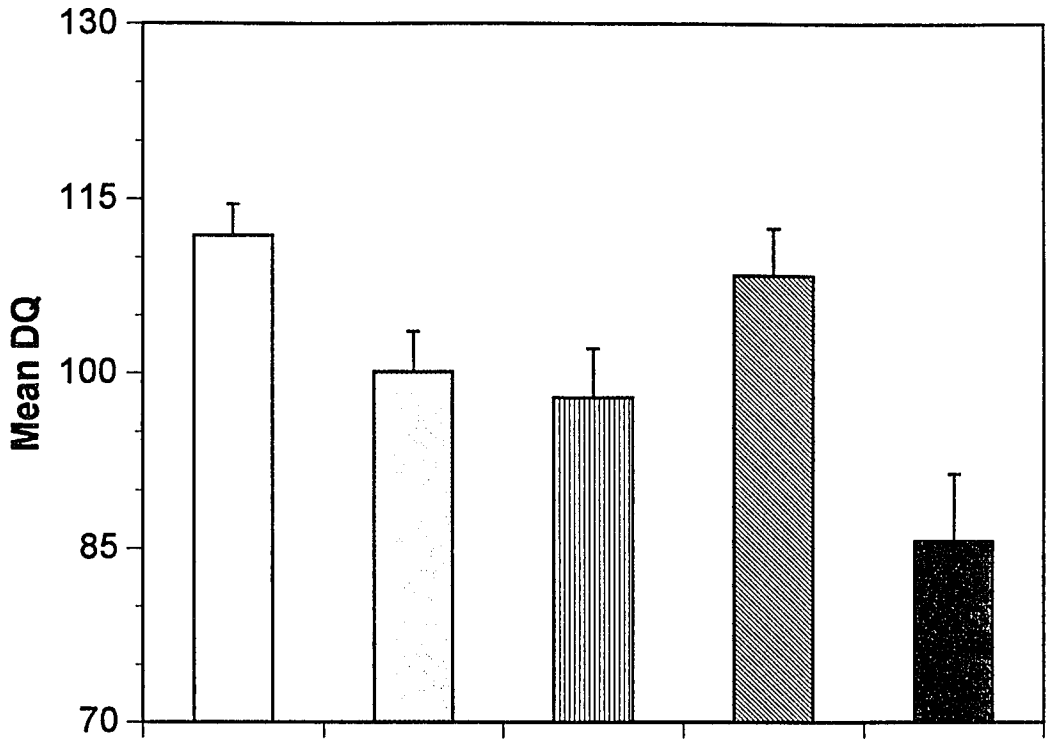
Group		FTN/N	NICU/N	BAER-only	Mild/Mod	Severe
n		32	20	13	14	8
DQ						
	M	111.8	100.1	97.9	108.4	85.6
	SD	11.8	18.8	12.7	18.5	15.3
	Range	83.4 - 140.0	62.4 - 146.8	81.5 - 132.1	72.4 - 133.4	66.3 - 110.6
Locomotor SQ						
	M	110.6	99.6	107.8	110.7	81.8
	SD	19.6	21.8	14.3	25.5	25.4
	Range	76.3 - 157.9	56.7 - 148.0	85.2 - 135.0	67.2 - 148.1	52.7 - 126.9
Personal-social SQ						
	M	120.9	108.6	109.7	116.6	95.5
	SD	22.3	24.8	22.0	26.9	22.9
	Range	80.5 - 167-4	68.1 - 169.2	80.3 - 164.4	64.1- 145.5	58.5 - 126.9
Hearing & Speech SQ						
	M	109.6	96.1	90.5	105.2	78.6
	SD	22.7	26.6	15.6	25.9	7.2
	Range	57.9 - 155-4	51.1- 162-1	63.9 - 123.3	60.5 - 151.1	63.9 - 86.5
Eye-hand coordination SQ						
	M	101.2	89.8	89.9	94.9	77.7
	SD	10.9	14.4	14.1	17.1	17.3
	Range	76.9 - 138.1	56.7- 110.9	68.3 - 111.4	67.2 - 131.0	52.7 - 98.6
Performance						
	M	120.3	107.4	95.4	120.5	90.6
	SD	15.3	19.5	12.9	15.9	16.8
	Range	79.3 - 151.3	62.4 - 142.3	79.3 - 123.3	85.4 - 149.6	76.1- 121.2
Practical reasoning SQ						
	M	108.0	98.9	94.1	102.5	88.9
	SD	14.5	22.8	16.8	19.1	14.1
	Range	84.1- 143.8	74.4 - 162.2	81.4 - 140.9	75.5 - 139.9	69.7 - 115.4

DQ scores were not affected by a number of factors that may have played a role in group inclusion, such that maternal education did not affect performance once grouping effect was entered into the model ($F=.8$, $p<.4$), and similarly birth-weight did not affect DQ once grouping effect was accounted for ($F= .1$, NS). DQ was marginally affected by maternal age ($F = 2.8$, $p < .06$). Maternal ages at the tails of the distribution (below 20 and above 35 years) were associated with lower DQ scores.

Overall, the FTN/N group had higher DQ scores than other groups, scoring in the high average range ($M=111.8$). The scores of the NICU/N group and the BAER-only group were both in the average range ($\underline{M} = 100.1$ and $\underline{M} = 97.9$, respectively), but as discussed below, the pattern of performance in these two groups differed. Mean DQs of the Mild/Mod group were higher than those of any other risk group ($\underline{M} = 108.4$). Overall group differences on DQs resulted from a significantly lowered score of the Severe group ($\underline{M} = 85.6$), and a somewhat lowered score of the NICU/N and the BAER-only groups.

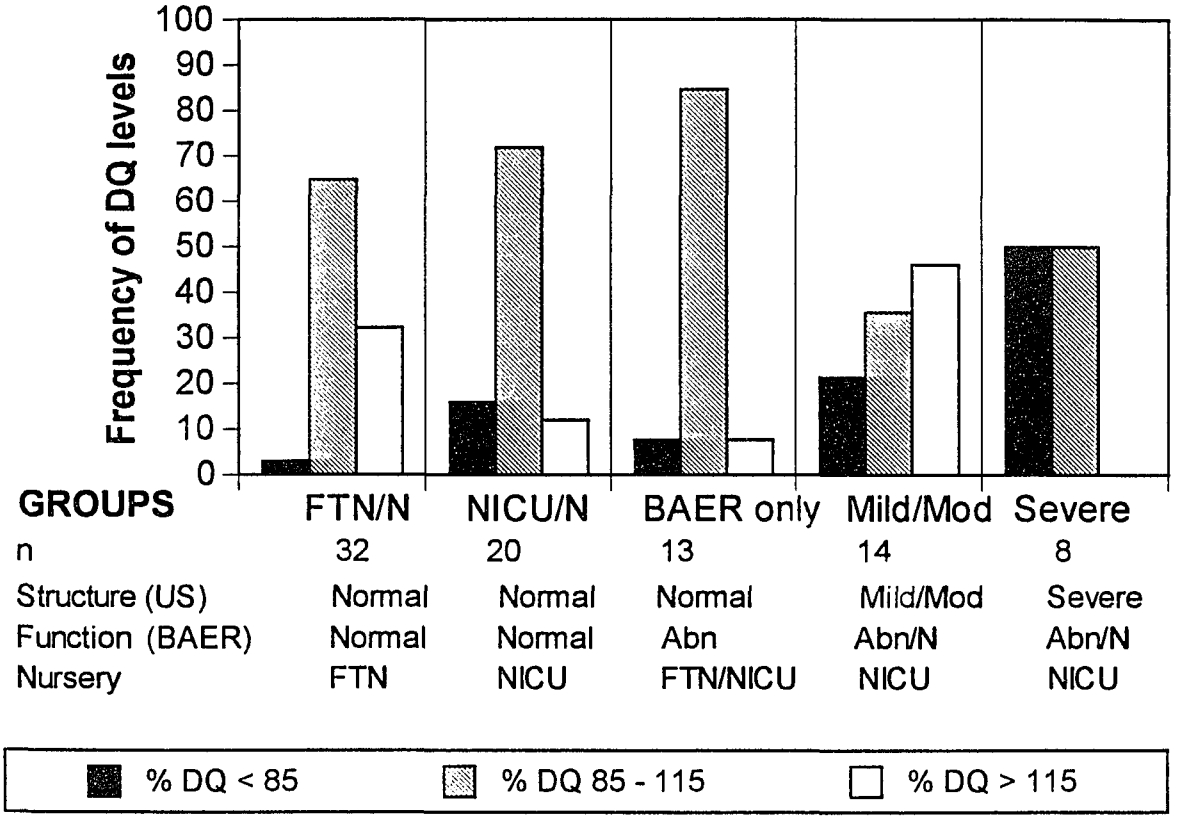
Figure 6 shows the distribution of GMDS score ranges among the groups. (Likelihood ratio of $\chi^2_{(10)} = 21.2$, $\underline{p} < .002$), considering the normal range as ± 1 SD (15 points) around the mean of 100 (e.g., between 85 - 115). In general, there was a greater frequency of DQs below the normal range in groups with structural damage, compared to those without evidence of structural damage ($\underline{F} = 5.4$, $\underline{p} < .006$). Half of the subjects in the Severe group had DQ below average and none of them had DQs above the normal range. Interestingly, in the Mild/Mod group, 40% of the subjects had DQs above the normal range, while 23% had DQ scores below the normal range. This group diverged from an otherwise linear trend of decreasing DQ the greater the CNS risk.

Figure 5. Means and standard errors of the GMDS Developmental quotient (DQ) as a function of group.



GROUPS	FTN/N	NICU/N	BAER-only	Mild/Mod	Severe
n	32	20	13	14	8
Structural (US)	Normal	Normal	Normal	Mild/Mod	Severe
Functional (BAER)	Normal	Normal	Abn	Abn/N	Abn/N
Nursery	FTN	NICU	FTN/NICU	NICU	NICU

Figure 6. Frequency of DQ scores, below the normal range, within the normal range, and above the normal range, as a function of group.


Frequency of DQ levels
100
90
80
70
60
50
40
30
20
10
0
GROUPS
FTN/N
NICU/N
BAER only
Mild/Mod
Severe
n
32
20
13
14
8
Structure (US)
Normal
Normal
Normal
Mild/Mod
Severe
Function (BAER)
Normal
Normal
Abn
Abn/N
Abn/N
Nursery
FTN
NICU
FTN/NICU
NICU
NICU
% DQ < 85
% DQ 85 - 115
% DQ > 115

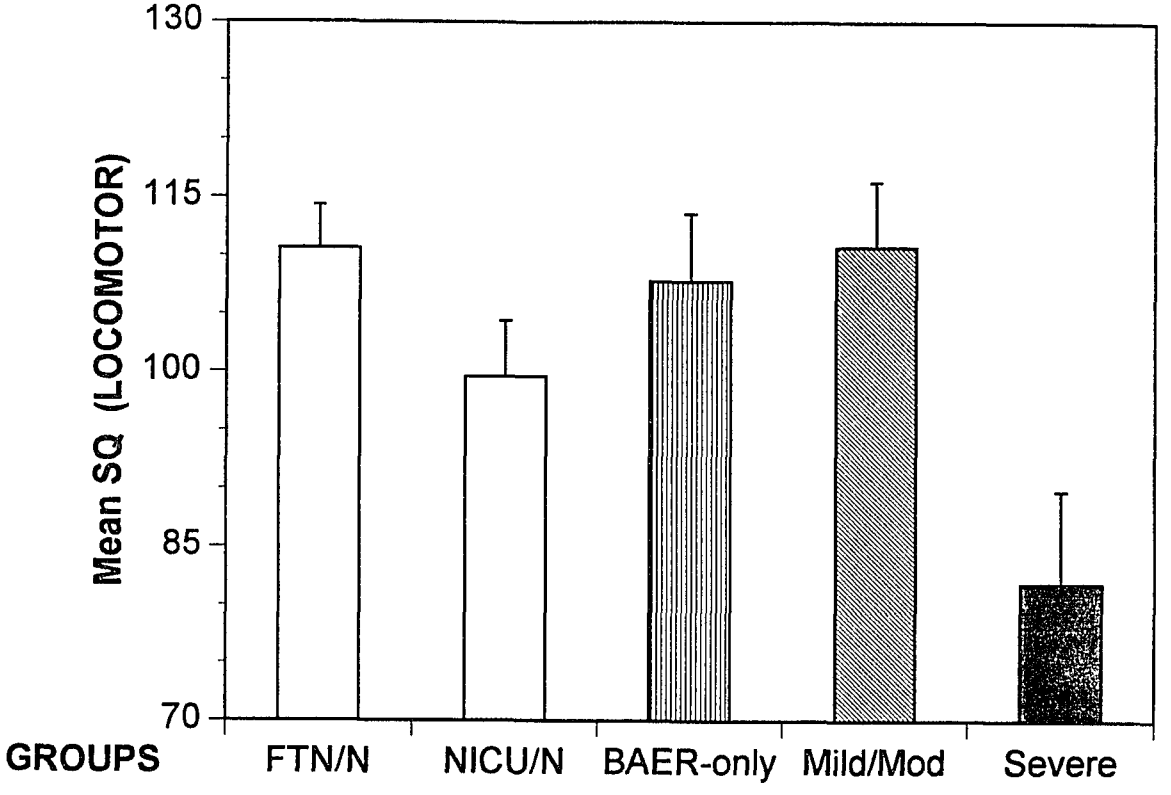
Scale A: Locomotor

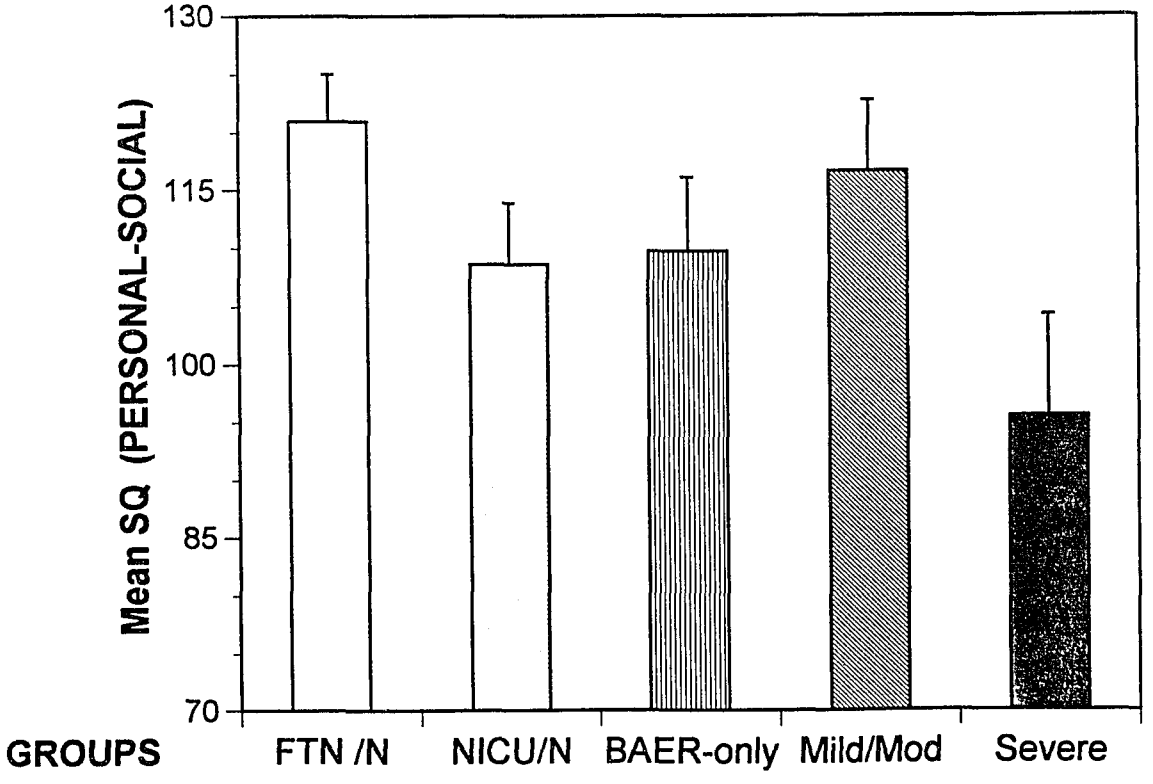
The Locomotor scale serves to evaluate gross motor milestones and motor organization. Influence of clinical grouping on locomotor development (Figure 7) was marginally significant ($F = 3.1$, $p < .08$), and accounted for only 3.6 % of the variance. The effect was mainly due to the difference between the Severe group who scored lowest and all of the other groups. The effect of group membership was diluted by two findings: first, all groups except for the BAER-only group, had relatively great variability in performance on this scale; second, the NICU/N group had low scores relative to the other normal and mildly injured groups. NICU/N performed lower than BAER-only and the Mild/Moderate groups, while the BAER-only group scored well. None of the children in the BAER-only group performed below the normal range on this scale.

A number of investigators found that gross motor development is related both to birth depression or asphyxia as measured by Apgar scores and to IVH. In the present study, consistent with these findings, the relationship between Apgar score at 1 min and locomotor development was significant ($F = 20.5$, $p < .000$), accounting for 30.4 % of the variance on this scale. Similarly, Apgar scores at 5 min affected locomotor performance ($F=10.2$, $p < .002$), accounting for 15% of the variance. The relationship between the presence and magnitude of IVH (grouped in 3 levels: 1= no IVH, 2 = Mild/mod IVH and 3 = Severe IVH) was tested and found to be significant ($F = 4.7$, $p < .01$), accounting for 10.3 % of the variance in locomotor scores. As expected, ICR H/L grouping did not significantly affect locomotor scores ($F = 0.9$, NS).

Figure 7. Means and standard errors of the GMDS - Scale A: Locomotor sub quotient (SQ), as a function of group.

Figure 8. Means and standard errors of the GMDS - Scale B: Personal-Social sub quotient (SQ), as a function of group.





Structure	(US)	Normal	Normal	Normal	Mild/Mod	Severe
Function	(BAER)	Normal	Normal	Abn	Abn/N	Abn/N
Nursery		FTN	NICU	FTN/NICU	NICU	NICU

Scale B: Personal -Social.

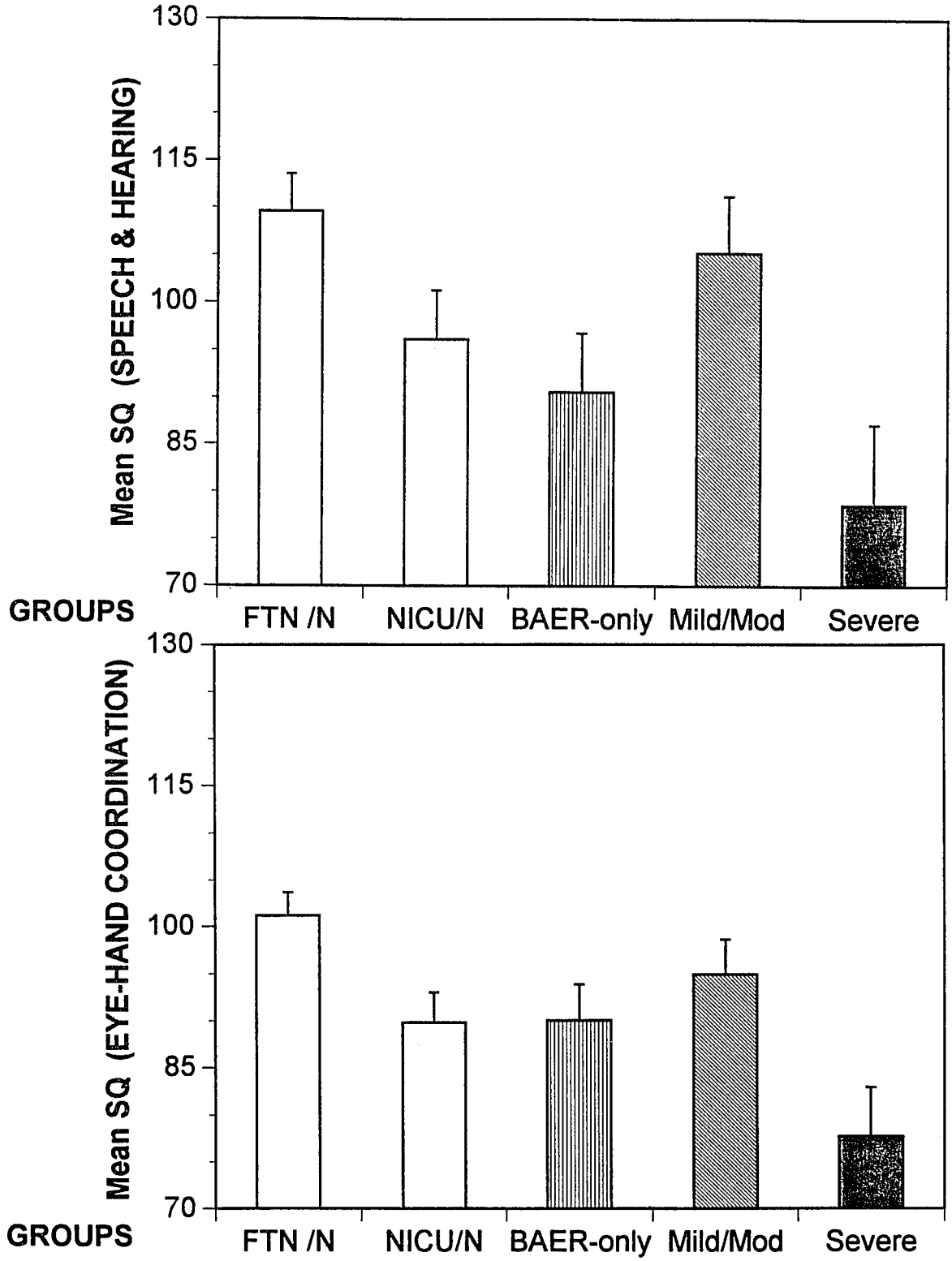
The Personal - Social scale contains items concerning independent self care, general knowledge about self and social interactions. There were significant differences based on clinical groups ($F = 4.0$, $p < .05$) (Figure 8; Table 6). However, these accounted for only 4.7 % of the total variance. All the groups, except for the Severe group, scored in the high average range (from $M = 108.6$ in the BAER-only group to $M = 120.9$ in the FTN/N group). As with other scales, the Severe group scored significantly lower than the other groups ($M = 95.5$). No relationships were found between personal-social skills and the presence or absence of IVH ($F = 0.1$, NS) or between these skills and ICR status ($F = 1.8$, NS).

Scale C: Hearing and Speech.

The Hearing and Speech scale primarily taps language production by evaluating spontaneous output, naming and auditory span. Significant differences were found among groups ($F = 6.7$, $p < .01$) (Figure 9; Table 6) despite significant variability within most groups. Least variability was found in the Severe group in which all children performed below, or within the low normal range ($M = 78.6$). The FTN/N group and the Mild/Moderate group performed at a similar level ($M = 109.6$ and $M = 105.2$, respectively), but the BAER-only group, and to a lesser degree the NICU/N group, showed lower verbal skills ($M = 90.03$ and $M = 96.1$, respectively).

Figure 9. Mean standard errors ogf the GMDS- Scale C: Hearing & Speech sub quotient (SQ), as a function of group.

Figure 10. Mean standard errors of the GMDS- Scale D: Eye-Hand Coordination sub quotient (SQ), as a function of group



Structure	(US)	Normal	Normal	Normal	Mild/Mod	Severe
Function	(BAER)	Normal	Normal	Abn	Abn/N	Abn/N
Nursery		FTN	FTN	FTN/NICU	NICU	NICU

The lowest scores of the BAER-only and Severe groups (M = 78.6) resulted in a significant effect of ICR on this scale (F = 6.4, p <.01), accounting for as much variance as did the clinical grouping (7.2%).

An association was found between Wave I-III interval of the BAER and Hearing & Speech SQ (F = 4.0, p < .05), accounting for 8.8% of the variance. A relationship also was found between IVH grouping (3 levels) and Hearing & Speech SQ (F = 3.4, p < .04). As has been found with other intelligence scales (e.g., WISC-R) scores on this scale correlated highly with DQ (F = 223.2, p <.000), accounting for 72.9 % of the variance.

Scale D: Eye-Hand Coordination.

The Eye-Hand Coordination scale, involving fine motor coordination, primarily spatial construction and graphomotor abilities, yielded somewhat low scores, even for the FTN/N group (Figure 10; Table 6). There was a relatively linear relationship between clinical groups and performance on this scale (F = 11.3, p < .001), accounting for 12 % of the variance. As was the case for other scales in which performance depends on motor development, there was a significant influence of IVH on performance (F = 4.7, p < .01), as well as significant effect of Apgar scores at 1 min on coordination (F = 6.4, p <.01), accounting for 12 % of the variance. The effect of Apgar at 5 min was not significant (F = 2.2, NS). This effect was in part the result of a relatively greater difference between the performance of Mild/Mod group and the FTN/N group on this scale as compared to

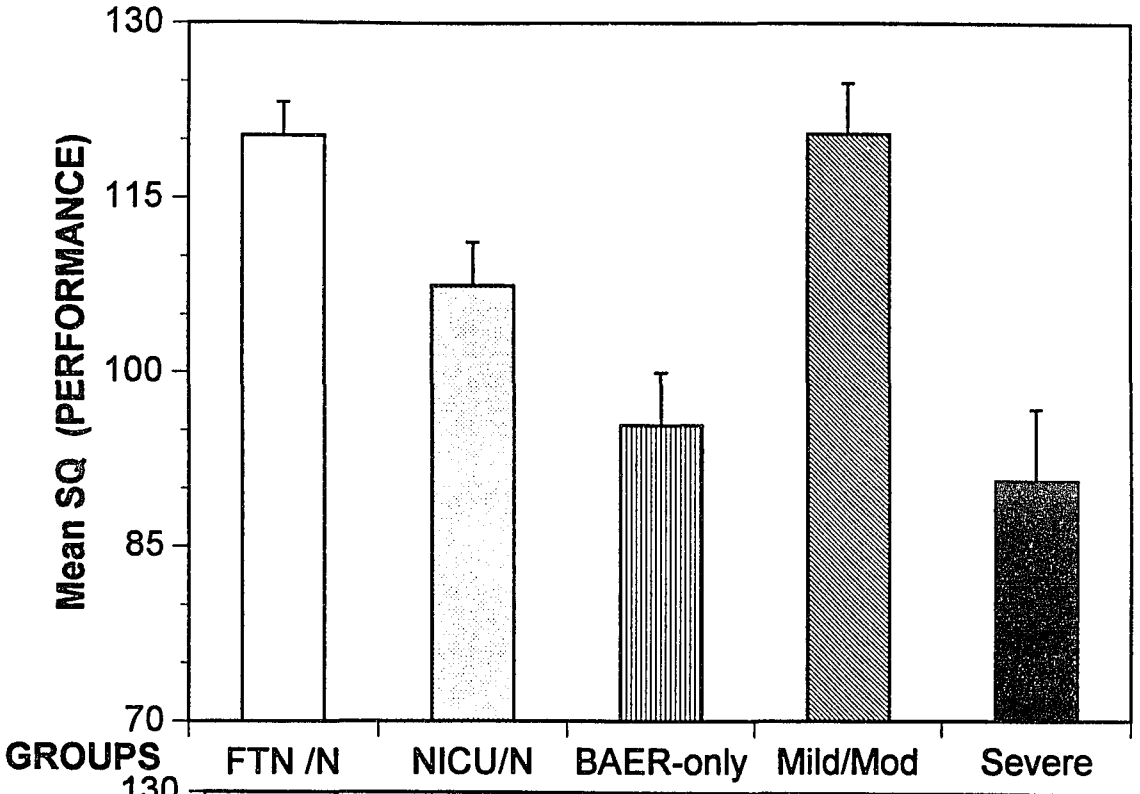
other scales (M = 94.5, M = 101.2, respectively) and the Severe group who performed significantly below the normal range (M = 77.7). The BAER-only group performed at a level similar to that of the NICU/N (M = 89.9 and M = 89.8, respectively). The effect of H/L ICR on Eye-Hand Coordination was also significant (F = 4.8, p <.03), however, it accounted for only 3% of the variance.

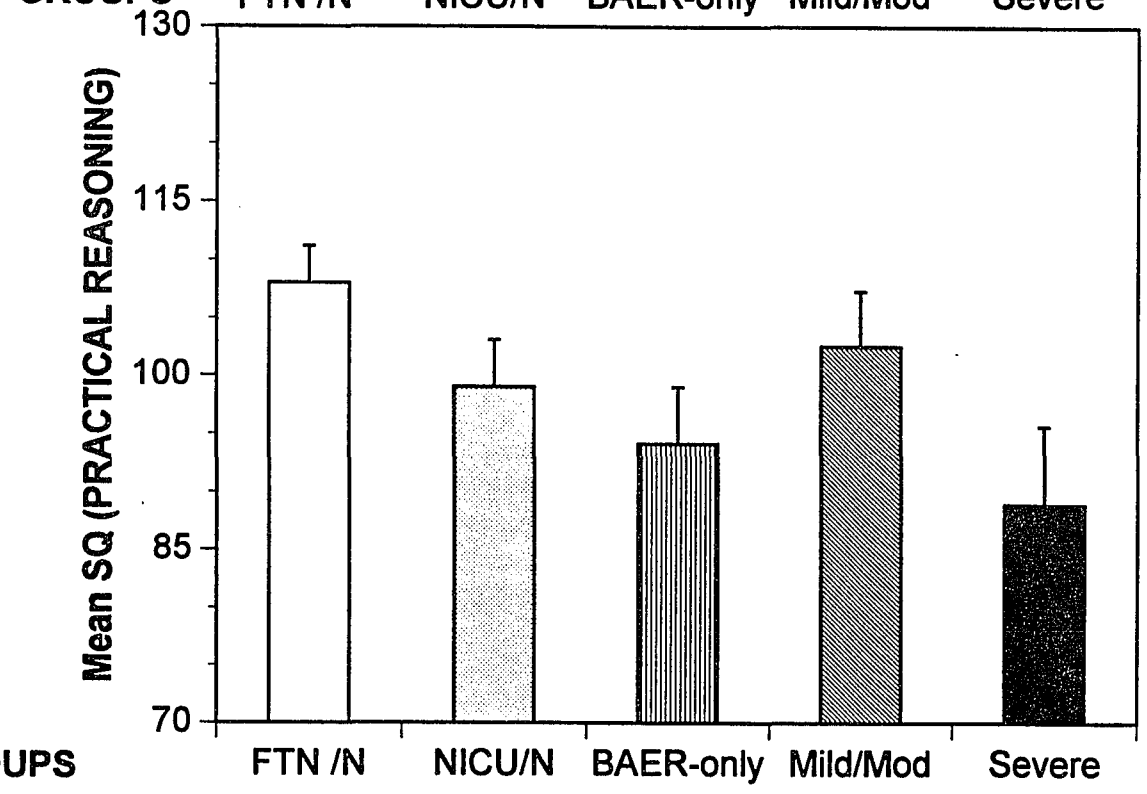
Scale E: Performance.

The performance scale contains mostly items that require construction abilities and performance under time pressure in addition to fine motor coordination ability. This scale yielded a pattern among groups that is similar to that of the overall DQ (Figure 11 and Figure 5; Table 6). Clinical group effect was significant (F = 9.7, p < .000) and accounted for 32.8% of the variance. The effect was primarily due to the low scores of the Severe and BAER-only groups (M = 90.6, M = 95.4; respectively) and also to the less affected scores of the NICU/N group (M = 107.4). Indeed, analysis by ICR was significant (F = 15.6, p < .000), accounting for 15.8 % of the variance, while IVH yes/no did not affect performance on this scale (F =.01, NS).

Figure 11. Means and standard errors of the GMDS - Scale E: Performance sub quotient (SQ), as a function of group.

Figure 12. Means and standard errors of the GMDS - Scale F: Practical reasoning sub quotient (SQ), as a function of group.





Structure	(US)	Normal	Normal	Normal	Mild/Mod	Severe
Function	(BAER)	Normal	Normal	Abn	Abn/N	Abn/N
Nursery		FTN	NICU	FTN/NICU	NICU	NICU

Scale F: Practical reasoning.

This scale primarily requires general knowledge about the world and ability to express such knowledge by using verbal concepts. At three years of age, the scale mostly taps concepts such as size, length, weight, number and money. Standardization of the scale is such that it has relatively limited ability to show individual differences in three year old children. Nevertheless, minor but significant differences among groups were found ($F = 5.8$, $p < .02$) (Figure 12; Table 6), accounting for 6.6 % of the variance.

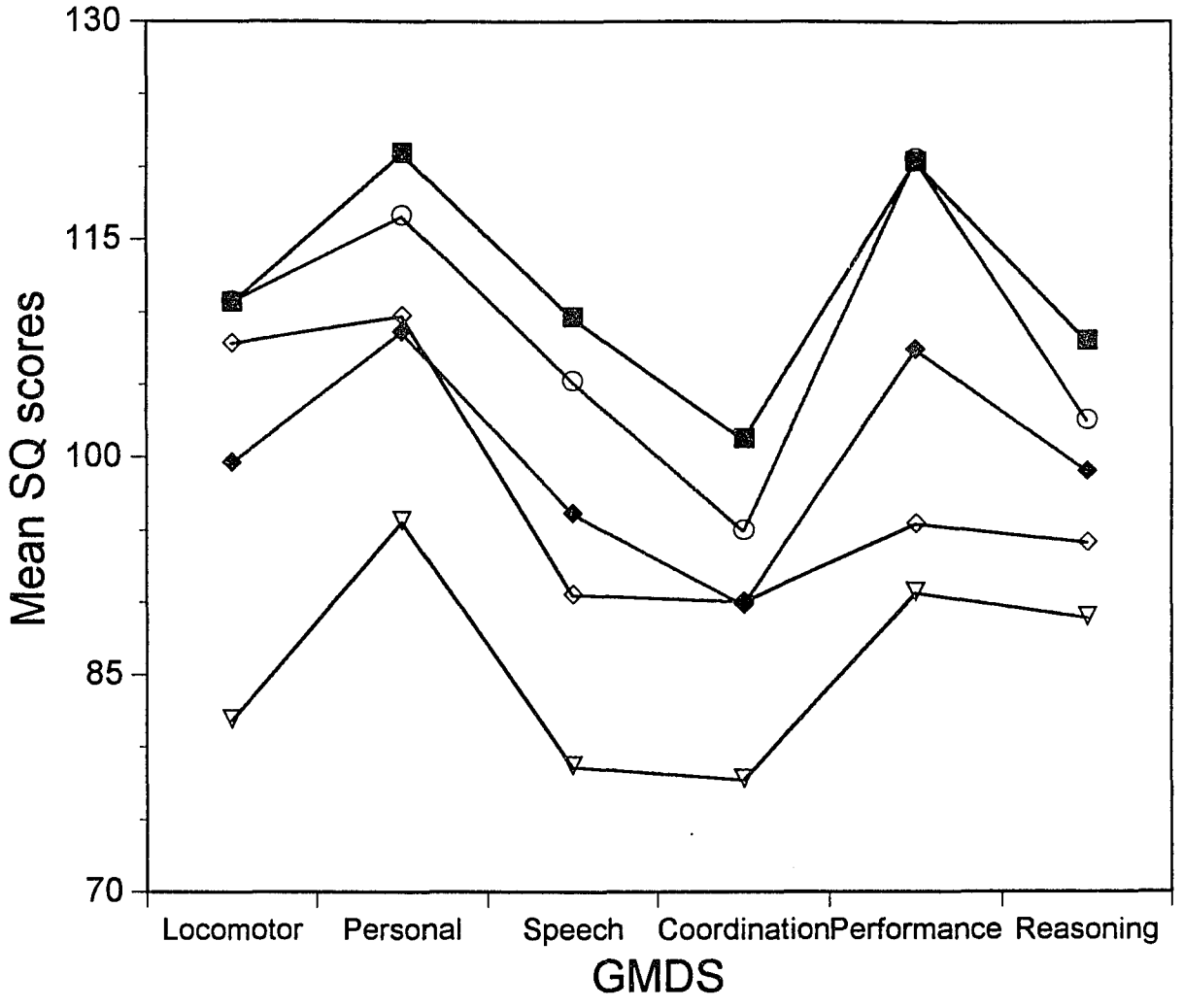
Cognitive Profiles

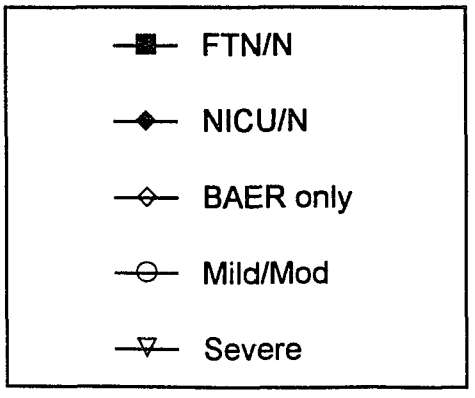
Figure 13 presents a comparison of groups' performances across scales. Overall performance was best in the FTN/N group, followed by a narrow margin by the Mild/Mod group. The Mild/Mod group performed as well as the FTN/N group on the locomotor and performance scales, and lagged minimally behind the FTN/N group on the other scales. The Mild/Mod group differed from the FTN/N group mostly on the Eye-Hand Coordination scale. The NICU/N group had an overall performance pattern that resembled that of the FTN/N and the Mild/Mod groups, though at a somewhat lower performance level. The NICU/N profile was indicative of lowered performance level on scales that involved motor coordination or integration (particularly Locomotor, Hearing & Speech, and Performance). Performance of the NICU/N was similar to that of the BAER-only group on the Personal-Social and Eye-Hand Coordination scales, but better

than the BAER-only group on the Performance, Practical Reasoning and Speech & Hearing scales. The BAER-only group outperformed the NICU/N group on the Locomotor scale. The BAER-only group scored lower on all scales relative to the other risk groups, but was particularly affected in the areas of Hearing & Speech, Eye-Hand Coordination, Performance and Practical Reasoning. Their Locomotor and Personal Social scores were above average. The Severe group showed the greatest deficits in all domains relatively to all other groups, but were less affected in the area of personal-social skills.

Analysis for gender effect on GMDS sub quotients showed that gender had a significant effect only on the Social Personal SQ. Females scored higher than did males ($\underline{M}$ = 119.9, $\underline{M}$ = 107.5, respectively, $\underline{F}$ = 5.9, $\underline{p} < .02$), with gender accounting for 7 % of the variance.

Figure 13. Figure shows the various quotient scores for the different groups.


130
115
100
85
70
Mean SQ scores
Locomotor
Personal
Speech
Coordination
Performance
Reasoning
GMDS


FTN/N
NICU/N
BAER only
Mild/Mod
Severe

Inhibitory Control

RSANT

All of the subjects completed at least two thirds of the 15-stimulus RSANT series. Five children (one from the NICU/N group, one from the BAER-only group, and three children from the Severe group) did not complete the full series of RSANT. All of the children in the FTN/N and the Mild/mod groups completed the task. A value of mean + 1 SD was entered in lieu of the missing completion time data. The analysis of perseverative errors was performed without the data from the five children who did not complete the series.

Completion time.

Table 7 shows Completion time as a function of clinical group. For the purposes of statistical analysis, Completion time values were adjusted by entering Performance SQ and Speech SQ into the multivariate analysis as covariates. The analysis of variance (Table 8) showed that clinical group and Speech SQ factors were significantly affecting performance ($F = 2.6$, $p < .05$ and $F = 3.6$, $P < .06$, respectively), accounting for 44% of the variance. Further analysis indicated that Completion time performance was not related to maternal education ($F = .1$, NS) or to gender ($F = .01$, NS) once group effect was accounted for.

Table 7

RSANT: Completion time and perseverative errors as a function of group

Groups	FTN/N	NICU/N	BAER-only	Mild/Mod	Severe
Completion time (s)					
M	33.3	42.3	42.0	40.3	57.6
SD	8.6	13.9	9.1	12.2	16.2
Range	21-50	28-65	27-55	22-60	43-75
Errors (%)					
M	15.1	13.3	17.8	15.2	38.7
SD	11.0	9.9	14.4	12.5	36.9
Range	0-40	0-27	0- 40	0-33	0-80

Table 8

RSANT: Summary table of ANOVA of completion time on RSANT on CNS groups

Source	SS	df	MS	F-Ratio	p
Groups	1166.6	4	291.6	2.6	.05
Speech	397.1	1	397.1	3.6	.06
Performance	65.8	1	65.8	0.6	.4
Error	4722	54	109.8		

Squared Multiple R = 44%

RSANT: Summary table of ANOVA of perseverative errors on ICR grouping

Source	SS	df	MS	F-Ratio	p
Groups	29.9	1	29.9	5.1	.03
Speech	11.9	1	11.9	2.1	.15
Performance	12.1	1	12.1	2.1	.15
Error	4722	54	109.8		

Squared Multiple R =15%

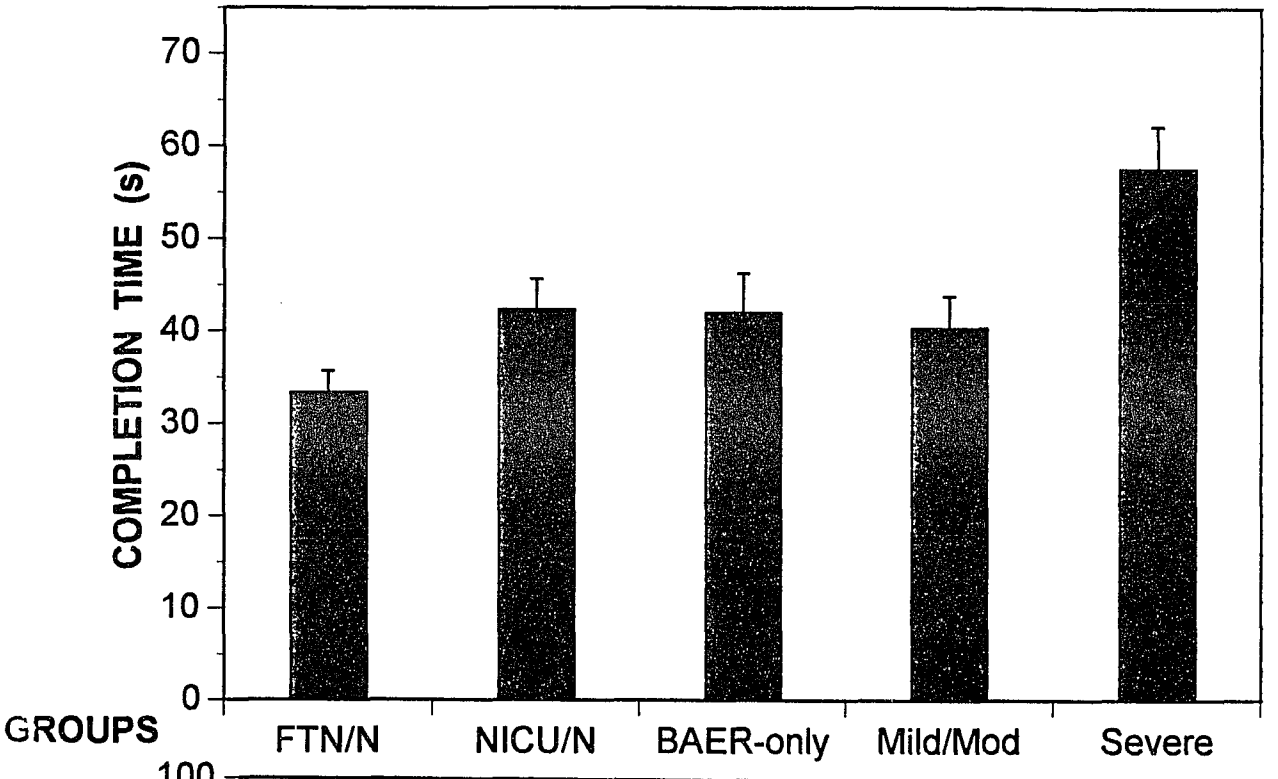
The FTN/N group performed at the fastest rate. The NICU/N group, the BAER-only group and the Mild/Mod group completed the series at a rate which was about 33% slower than that of the FTN/N group (Figure 14). Slowest to complete the series was the Severe group, for whom it took an average of 40% more time than for the mild groups and about 75% more time than for the FTN/N group.

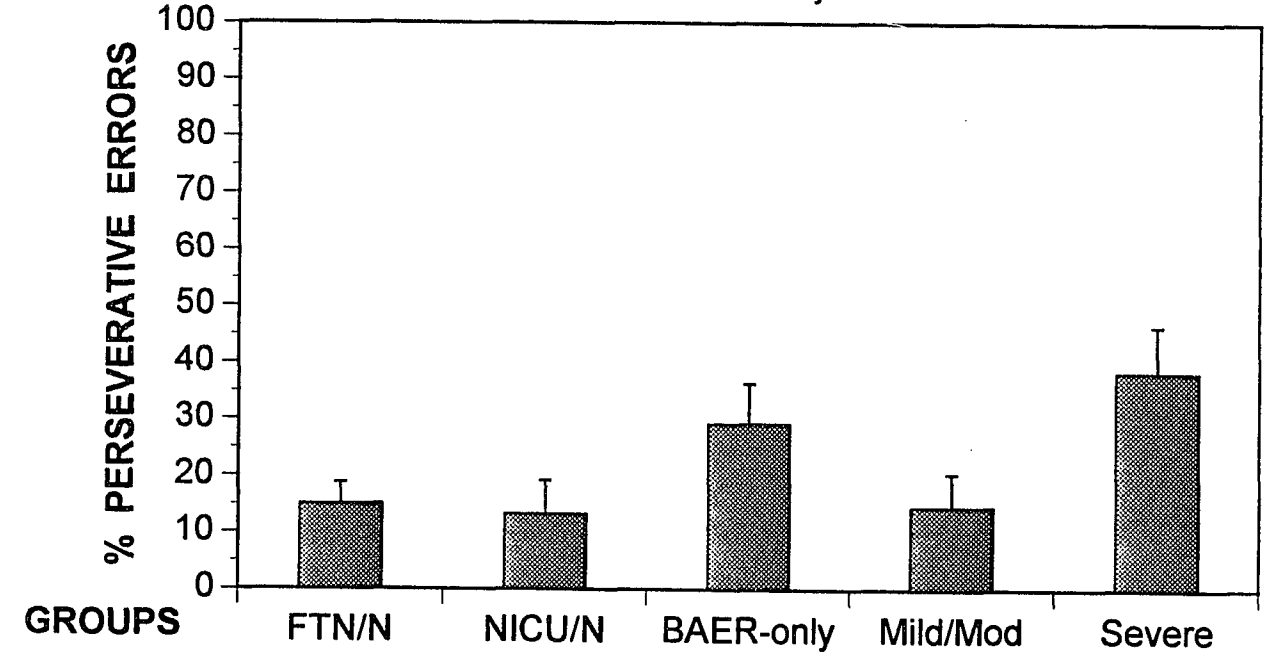
Perseverative behavior.

Table 7 shows the percentage of perseverative errors for all the groups. Since the perseverative behavior was hypothesized to be a marker of poor IC, an analysis of H/L ICR grouping to perseverative behavior was evaluated (Table 8). As was the case for the completion time variable, Hearing & Speech SQ and Performance SQ were included as covariates in the ANOVA in order to determine whether the effect of ICR remained after adjusting the scores for verbal abilities and for ability to perform under time pressure. In fact, neither Hearing & Speech nor Performance SQ affected the perseverative score significantly, while ICR grouping did affect performance ($F = 5.1$, $p < .03$). The three factors (Hearing & Speech SQ, Performance SQ, and Groups) accounted for 15% of the variance. Maternal education effect on errors was not significant ($F = .4$, NS), nor was that of gender ($F = .8$, NS).

Figure 14. Means and standard errors for completion time of RSANT stimulus series as a function of group.

Figure 15. Means and standard errors perseverative errors (in percents) on RSANT stimuli series as a function of group.





n	22	12	9	13	8
Structure (US)	Normal	Normal	Normal	Mild/Mod	Severe
Function (BAER)	Normal	Normal	Abn	Abn/N	Abn/N
Nursery	FTN	NICU	FTN/NICU	NICU	NICU

Comparing the percents of errors made by the various groups (Figure 15), NICU/N made the fewest errors. FTN/N and the Mild/mod group lagged by a narrow margin with a mean of 15% error rate. The BAER-only group made 20% more errors than the FTN/N group or the Mild/Mod group. Most of the clinical group effect is due to the difference between the control and Mild/Mod groups and the Severe group, who made on average more errors than any other group, approximately 150% more errors than the FTN/N group. Most of the subjects in all the groups tended to perseverate to some degree. Even after adjusting the scores for verbal and performance abilities, the H- ICR grouping still made significantly more perseverative errors than other groups. The number of errors were not affected by gender when clinical grouping was treated as a covariate in the analysis of variance (effect of groups $F = 7.0, p < .01$; effect of gender $F = 1.6, p < .2$). The model accounted for 15 % of the variance.

GMT

The results for the GMT are presented in Table 9. Kruskal - Wallis U Test statistical analysis of the clinical groups and the categorical scores '0', '1' and '2' was significant for each of the GMT components (Table 10), indicating that the distribution of the scores was dependent on group.

Table 9

GMT: distribution of scores within groups

Groups	FTN/N	NICU/N	BAER-only	Mild/Mod	Severe	n
GMT components						
Line Formation						
0	0	0	22.3	9.7	50.0	6
1	21.8	27.2	33.7	27.7	50.0	18
2	78.2	72.8	44.0	63.6	0	41
Line Tracing						
0	0	0	6.7	18.2	50.0	9
1	29.1	40.0	33.3	27.3	33.5	21
2	70.8	53.3	33.3	54.5	16.7	35
Dotted Line Formation						
0	0	6.7	22.0	0	33.3	5
1	24.9	46.7	66.7	36.4	50.0	26
2	75.1	46.7	11.1	63.6	16.7	34
Dotted Line Tracing						
0	4.2	26.7	44.4	9.1	50.0	13
1	54.1	53.3	55.5	45.5	50.0	34
2	41.6	20.0	0	45.5	0	18

Table 10:

GMT: Univariate Kruskal-Wallis U Statistics of scores distribution as a function of group (assuming χ^2 distribution with 4 df)

GMT component	Rank Sum	H	Probability
Line formation		18.6	.001
FTN	932.0		
NICU/N	557.0		
BAER only	233.5		
Mild/Mod	365.0		
Severe	57.0		
Line tracing		11.5	.02
FTN	956.0		
NICU/N	509.0		
BAER only	219.0		
Mild/Mod	358.0		
Severe	103.0		
Dotted line formation		17.7	.001
FTN	984.0		
NICU/N	472.0		
BAER only	165.5		
Mild/Mod	413.5		
Severe	110.0		
Dotted line tracing		16.2	.003
FTN	968.0		
NICU/N	441.0		
BAER only	180.5		
Mild/Mod	442.0		
Severe	112.5		

Figures 16-19 show the distribution of the IC categorical scores for each of the GMT components for the different groups. Scores of '2' for the Line formation component predominated performance of the FTN/N, NICU/N and Mild/mod group, while '0' scores were seen in the three impaired groups (BAER-only, Mild/Mod and Severe). The BAER-only group had more type '0' responses and less type '2' responses than the Mild/Mod or the control groups. None of the children in the Severe group performed to criterion on this component; half failed to shift to the GMT, and the other half did not inhibit the motion (Figure 16). Results for the Line tracing component were similar to, though less marked, than those for the Line formation component (Figure 17). Response type frequencies on the Dotted Line component approached most closely the expectations concerning H-ICR grouping performance. All groups, with the exception of the FTN/N group, encountered some degree of control difficulty on this component (Figure 18). Most of those scoring 0 on this condition were either from the BAER-only group or from the Severe group. Most of those with well controlled output were from the FTN/N, NICU/N or the Mild/mod groups.

The Dotted Line tracing component, the most demanding component, posed most difficulty to the BAER-only group who most often scored 0; the FTN/N and the Mild/mod groups scored mostly 1 and 2. Still, regardless of group, 50 percent of the children made an error of either type (Figure 19).

Figure 16. Distribution of GMT scores on the Line formation component as a function of group.

Figure 17. Distribution of GMT scores on the Line tracing component as a function of group.

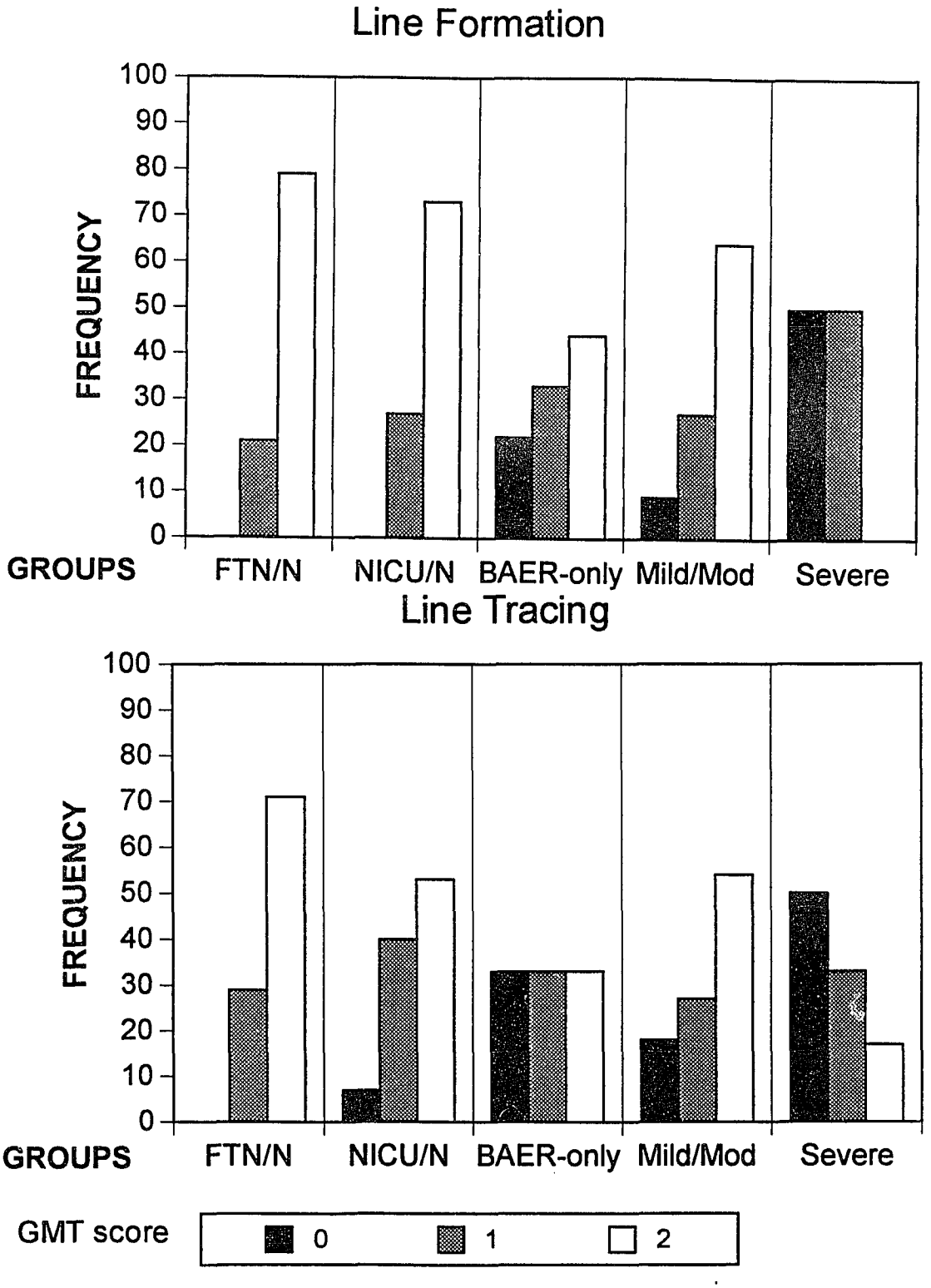
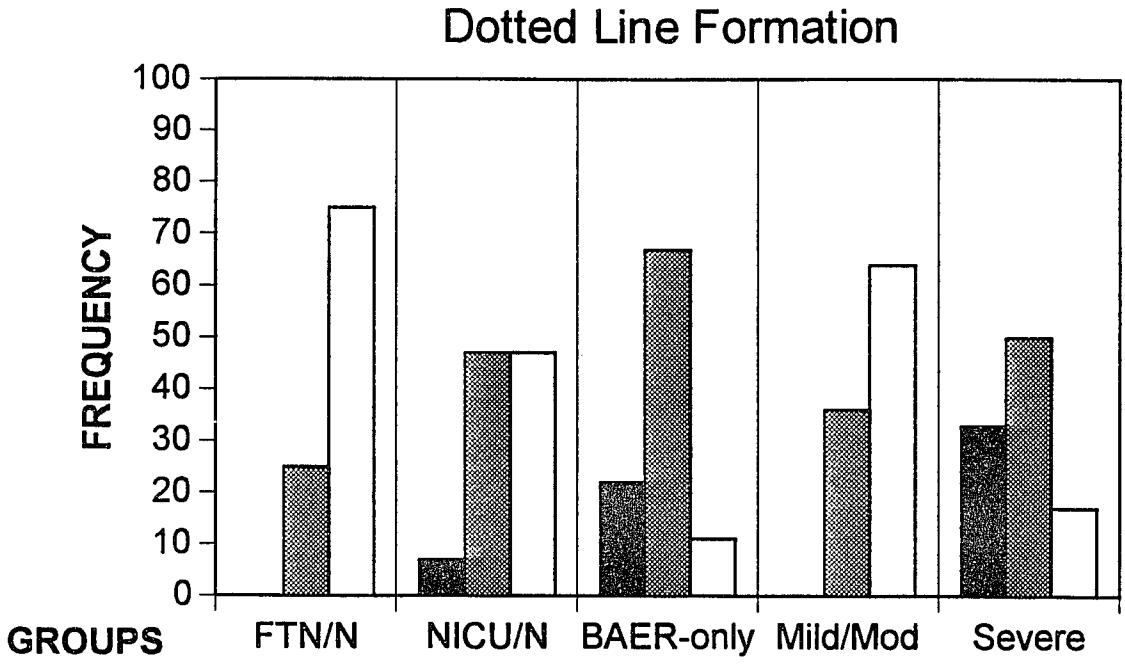
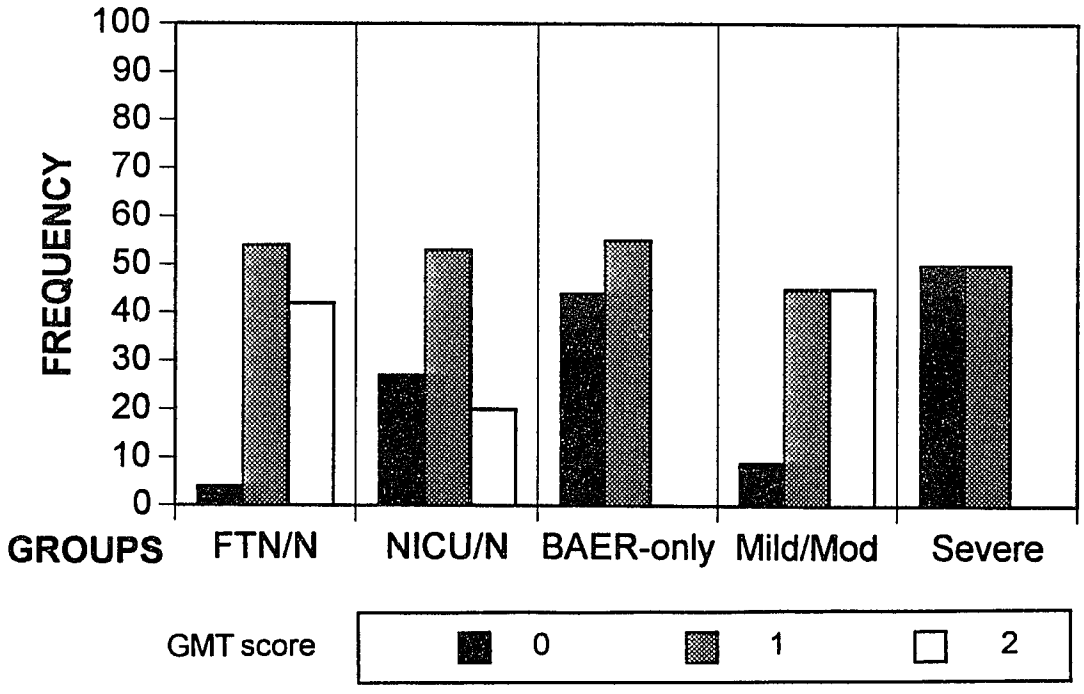

Line Formation
100
90
80
70
60
50
40
30
20
10
0
FREQUENCY
GROUPS
FTN/N
NICU/N
BAER-only
Mild/Mod
Severe
Line Tracing
100
90
80
70
60
50
40
30
20
10
0
FREQUENCY
GROUPS
FTN/N
NICU/N
BAER-only
Mild/Mod
Severe
GMT score
0
1
2

Figure 18. Distribution of GMT scores on the Dotted Line formation component as a function of group.

Figure 19. Distribution of GMT scores on the Dotted Line tracing component as a function of group.


Dotted Line Formation
FREQUENCY
100
90
80
70
60
50
40
30
20
10
0
GROUPS
FTN/N
NICU/N
BAER-only
Mild/Mod
Severe


Dotted Line Tracing
FREQUENCY
100
90
80
70
60
50
40
30
20
10
0
GROUPS
FTN/N
NICU/N
BAER-only
Mild/Mod
Severe
GMT score
0
1
2

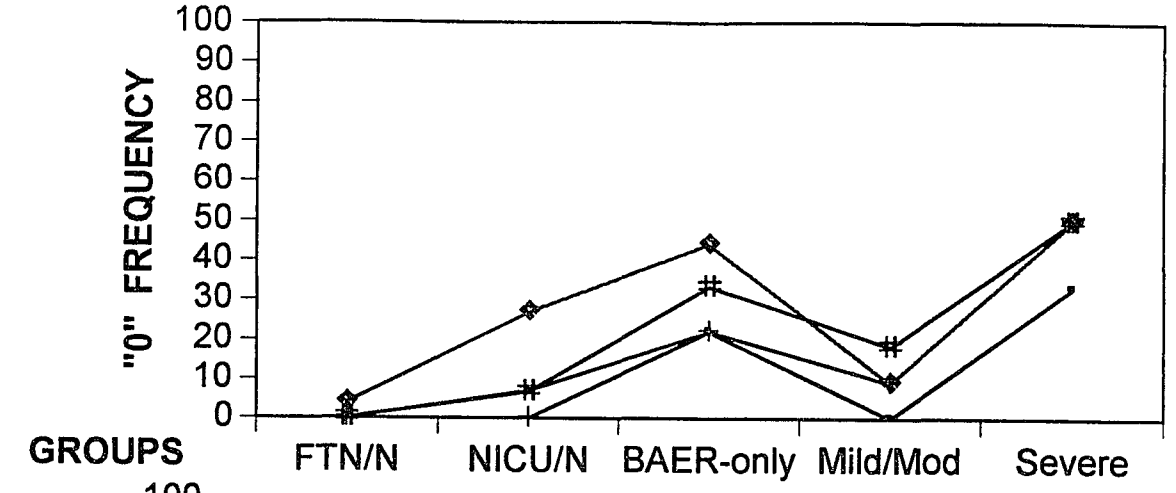
Even though the different components did not appear to impose greater demand on the FTN/N group, analysis showed that GMT components imposed differential demands on the clinical groups, such that the Line components evoked more errors than Dot components ($F = 12.0$, $p < .001$) and Tracing evoked more errors than Forming components ($F = 18.4$, $p < .000$). Tracing a Dotted line was disproportionately more difficult than the other components ($F = 8.0$, $p < .01$). As indicated from Figures 19, 20 and 21, groups' effect for any score did not change significantly as a function of GMT component. The BAER-only group was most similar to the severe group with least occurrence of non-perseverative behavior and most difficulty shifting set. They also showed a greater likelihood of making type 1 error on the Dotted Line Formation condition.

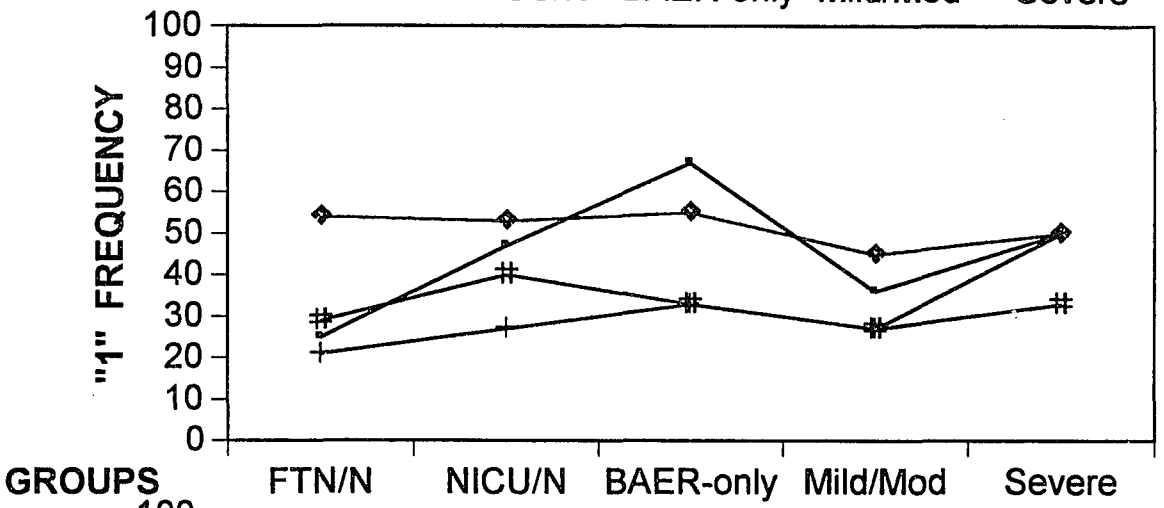
Gender did not affect score type on GMT once the effect of gender on ICR inclusion was acounted for. In order to test the degree of association between gender and the occurrence of error type, the Matel- Haenszel statistic without continuity correction was used (Table 11). The analysis showed that the association between GMT scores and gender, with ICR grouping as a stratification variable, is not significant on any of the three possible behaviors scored.

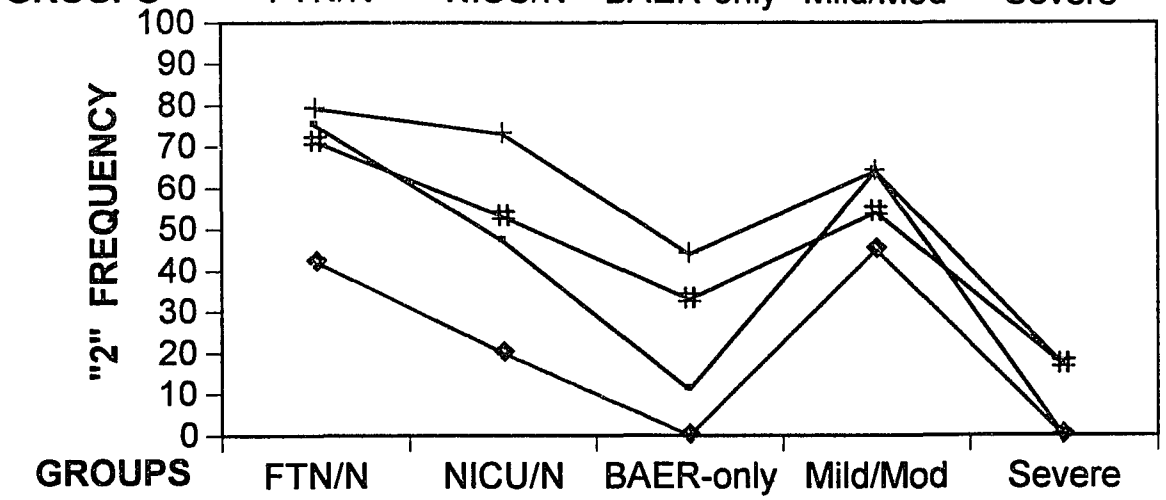
Figure 20. Distribution of '0' score on the four GMT components as a function of group.

Figure 21. Distribution of '1' score on the four GMT components as a function of group.

Figure 22. Distribution of '2' score on the four GMT components as a function of group.







Sructure (US)	Normal	Normal	Normal	Mild/Mod	Severe
Function (BAER)	Normal	Normal	Abn	Abn/N	Abn/N
Nursery	FTN	NICU	FTN/NICU	NICU	NICU

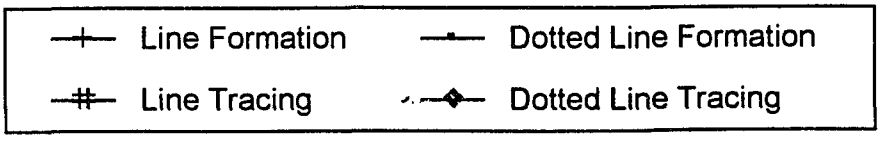


Table 11
Mantel- Haenszel statistic without continuity correction for gender x scores across all components (stratification variable: groups)

Error type	Mantel-Haenszel Chi-Square	p
0	2.4	.1
1	0.9	.4
2	0.1	.7

IV. Discussion

Neonatal neural-compromise affected cognitive development and IC skills at three years predominantly in the predicted manner. Cognitive outcome after mild structural cerebral damage was better than after severe structural damage; BAER abnormalities in the absence of severe US findings were associated with cognitive deficits whereas cerebral damage was not associated with such cognitive deficits, except when the cerebral finding included parenchymal involvement. Finally, IC deficits were associated with BAER malfunction, again in the absence of US findings or with the more severe cerebral involvement.

The FTN/N group, comprised of healthy fullterm children, from the Full Term nursery, had no significant perinatal history of medical problems and showed intact performance. At the time of assignment to this group, normality was assumed for most subject, rather than assessed; there was no neonatal evaluation of neural status with US or BAER. However, the assumption of normality was validated in the course of the study through the behavioral data generated. Inclusion of subjects who were not, in fact, normal could have limited the study's power to reject the null hypothesis. Such a misassignment could have occurred, primarily due to two reasons: undetected crack-cocaine exposure and unknown BAER abnormality. Crack-cocaine exposure could have gone undetected as there was no screening in the Full Term nursery unless there was a

history of maternal drug use. A BAER abnormality could have been missed as BAER screening was not part of the protocol in the Full Term nursery. Hence, there is some risk that differences between the FTN/N control group and the BAER-only group are in fact attenuated. Nevertheless, subjects in the FTN/N group performed better than those in other groups, except for a slight increase in the rate of errors on the RSANT, relative to the NICU/N group, and except for a couple of children who scored below the normal range on the GMDS.

General developmental quotients of the FTN/N group were in the high average range, comparable to those reported using other intelligence tests with non-referred young school aged children[2] without known neural compromising conditions. Performance of the FTN/N group on the IC tasks was in most cases superior to that of the other groups. The children processed information faster and made significantly less errors on both the verbal and the manual tests of IC, verifying that this group indeed was at no greater than normal developmental risk, as predicted by their neonatal status.

The FTN/N group showed some minimal perseverative behavior on both the RSANT and the GMT tasks. This indicates that perseveration at this age is a normal behavior that is elicited under particular testing conditions as suggested by Diamond (1991) and Reason and Mycielska (1982). It appears that, for this age group, the particular tasks used provided such eliciting conditions. The FTN/N group was little

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[2] Kamphaus (1993) meta analysis of WISC-R means, based on Gresham & Reschly (1986), Kaufman & Kaufman (1983), Zins & Barnett (1984) and Rothlisberg (1987) is indicative of similar level of performance

affected by increased demand for motor regulation and their performance on three of the four GMT components was similar with minimal perseveration. However, in the Dotted Line Tracing component, which was the most demanding both in terms of graphomotor ability and in terms of IC, they showed markedly increased perseverative errors. It is probably the case that normal older cohorts would also show perseverative behavior, but only under age appropriate, demanding, conditions.

The NICU/N group was an important control group since it consisted of infants recruited from the NICU as were most of the children in the risk groups. Their mean BW, EGA and Apgar scores, as well as head circumference and crown-heel length, resembled those of the risk groups, thus limiting the weight of these variables as sources for between subjects effects. In addition, unlike the FTN/N group, the assumption of normality was tested in the majority of children in this group; they had normal BAERs and, even in those who were too healthy to warrant US, the risk of structural damage having gone undetected was minimal (about 5%, Karmel et al., 1988).

The NICU/N group, more than any other group, allowed evaluation of the effect of premature birth and its related complications on cognitive and behavioral outcome in the absence of detectable neurostructural or neurofunctional abnormalities. According to Sarnat and Sarnat (1994), the factors predisposing to an adverse long term neurologic outcome relate to postnatal complications, such as ischemic/hypoxic insults, PVLM, IVH, hydrocephalus or meningitis, but not to the maturity of the CNS at the time of birth (provided only that brainstem functions have already developed). Premature infants mature at the same rate as they would in utero had they been carried uneventfully to a

term delivery. Therefore, any dysfunction should be interpreted as resulting from some neonatal complication rather than from prematurity per se.

The NICU/N group diverged somewhat from the original predictions with regard to outcome. Its overall pattern of performance was indicative of some minimal, though significant, difficulty in performing on tasks that involve motor elements (both gross and fine), as evident in the decreased performance of the NICU/N group on locomotor and eye-hand coordination items. This difficulty also impeded performance of this group on the more demanding components of the GMT. In addition a minimal but significant slowed processing was noted on completion time of the RSANT. This pattern of results is consistent with other reports with regard to the effects of transient hypoxia, as evidenced by low Apgar scores at birth, even in the absence of IVH (Amiel- Tison, Cabrol, & Shneider, 1994).

Mild motor weakness, such as was found in the NICU/N group, has been described as an aspect of prematurity and its related symptomatology. Hypoxic events have been shown to affect motor development and regulation of motor output (Vidos, 1987). Hypertonic extremities along with possible signs of hyperexcitability have been described in prematurely born infants in the event of hemodynamic failure, or mild hypoxic-ischemic event, even in the absence of IVH (Amiel-Tison, Cabrol, Schneider, 1994; Gardner et al., 1990). A similar outcome has been described after short term respiratory stress syndrome without hemorrhage (Landry, Fletcher, Denson, 1993), and, it should be noted, this may have accompanied birth in some of the children in the NICU/N group. In fact, comparison of group data in the present study indicated that deficient

locomotor development was related to depressed Apgar scores and also to having IVH, but not to IC risk.

The NICU/N infants who scored within the normal range on the BAER and had no IVH evident on US were not expected to show behavioral deficiencies. Nevertheless, they showed slowed processing, seen on RSANT Completion time, as did the mild risk groups. However, they made less perseverative errors than any other group on this task, supporting a lack of association between transient hypoxia and respiratory distress and the development of IC. It should be noted that the group was heterogenous with regard to a number of metabolic variables related to the conditions that brought about the birth and its related complications. Some of the children had low Apgar scores and/or needed ventilation. A possible mechanism to explain the relationship between depressed Apgar scores and slowed processing was suggested by Pokorny, Langmeier, Trojan and Mares (1987) who, using a rat model, found an association between postnatal hypoxia and the rate of developmental increase in the thickness of the myelin sheaths and in the number of lamellae. These deficits may affect the division and functional maturation of glial elements in a manner that is similar to that associated with other stressors such as malnutrition, thus influencing processing rate.

The Mild/Mod group differed from the NICU/N group in that it was comprised of younger less mature infants, typically born 6 - 10 weeks prematurely. At this stage of development there is greater susceptibility to the development of IVH, without intra parenchymal involvement than is the case in more mature infants.

Some children in the Mild/Moderate group showed diffuse cognitive effects (24%

had DQs below the normal range). In addition, residual specific domains of difficulty were noted for most children, most consistently in the eye-hand coordination domain. Overall, this group showed some minimal but significant slowing in processing, similar to that seen for BAER-only group, as indicated by their longer completion time on the RSANT. This is consistent with reports with regard to other mild brain damaged cohorts (e.g., Bond, 1986, Lezak, 1983; Tromp & Theo, 1991). At the same time, as expected, children in the Mild/Mod group did not show differences in perseverative behavior from that of normal controls on either IC task, indicating a lack of association between perinatal mild/moderate cerebral damage and the development of deficient IC skills.

The overall pattern of results for this group was indicative of a relatively intact outcome with mild difficulty on the Eye -Hand Coordination scale of the GMDS-II and some slowed processing on the RSANT, as was true for the BAER-only group. The performance of the Mild/Mod group on the IC measures was not different from the performance of the control groups. Stewart and Pezzani-Goldsmith (1994) also found that children with uncomplicated periventricular hemorrhage, not marked by periventricular echodensities and with no evidence of dilatation due to cerebrospinal fluid, had no different risk for neuro-developmental disabilities than did children with normal US scans.

An association between high biological vulnerability and low cognitive performance has consistently been reported over the last decades (Field, Dempsey, & Shuman, 1979; Hunt & Cooper, 1989; Landry, Fletcher & Denson, 1993; Landry, Fletcher, Zarling, Chapieski, & Francis, 1984; Liaw & Brooks - Gunn 1993; Meisels,

Plunkett, Pasick, Stiefel, Roloff, 1978, Stewart & Pezzani-Goldsmith, 1994). Severe injury, involving cerebral areas and possibly deep areas of the CNS, may combine a number of pathogenic processes that are devastating both in terms of overall performance and in terms of effects on individual systems.

The Severe group, which was assumed to have CNS pathology involving both cerebral and infra-cerebral levels, indeed showed deficits relative to other risk groups in all the domains tested; cognitive development was lowered in all areas, processing was markedly slowed and perseverative behavior was noted on both the verbal and manual motor regulation tasks, indicating IC deficits.

Children in the Severe group showed the slowest processing rate and most evidence of IC deficits, seen on the perseverative errors measure, relative to other groups. In addition it was noted that, of the five children who did not finish the RSANT series, three were from the Severe group, which is even more significant since it represents 38% of the group. Failure to complete the series may represent a particular difficulty in itself, as it probably reflects impersistence. Thus, impersistence (premature termination of an on-going activity) was seen most often in the same group in which perseverative behavior (delayed termination of an on-going activity) was seen, suggesting that each of the two behaviors may be the aftermath of the same pathogenic process.

The Severe group showed more difficulties than the other groups on the GMT, by making the most type '0' and type '1' errors on the least demanding (Line Formation) as well as the more demanding components. With regard to verbal perseverative errors, these were found most often in the Severe group, and with a lesser frequency in the

BAER-only group. The H-ICR group as a whole demonstrated its IC deficiency by having difficulty shifting rapidly from one stimulus to another, even after taking into consideration its overall slowed performance.

In view of the major CNS damage, the early age at which it was incurred and the relatively long period during which survival was threatened for many subjects in the severe group, these finding were expected and are in accordance with other studies concerning long term effects of severe brain damage on mental development (Caputo et al 1981; Hunt, 1981; Kamphaus, 1993; Sostek, 1982, Stewart & Pezzani-Goldsmith, 1994).

Overall cognitive performance of the BAER-only group was within normal limits, with intact Locomotor and Personal-social SQs, which were similar to those of the FTN/N group. However, relatively low performance was noted in Hearing and Speech, Eye-Hand Coordination, Performance and Practical-Reasoning SQs. This pattern of deficits, which were similar to, but of lesser magnitude than those of the Severe group, suggests that damage in low levels of the CNS, reflected by neonatal neurofunctional abnormalities, affects performance in many domains that are generally thought to necessitate cortical involvement. These domains include verbal skills, which may also be affected directly by the involvement of the central auditory pathway (Danto, Heiweil, Risucci, & Wilson, 1987).

The BAER-only group showed slowed processing time that was similar to that of the other mild risk group. However, perseverative behavior, indicative of deficient IC, was more marked for these children than that noted for children in the other mild risk group, indicating a specific deficiency in this domain. Children in the BAER-only group,

who were hypothesized to have had core pathology at infra-cerebral levels of the CNS, also showed difficulties on a greater number of cognitive functions relative to the Mild/Mod group, whose pathology was in cerebral areas. In the BAER-only group, difficulties were found in speech, language and practical reasoning, as well as on eye-hand coordination and visuo-spatial construction tasks. As locomotor scores were well within normal limits, deficits seen in these tasks probably do not reflect motor difficulty per se, but rather a disability in regulating output.

The combination of deficits shown by the BAER-only children including problems with verbal skills, eye-hand coordination perseveration etc., are reminiscent of the pattern of symptoms suggested by Greenspan (1979) to be reflecting "poor internalization of behavior organization." However, it should be noted that BAER-only children did not display problems on the Personal-Social scale, contrary to what would be predicted by Greenspan's view.

The finding of lower developmental quotients in the Severe and the BAER-only groups raises a question concerning a possible association between the severity of brainstem involvement, as measured by BAER's major components, and DQ. Indeed, the groups that were at high risk for IC deficits had the most abnormal BAER component latencies, as well as relatively low DQs; additionally, longer I-V intervals were associated with lower DQs. While the timing of BAER components is inversely correlated with DQ, this is not necessarily a causal relationship.

In addition to showing cognitive deficits, the BAER-only group showed, as expected, more IC deficits than did the other mild risk group, the Mild/Mod group. The

BAER-only group made more perseverative errors than did the NICU/N group or the Mild/Mod group on the RSANT, even though it took both mild-risk groups about the same time to complete the series; both mild-risk groups were equally and minimally affected with regard to processing rate.

IC deficits of the BAER-only group were also evident on the GMT. On all GMT components, they showed more difficulties in shifting to a new component of motion, making consistently more type '0' errors than did the Mild/Mod and the NICU/N groups. In addition, the BAER-only group made type '1' errors more often than did these groups, evident only on the GMT core component (the Dotted Line Formation). For the other three GMT components, there was no difference in frequency of making type '1' errors between the BAER-only, Mild/Mod and the NICU/N groups. Their probability of making this type of error increased with increased graphomotor-IC demand (30% on Line Formation, 30% - 40% on Line Tracing, and 50% on Dotted Line Tracing). This trend for the BAER-only, Mild/Mod and the NICU/N groups may indicate that the tendency to make type '1' errors is sensitive to minor neural compromise, but lacks the specificity to discriminate among different injury types. It may be a result of the high demand for control in these tasks, as reflected in the relatively high rate of type '1' error in the most demanding component (Dotted Line Tracing), even for the FTN/N group.

As expected, type '0' error rate did differentiate the BAER-only group from the other risk and control groups, as did the Perseverative Errors measure of the RSANT. Hence, the BAER-only group showed a specific shifting difficulty, which was evident both graphomotorically and verbally, and is indicative of a deficiency in IC ability that is

independent of output modality. This did not characterize the other mild risk group or the control groups.

In considering the effectiveness of the various outcome measures, it was apparent that, while the different diagnostic groups showed a differential pattern of strengths and weaknesses on most outcome measures, they all showed relative strength on the Personal-Social scale of the GMDS-II. Performance on the Personal-Social scale, indicating self-knowledge, may be accompanied for some individuals by an internalized conceptualization of self identity, while for others it may represent general knowledge about the world. This latter would be expected to be related to mental development. The scale items and mode of administration did not distinguish between the two. Assuming that the scale represents primarily general knowledge, then it would be expected to be lowered by brain damage, but to be relatively independent of type of damage. Indeed this scale was less affected than others by damage to the CNS. Either the scale is not sensitive to the relevant CNS damage, or, alternatively, personal-social functioning is particularly amenable to cultural /environmental factors, which by three years of age have attenuated the deficits. This latter interpretation is partly supported by the fact that this scale was also the only scale for which a gender effect was shown.

In contrast to scores on the Personal-Social scale, the RSANT Completion time measure proved to be highly sensitive to any degree of CNS risk. It was not only affected by known CNS risk, such as by any grade of IVH or by BAER abnormality, but was also affected in the NICU/N group, indicative of an association between even small degrees of neural compromise and processing speed.

The overall pattern of results supported the primary hypothesis of the study that early maturational processes in the brainstem provide limited plasticity to overcome pathogenic processes. Thus, brainstem malfunction in the perinatal period results not only in the development of IC deficiencies, but also in compromise in a number of functions that are thought to involve cortical structures.

It is suggested that BAER abnormality may, in fact, result from either or both of two processes: it may result from primary insult to brainstem structures, or it may be secondary to cerebral damage. In the first case, widespread cognitive sequelae would be anticipated, on the basis of early interference with ascending pathways. In the second case, the BAER abnormality probably reflects temporary phenomena, such as edema or pressure, which may alter feedback mechanisms, but should result in less wide spread cognitive effects.

In fact, in the group in which primary brainstem involvement was hypothesized (BAER-only), deficits were noted in a number of cognitive domains and perseverative behavior was marked. In groups in which mild or moderate cerebral damage coexisted with BAER abnormality, they were discrete, rather than pervasive, cognitive difficulties and no IC deficits.

Conclusions based on the results of this study must be tempered by a number of considerations. First, and most important, birth weight was not equivalent between groups. VLBW infants were more likely to be in the severe group. Further, neonates in the NICU/N were more mature than neonates in the mild risk groups. However, a wide distribution of neonatal measures characterized the data set in all the clinical groups.

Prematurity by itself did not necessarily determine the manner, degree and level at which the CNS would be affected. VLBW children, as well as full-term children, were found in all risk groups. Still, the phenomenon seen in other studies, whereby prematurity, estimated by BW and EGA, constitutes a risk factor, was partially supported by the finding that greater prematurity was related to greater likelihood of depressed Apgar scores at birth, to having IVH and to developing IVH of a greater Grade, but did not mediate poorer outcome directly.

An important comparison between the two mild risk groups, the Mild/Mod group, with structural cerebral damage, and the BAER-only group, without cerebral structural damage, showed that the group means for the neonatal demographic measures did not differ, although there was greater variability in the BAER-only group. Similarly, subject variables cannot account for significant differences on outcome measures seen between these three groups. Similar findings, based on groups with disabilities and groups with normal or suspected disabilities, have been reported in retrospective studies (Field, Dempsey, & Shuman, 1981; Hunt, 1981; Lane, Attanasio, & Huselid, submitted, 1995; Sameroff, 1981).

A consideration that applies particularly to the Mild/Mod group concerns the possible unequal influence of demographic variables. In the Mild/Mod group most of the subjects were female and maternal education was, on average, higher than for the other risk groups. Both factors have been shown to be related to recovery after neonatal damage, especially when the damage is mild or moderate rather than severe.

With regard to gender, males have been described as having more IC related

symptomatology than do females (e.g., in ADHD cohorts). DSM-IV reports a prevalence ratio of at least 4:1 males to females (depending on cohort's inclusion criteria). Since the clinical groups that comprised the H-ICR group were selected on the basis of an a priori hypothesis that their particular neural compromise would result in IC deficits, the finding that males were 2.4 times more likely than females to be in the H-ICR group is of interest. This might indicate that it is a differential susceptibility between the genders to specific types of CNS damage that mediates the differential susceptibility to conditions characterized by problems with IC.

As far as response to neonatal CNS injury is concerned, a number of studies have indicated a differential recovery rate for the two genders, favoring females (e.g. Goldman-Rakic, 1987; Fitch, Tallal, Brown & Rosen; 1994). This, it has been suggested, may be due to differential hormonal mechanisms of recovery for the two genders (Toran-Allerand, 1986), and/or to gender differences in CNS organization (deLacosta & Horvath, 1991; Goldman-Rakic,1987). The present study did not reveal a gender difference in performance on any of the outcome measures, other than on the Personal-Social scale of the GMDS, once gender prevalence between groups was taken into account. Performance on the Personal-Social Scale was higher for females than for males. It is possible, of course, that gender related differences would emerge at later ages, when cortical projections have further matured, since data concerning different recovery courses for males and females relate particularly to differential cortical functioning (Goldman- Rakic, 1987).

Regarding other factors that may affect recovery, Caputo, Goldstein, and Taub

(1981), Elardo, Bradley, and Caldwell (1975), and Sameroff (1981) all reported that variables, such as parenting skills and child rearing approaches, financial, social and emotional support, medical status after discharge, and nutrition, affected outcome after any form of neonatal medical risk. On the other hand, more recent studies by Korner et al. (1993) and McCarton, Vaughan and Golden (1988) reported that, for at risk infants, factors such as early intervention, maternal education and race had less bearing than did neonatal neurological status on outcome at two years, particularly with significant neonatal risk conditions. In the present study, level of maternal education did not appear to influence either the nature of the neonatal insult, as indexed by the diagnostic categorization of the subjects, or the study's outcome measures.

The apparent discrepancy between the present study, that of Korner et al., and the latter authors might be explained on the basis of a possible interaction between biological risk and external factors (Bendersky and Lewis, 1994). They reported an interaction of family risk indicator and IVH severity in the mild but not in Severe group cases. Due to lack of family risk indicators and limited cell size, this association could not be directly addressed in the present study.

While the Mild/Mod group outperformed the Severe group, it is possible that differences should not be explained solely on the basis of degree of damage, as outcome may have been modified by the levels of maternal education and of intervention. Children in the risk groups in this study were evaluated every three months, and at each visit the caretakers were given an opportunity to express their concerns about their child and about child rearing issues and received specific feedback concerning strengths,

weaknesses and domains that needed special care. In addition, and depending on performance, children were referred for specialized therapy such as physical, occupational or speech therapy. Thus, some of the children, particularly in the Severe group received more frequent intervention than was the case for children in other groups.

It might have been anticipated that more educated mothers would utilize information provided about their children more productively than would be the case for less educated mothers, thus dispropotionately benefitting their children. This effect would be expected particularly in the Severe group, who received the most frequent feedback. Unfortunately, this interaction could not be addressed specifically because there was a lower overall maternal educational level for the Severe group as opposed to the Mild/Mod group.

Maternal age in the present study fell between 16 and 38 years. Post hoc analysis showed that children of the youngest mothers (< 20) and oldest mothers (> 35) performed at a lower level than children whose mothers were 20 to 35 years old. Such an association between maternal age and neonatal risk has been reported previously. Caputo et al (1981) found an association between very young maternal age (<16 years) or very old maternal age (>40) and developmental abnormalities, such as cerebral palsy, epilepsy, intellectual deficits, behavioral disorders, learning disabilities, visual and hearing disorders, and emotional problems. Similarly, Amiel-Tison et al (1994) suggested that the optimal maternal age, from the point of view of neonatal health, is between 20-40 years of age. The mechanisms involved are assumed to be complex, since they may operate both prenatally as well as postnatally, and not necessarily in the same direction

for both tails of the distribution.

The cognitive and behavioral outcome patterns found in the study are suggestive of three neuroanatomical substrates whose involvement may underlie the behavioral deficits seen after primary brainstem damage. First, a possible pathway for the influence of brainstem structures on inhibitory control behaviors would be the dopaminergic system of the striatum with its connections to brainstem nuclei and particularly to the substantia nigra, the subthalamic nucleus and to portions of the ventral tier thalamic nuclei. This system influences motor activity by way of thalamic neurons that project on regions of the frontal cortex (Diamond, 1991, 1993; Guyton, 1991). Nuclear subdivisions of the thalamus receiving these outputs from the globus pallidus and the substantia nigra do not exert their major effects on the primary motor cortex (which could explain the intact locomotor performance of the BAER-only children). The outputs project to the premotor and the supplementary motor areas. A further possible involvement is that of neonatal abnormalities in the reticular activating system and its limbic-frontal projections, which have been thought to be involved in some forms of ADD (e.g., Kløve, 1987). A third possibility is that of serotonergic involvement, which has projections to the reticular activating system and the limbic system and has been implicated in populations with symptoms of impulsivity.

Pappius and Wolfe (1986) have suggested a working hypothesis concerning the neurochemical sequelae of brain damage, such as that caused by ischemia, hypoxemia, toxins, infections, degenerative disease and trauma, and their role in functional disturbances. They argued that changes in synaptic transmission, as evaluated by means

such as evoked potentials, result from brain lesions that affect the release of arachidonic acid and catecholamines, which in turn affect the release of prostaglandin thromboxanes. These substances later affect the release of serotonin and alter Ca^{++} distribution to cause functional depression of the pathway. This may impact on processes, such as cell migration, dendritic arborization and myelination processes that are hypothesized to cause long term deficiencies in the system involved, but would not be seen by structural imagery techniques. These alterations, one could speculate, might result in behavioral dysfunctions.

With regard to specificity, Hinton (1994) suggested that mild forms of other developmental pathoneurogenic processes have similar behavioral profiles to those of the BAER-only group, particularly with regard to attention difficulties and a tendency for perseverative behavior and visuo-spatial difficulties. In individuals with mild forms of PKU, neurofibromatosis-1 or Turner's syndrome, and unaffected female carriers of Fragile X, all seem to show similar neuropsychological profiles, which may or may not reflect a similar pathogenic process.

The pattern of results seen in this study shows that neonatal neural compromise affects general development and IC skills measured at three years, depending on the level and the magnitude of the damage. The dissociation between developmental outcome from a primarily cerebral locus of damage vs a primarily brainstem malfunction, is indicative of the significant role the lower levels of the CNS play in determining cognitive outcome. Involvement of lower levels of the CNS, more typical in males than females, was found to affect development of both general cognitive abilities and IC skills.

Involvement of cerebral areas resulted in only discrete cognitive effects.

There was a double dissociation between locomotor development and inhibition of motor output, in the NICU/N and BAER-only groups. This supports the idea of an association between neonatal brainstem abnormality, cortical involvement based on a brainstem/striatal/prefrontal pathway, and the development of cognitive dysfunctions. Mild verbal and coordination difficulties in the BAER-only group further support the idea of cortical involvement. These findings suggest that assessment of function of brainstem levels of the CNS using markers such as a BAER abnormality in the context of other information contributes to understanding the origins of different neuropsychological developmental trajectories in young children after neonatal neural compromise.

Appendices

Appendix A

Cranial US procedure

Available for purposes of the study from Karmel and Gardner. US procedure was adapted from Gardner, Karmel, Magnano, Norton & Brown (1990). Each Cranial US was performed at the infant's bedside on the NICU or Full term nursery under clinical protocols approved by the Hospital's Institutional Review Board. A portable real-time sector scanner (Diasonic, Inc., model DRF-100) with a 6 MHz transducer was used to image the brain through the anterior fontanelle. Hard copies of coronal and sagittal views were stored on film and served as clinical records. Video-tapes of the dynamic US images were made . US interpretations were taken from the record and reviewed as to the accuracy of diagnosis. Findings were interpreted for signs of structural abnormalities. Subependymal hemorrhage was diagnosed only if abnormal increased echogenicity was seen in the region of the germinal groove - the junction between the head of the caudate nucleus and the body of the thalamus - on both coronal and sagittal views. Intraventricular extension of hemorrhage was considered if the choroid was abnormally irregular in contour or if echogenic material was present within the ventricular system in locations in which normal choroid does not occur (e.g., the occipital horns). The lateral ventricular size was measured on sagittal views at the germinal groove. IVH were graded according to Papile et al. (1978). Hyperechoic PVLM was diagnosed if irregular areas of increased echoes were seen in the parenchyma surrounding but not immediately adjacent to the ventricular system.

Cystic leukomalacia was defined as discrete lucencies within the parenchyma that did not communicate with the ventricles. Porencephaly was considered as cystic areas of brain parenchyma that communicated freely with the ventricles. Cerebral edema was defined by a complex of findings: effacement of normal gyral markings adjusted to the infant's EGA, slit-like ventricles, and/ or depression of one or both of the sylvian fissures. Parenchymal hemorrhage was diagnosed as areas of increased echogenicity either extending from ventricular hemorrhage or within the parenchyma remote from the periventicular mantle.

All films and tapes were judged by 2 independent readers. All discrepancies, when occurred, were mediated between them.

Appendix B:

BAER procedure

BAER studies were performed by Karmel & Gardner within the first week of life at least 24 hr after birth, except for infants born younger than 30 - 31 weeks EGA whose evaluation was postponed at times until the infant was stabilized. BAER procedure was adapted from Karmel, Gardner, Zappulla, Magnano, & Brown (1988). Each BAER was performed at the infant's bedside on the St Vincent's NICU or Full term nursery under clinical protocols approved by the Hospital's Institutional Review Board. Auditory stimuli were presented through a miniature earphone (Sony MDK-44) mounted with cotton-backing in a standard nursery nipple. The nipple was taped over the external auditory canal to form an acoustic chamber. This apparatus allowed testing of even the smallest infants in all circumstances in the NICU (including while intubated or in an oxygen head box) without having to manipulate the infant during testing.

Stimuli were presented at 10.1 Hz and consistent of 100 μsec square wave monaural clicks 75 dB above adult nHL. This level is estimated to be equivalent to 90 dB SPL to the infant. Intensity levels were estimated neurophysically by matching the click intensity generated by the equipment and earphones with those obtained from a Nicolet stimulus generator Model 1007A and TDH-39P earphones. The particular rate and intensity were selected on the basis that they provide the most reliable identification of major component latencies (Wave I, III, & V) and inter-peak latencies

(IPL)s.

One channel of brain electrical activity was recorded ipsilateral to the side of the click stimulation, typically the left ear. One electrode (active) was placed in the midline immediately behind the anterior fontanelle. The other (referent) was attached to the mastoid behind the stimulated ear. The forehead was used for placement of a third electrode (ground). Responses were filtered between 100 Hz (-6 dB) and 3000 Hz (-12 dB). Data were digitized at 50 μsec intervals for 10 *m*sec (200 points) and averaged to produce the BAER wave form. The peak-to-peak voltage level was used to establish an artifact- rejection algorithm.

Each BAER wave form represented 1024 artifact-free trials. A composite wave form consisting of the average of three wave forms was used to identify component latencies of all major positive components. Waves I, III and V were identified by visual inspection in the 90 dB recording, whenever possible. When not possible, additional recordings were made at 85 or 80 dB SPL to observe whether the expected shifts toward longer component latencies at the lower intensity were present.

An independent study of the reliability of BAER by testing both A) Test-retest reliability and B) inter-scorer reliability, with an independent sample (n=62) of children born in 1990 was conducted.

A). 12 infants were randomly selected from the recruited sample of infants. Each infant was tested three times with no delay between tests. Each wave form was independently scored, and Pearson product moment correlation was then computed.

All correlations of the major variables within each subject were highly significant ($p < 0.001$):

Pearson r for Wave I	0.93 - 0.95	IPL I - III	0.92 - 1.0
Wave III	0.93 - 0.96	IPL III - V	0.94 - 1.0
Wave V	0.75 - 0.98	IPL I - V	0.89 - 1.0
		D score	0.89 - 0.98

B) Inter-scorer reliability was evaluated, using two independent judges, as well as computerized scores (D scores, validated on an independent sample: y = 4.87 (Wave I latency) + 2.07 (Wave III-V latency interval) - 0.82 (Wave I-III latency interval)-11.21). All three (judges and computer) were blind to any identifying variables about the infant, except for EGA (known to affect the IPL I - III in a typical manner) and post conceptual age (to allow differential considerations of minor abnormalities that are resolving gradually postpartum). The sample consisted of 34 observations drawn at random. Correlation between the independent judges was found to be 0.94. The correlation of the scorers with the computerized score was 0.82 and 0.70. All three correlations were highly significant ($F = 24$, $p < .0001$).

Appendix C

Informed consent form

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Developmental Followup Study of Toddlers

You are being asked to provide consent for your child to participate in a research study. The way in which children react to their surrounding is important for their learning about the world. During development children regain more control in interacting with objects and people in their environment. They also learn to inhibit acting impulsively, and to plan ahead. The purpose of this study is to find why do some children can control their activity and attention more efficiently than others, and to find out if these abilities have anything to do with being born healthy at term, with being born early, or with having difficulties at birth. Since your child has been participating in the Arousal and Attention study of Judith M. Gardner, Ph. D. we will be able compare their behavior as a baby with his/ her behavior now as a child.

When your child is between the ages of 2 and 3 years old, we will observe them while playing with toys. For example, building a tower with cubes, scribbling, swinging and naming pictures. We will look at their motor coordination, cognitive development and attention. All the tasks are designed to be enjoyable and safe for the children. Parts of the sessions would be videotaped for later scoring.

Approximately 200 children are expected to be studied under this protocol. There will be no costs incurred as a consequence of participation, and there will be a $25 reimbursement to cover travel expenses.

Information from these tests, along with the information in the child's birth record will be examined in order to analyze and publish the data from all children. The information will be kept confidential, and necessary steps will be taken to safeguard and protect privacy against public disclosure. All procedures are non-invasive and do not involve any foreseeable risks or discomforts. There is no direct benefit from the tests, which are designed to evaluate some contributing factors to the child's behavior and cognitive capacities. If unusual or clinically significant behavior is observed, the child's parents will be informed.

The activities of this research program are under the supervision of Judith M. Gardner, Ph.D and her associates. If you have any questions at any time about this study or your rights as a participant in it, please contact Dr. Judith M. Gardner at telephone number (718) 494 5178.

Participation in this study is voluntary. Refusal to participate will involve no penalty or loss of benefits to which the child is otherwise entitled. Permission can be withdrawn at any time and for any reason.

I understand the above and grant this consent as a voluntary contribution in the interest of research:

(Signature of Parent) (Date)

(Print Name of Parent) (Telephone)

(Address - Number and Street)

(City, State, and Zip Code)

I have fully explained the above including any risks or benefits, and believe the volunteer understands the nature and purposes of the study. I also have offered to answer any questions relating to the study and have fully and completely answered all such questions:

(Signature of Investigator) (Date)

(Print Name of Investigator)

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