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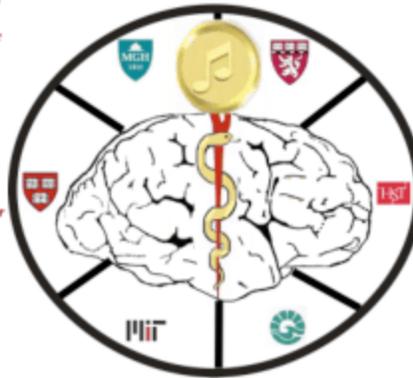
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The Jeffrey Epstein Project for Brain Development in Critically-Ill Infants

Effects of Early Auditory Enrichment on Language Acquisition and Cognitive Development in Critically-Ill Premature Infants

Contact:

Mark Jude Tramo, MD PhD

Executive Board, The Institute for Music & Brain Science



PROPOSAL FOR THE JEFFREY EPSTEIN FOUNDATION

Project Title: *The Jeffrey Epstein Project for Infant Brain Development: Effects of Early Auditory Enrichment on Language Acquisition and Cognitive Development in Critically-Ill Premature Infants*

Principal investigator: Mark Jude Tramo MD PhD

Co-Investigators: Nicholas T. Zervas MD, Jonathan Cronin MD, Margaret Settle RN MSc, Stella Kourembanas MD

Institution: The Institute for Music & Brain Science



Total Budget:	\$502,080	Length of study:	2 years
# of Subjects:	300	Age of Subjects:	24-60 wks gestational age at enrollment 1-60 months at long-term follow-up

Objectives

The Jeffrey Epstein Project for Infant Brain Development undertakes a multi-center, prospective, randomized-controlled clinical trial investigating the effects of auditory enrichment on neurophysiological, behavioral, immunological, and endocrinological endpoints in Neonatal ICU patients. A unique, multi-disciplinary team of clinicians, neuroscientists, engineers, and musicians affiliated with The Institute for Music & Brain Science will combine expertise in perinatology, cortical physiology, cognitive psychology, and music composition and production in order to achieve the following goals:

- Quantify and objectify the benefits of non-pharmacological treatment — controlled auditory stimulation (e.g., vocal music during painful procedures; Tramo et al. 2006, Appendix) — on pain, stress, morbidity, mortality, and cost during the infants' NICU stay, and on morbidity and cognitive development during the first 2 years of life.
- Conduct this initial trial with sufficient rigor and power to publish its results in high-impact, peer-reviewed medical journals [e.g., *Journal of the American Medical Association*, Appendix] and qualify for funding of a large, multi-center clinical trial.

- Ultimately, translate our results into standardized protocols that will be implemented nationally and internationally in order to improve brain development and the achievement of cognitive milestones for millions of at-risk infants in future decades.

Working Hypotheses

Enrichment of the Neonatal ICU sound environment will:

- Decrease stress-related behaviors (e.g., startle, posturing, crying)
- Accelerate weight gain
- Decrease the number and duration of cardiopulmonary alarms, endotracheal suctioning, oxygen treatment, or pharmacologic treatment
- Decrease high levels of circulating cortisol, a potential neurotoxin, that are evoked by pain and stress
- Promote immunocompetence
- Decrease ICU mortality (e.g., via cardiopulmonary events or infection)
- Decrease the magnitude of physiological changes associated with acute pain caused by medically-necessary diagnostic and therapeutic procedures
- Decrease the length and cost of ICU/SCU stays
- Decrease the number, length, and cost of the post-ICU/SCU hospital stays and outpatient follow-up
- Decrease the severity and incidence of developmental brain abnormalities associated with developmental delays or chronic impairments in linguistic, social, and emotional functioning at ≤ 2 year follow-up

Background & Preliminary Results

When the life of a premature infant is saved by admitting her/him into an isolette in a Neonatal ICU, she can't see, move around, feel herself move, feel anyone touch or hold her, taste or smell her mother or mother's milk, but she can hear quite well. Her ears have already been hearing the reliable, steady, rhythm of her mother's heartbeat for a few months, yet she finds herself missing that auditory constant, any facsimile of mom's voice, and all other familiar sounds in her strange, new surrounds. If NICU protocol is adhering to American Association of Pediatrics (AAP 1997) recommendations, she is spared loud, startling sound in order to minimize stress and promote sleep. Still, she is an environment that deprives her of interesting new and familiar auditory stimuli that promote arousal and sensory exploration. Indeed, if the AAP recommendations are strictly followed, she hears very little at all — a few sounds above 45 dB SPL, about the intensity of a whisper, dozens of dB below that of mother's faithful heartbeat. What effect does chaotic or impoverished auditory stimulation during the first days-to-weeks of postnatal brain development have on the development of language cortex and, consequently, speech, reading, math, and social skills?

The AAP recommendations are an excellent first-step, a “better-to-be-safe-than-sorry” phase in the soundscaping of Neonatal ICU auditory environments. After all, no one presently knows what type,

intensity, timing, and duration of auditory stimulation would: 1) promote auditory and related cognitive development en route to singing babble by a few months and speaking words by a year or so; and 2) minimize ear trauma, emotional stress, and sleep disruption. If we were able to optimally stimulate the sensory system most amenable to enrichment in our NICU isolettes, might we be able to decrease the prevalence (25-40%) of language-based learning disorders in our growing population of premature infants (Marlow et al. 2005)? Would it benefit the infant if she were exposed to human speech, music, and environmental sounds? If so, whose speech, what type of music, how much of it, and when would she hear it? The dose and dose interval have not been worked out.

In the vein of considering sound as less of a potential environmental pollutant than the premature infant's window into the natural world: Is there a way to use sound as something to gate pain and stress when she suffers through bedside procedures like skin punctures (heel-sticks for serologic testing) and endotracheal suctioning (for hypoxemia)?

The following sections review our and others' previous empirical work and rational bases for the two main working hypotheses of the proposed research:

- Controlled auditory stimulation will have immediate benefits on the morbidity and cost of the infant's NICU stay, indexed by physiological, behavioral, immunologic, and endocrinologic variables.
- Controlled auditory stimulation will have long-term benefits on cognitive, emotional, and social development, indexed by clinical, behavioral, and physiologic variables.

Immediate Benefits of Controlled Auditory Stimulation

Frequent medical and nursing NICU procedures have deleterious consequences such as lowering infant pain thresholds and causing hypersensitivity to touch, unless they are incorporated into protocols that include procedures for mitigating stress (Speidel 1978; Grunau 2002). Given that the average number of invasive procedures per Neonatal ICU infant is approximately 60 (Barker & Rutter 1995), the potential for acute, recurrent pain and chronic pain to affect brain development in premature infants sufficient to result in cognitive and emotional complications (Huang et al. 2004) renders the need for improved pain management and standardized protocols — non-pharmacological as well as pharmacological — in Neonatal ICUs a priority (Halima, 2003; Larsson, 1999).

After the landmark, randomized-controlled clinical trial conducted at Boston Children's Hospital was published in *JAMA* over 13 years ago (Als et al. 1994), many academic medical centers in the U.S. and E.U. began implementing individualized, "developmentally-sensitive care" to NICU patients. Immediate benefits reported by Als and authors of studies published in nursing journals and elsewhere include: shorter duration of mechanical ventilation and supplemental oxygen; reduced incidence of intraventricular hemorrhage, pneumothorax, and severe bronchopulmonary dysplasia; earlier oral feeding; accelerated weight gain; shorter hospital stays; younger ages at hospital discharge; and reduced hospitalization-related costs (Als et al. 1994; Stevens et al. 1996; Petryshen et al. 1997).

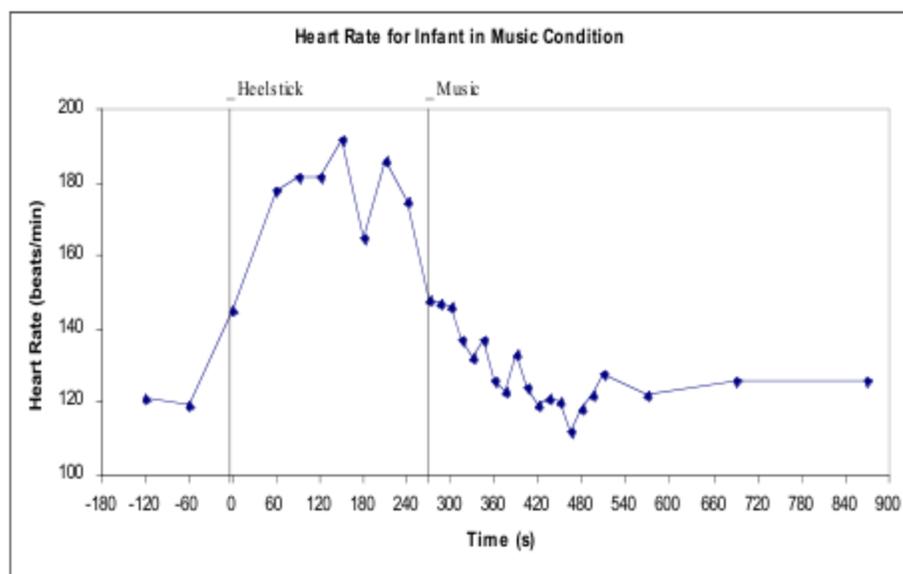
Given the advances in microcomputers and other NICU technologies in the decade-plus since Als et al., given the increased awareness of family, nurses, and doctors to the NICU patient's sensory

plight, and given their relatively small sample size of 38 infants (pre-randomization), we find it surprising that a similarly rigorous but larger and more recent study has not analyzed how much more we are reaping — or could be reaping — from developmentally-sensitive care that incorporates formal protocols for sensory/cognitive enrichment. Publication of such a study in a high-impact medical journal is needed to further increase the prevalence of “sensory-smart” practices to NICUs the world over. At present, only some approaches — “kangaroo” care, swaddling, pacifiers, light and noise management, regular scheduling of routine procedures — are feasible in critically-ill babies receiving mechanically-assisted ventilation and endogastric nutrition in temperature-controlled isolettes, and only some of them enrich the infant’s sensory wasteland. In contrast, controlled auditory stimulation is feasible in all hearing neonates, and delivering the sounds they heard in the womb or would be hearing at home is relatively straightforward. [Our Institute, whose Board includes acousticians, composers, and music producers, is working with the Clinical Systems Innovation Program at the Center for Integration of Medicine & Integrative Technology in Boston (<http://www.cimit.org>) and Central Texas Dynamics Research, L.L.C. to design and develop technologies that equip new prototypes of “postnatal womb” isolettes with a calibrated sound delivery system and synchronized multi-channel video-electrophysiologic data recording system in addition to the usual temperature, air, and humidity control systems.]

Large prospective, randomized-controlled clinical trials demonstrating immediate benefits of controlled auditory stimulation are in need, hence we are submitting this application; meanwhile, the results of small population studies from our and others’ units indicate the proposed research is likely to produce positive results that support the working hypotheses.

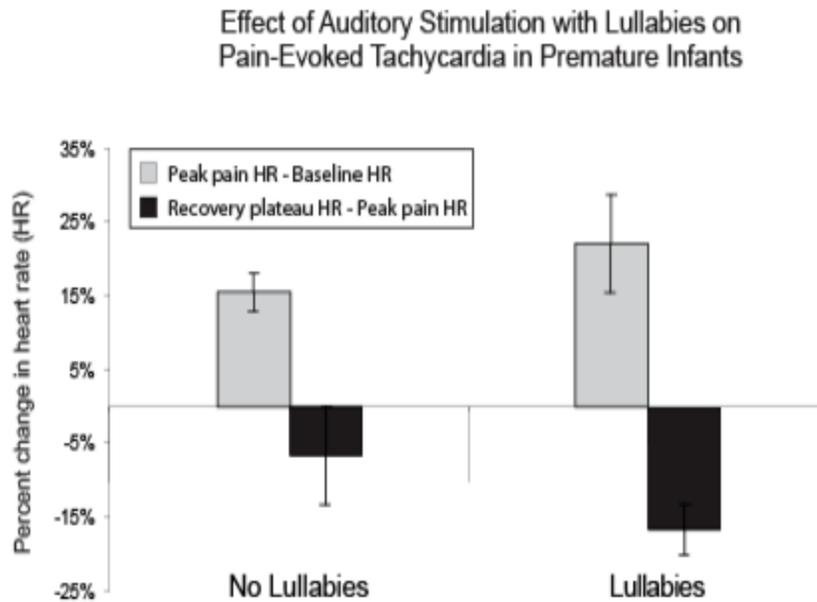
We recently completed a case-cohort study of physiological and behavioral responses to pain in the Neonatal Special Care Unit at Massachusetts General Hospital (Tramo et al. 2006, 2009). We monitored heart rate, respiratory rate, and oxygen saturation for several minutes before, during, and after skin puncture (heel-stick for blood drawing and serologic testing). Each infant was randomly assigned to a Test Group, who received calibrated, free-field auditory stimulation in their bassinets, and a Control Group, who did not. The test stimuli were recordings of North American and British lullabies sung by a woman with acoustic guitar accompaniment (e.g., *Row Your Boat*, intensity = 70 ± 5 dB SPL). Brainstem auditory-evoked potentials were normal in all patients.

The following figure shows single-patient data from the Test Group with heart rate plotted as a function of peri-stimulus time:



At 180 s pre-stress, the heart rate was 120 bpm. After unswaddling and immediately after having his skin punctured for blood tests, the infant's heart rate peaked at 194 bpm, a 62% increase from baseline. After re-swaddling and at the start of the lullaby, the heart rate fell to 146 bpm (22% above pre-stimulus baseline). The heart rate began to plateau around the pre-stimulus baseline about 6 mins after the lullaby started and reached the nadir of 110 bpm (6% below baseline) around 8 mins. This pattern was typical for the patients in our Test Group.

The bar graph below summarizes the results for the study population.



Gray bars show the immediate, dramatic effect pain has on heart rate in premature infants: in the No-Lullabies (control) and Lullabies (treatment) groups, this painful blood test procedure (heel-stick) increased heart rate >15% above the pre-pain baseline (grand mean 19%). One can infer from this observation that our experimental paradigm is unlikely to yield a result that causes us to falsely reject the working hypothesis because of a floor effect exerted by the dependent variable.

Black bars show the amount of decrease in heart rate 10 minutes after the painful stimulus. The Lullaby Group showed a $17 \pm 3\%$ decrease (mean \pm S.E.M., N=7). In contrast, the infants in the Control Group showed only a $7 \pm 6\%$ decrease (N=6). The difference in decrease in absolute heart rate was significant at the $p=0.0062$ level (two-tailed t-test). These observations suggest: 1) pain-evoked tachycardia persists for several minutes after heel-stick; and 2) lullabies normalize protracted pain-evoked tachycardia and may therefore decrease related complications in Neonatal ICU patients.

We also videotaped each infant and analyzed vocal and motor behaviors before, during, and after the painful stimulus. The behavioral results paralleled the physiological results: The Lullaby Group, but not the Control Group, made significantly fewer crying sounds after heel-stick.

In addition to electrophysiological variables like tachycardia, which indexes limbic influences on hypothalamic and other sympathetic efferent neurons that stimulate release of norepinephrine and other neurotransmitters, biochemical variables are affected by pain and stress. There is a strong

rational basis for predicting a correlation between chronically high levels of blood cortisol, abnormal brain development, and poor cognitive, emotional, and social skills owing to the devastating effects stress and high cortisol levels on neo- and mesocortical cytoarchitecture and connectivity patterns in animal models (for review see Teicher et al. 2002). Decreasing stress via controlled auditory stimulation might also decrease the risk of medical illnesses by modulating the immune system (McCraty et al. 1996). In the present research, we will measure the effects of auditory enrichment on salivary cortisol and IgA and correlate the changes with electrophysiological and behavioral changes associated with painful stimuli.

Although no prospective, randomized-controlled study approaching the rigor and statistical power of Als's has addressed the benefits of NICU auditory enrichment, the results of several smaller studies published in nursing journals and elsewhere indicate that auditory stimulation with music or human vocal sounds has immediate benefits on cardiorespiratory state, weight gain, length-of-stay, and behavioral state for NICU patients (for review see Standley 2002). The current proposal extends this work and undertakes new experiments that will:

- Define optimal “dosing” parameters (e.g., spectral, temporal, perceptual, and cultural features) for auditory stimuli in order to maximally enrich the infant’s sensory environment in the immediate term (i.e., during her/his NICU admission). Optimization will be empirically defined using:

- A. Stimulus-response paradigm with:

- i) A painful (unconditioned) stimulus (e.g., heel-stick, endotracheal suctioning);
- ii) Multiple, unconditioned emotional, vocal, motor, neurophysiological, endocrinological, and immunological responses;
- iii) An auditory stimulus that is temporally and otherwise unrelated to the painful stimulus *and* has been shown by us and others to modulate multiple unconditioned responses.

- B. Clinical paradigm combining auditory enrichment, measurement of multiple morbidity- and cost-related outcome measures, and optimal medical and nursing care of a wide range of severe perinatal illnesses diagnosed and treated in the NICU of an academic medical center.

- Correlate outcome measures

- A. Auditory-neurophysiologic (e.g., BAEP Wave V latency and amplitude at admission vs. discharge from the NICU)

- B. Autonomic-neurophysiologic (e.g., number of hypotensive episodes)

- C. Medical (e.g., exposure to CNS-active drugs)

- D. Behavioral (e.g., exploratory motor behaviors)

- E. Endocrinological (salivary cortisol)
- F. Immunological (salivary IgA)
- G. Costs of NICU and total inpatient stays.

Long-Term Benefits of Controlled Auditory Stimulation

In 2005, two important publications reported alarming observations about premature infancy. Together, they sounded a clarion about the risks and prevalence of long-term disability and the need for novel, cognitively-minded interventions that promote early brain development.

First, the March of Dimes reported a premature birth rate of 12% in the U.S. — a 30% increase since 1981. The associated health-care costs were \$18 billion. Put another way: about 40,000 premature infants are currently being admitted to NICUs around the country every year, and over half a million future children of pre-school, primary school, and secondary school age will have been a NICU patient. This estimate assumes the total number of U.S. births remains near 3.8 million per annum, as in recent years (U.S. Census Bureau, 2000 Census), and that 9% of all premature infants are admitted to NICUs (<http://www.lchp.org>).

Second, a large prospective, case-cohort study (EPICure) published in *The New England Journal of Medicine* reported that 41% of premature infants who survived birth at ≤ 25 weeks gestational age suffered cognitive impairment during early primary school age, and that previous studies probably underestimated the prevalence of neurodevelopmental complications (Marlow et al. 2005). The long-term educational, vocational, financial, social, and emotional consequences for the patient and her/his family are severe and hard to overestimate. And with care and productivity costs across the lifetime of the entire patient population reaching tens to hundreds of billions of dollars, global effects on the management and governance of health-care may be palpable. Given the scope and severity of the problem, all possible means of promoting normal development of sensorimotor systems and related cognitive systems during the infants first days of post-natal life and beyond should be explored.

Als et al. (1994) analyzed long-term as well as immediate-term benefits of individualized, developmentally-sensitive NICU care in infants born at 30 weeks gestational age or earlier. After just two weeks of post-natal life, the test group showed better outcomes than the control group with respect to electrophysiological (visual evoked potentials, autonomic) and behavioral (self-regulatory, motor) variables. At nine months, the test group scored higher on the Bayley Mental and Psychomotor Developmental Index and the Kangaroo Box Paradigm. This potential to positively and immediately affect cortical physiology and behavioral variables via sensory control may be critical to decrease the risk of long-term sequelae: if severe cognitive disability is present at 30 months of age, the chances of moderate or severe cognitive disability at 6 years is 86% (Marlow et al. 2005).

To our knowledge, no prospective, randomized-controlled study has investigated the potential long-term health benefits of scheduled, controlled, auditory stimulation in the hospital and home for a protracted period of time during these key, early stages of auditory and cognitive development. However, a strong rational basis for our working hypothesis is grounded in basic neurobiology,

particularly as it relates to the development of sensory cortex (Pallas 2001). Hubel and Wiesel's Nobel Prize-winning work in monkey and cat primary visual cortex on strabismus, visual deprivation, critical periods, and the development of ocular dominance columns is the classic model for understanding the irreversible pathophysiological consequences of early sensory deprivation (for review see Hubel 1988). More recently, auditory cortex neuronal response properties, connectivity patterns, and gene expression have been shown to be similarly affected by altering sensory input during neonatal life (Reale et al. 1987; Irvine et al. 2000; Chang and Merzenich 2003).

In addition to being relatively easy to introduce and control in the neonate's sensory environment, auditory stimulation can take advantage of the surprising array of phonological capacities — both linguistic and musical — that are primed and ready-to-go from birth (Eimas et al. 1971; Werker & Tees 1997; Tramo 2001; Trehub 2003). Our work on auditory modulation of pain-evoked tachycardia suggests infants respond to lullabies as early as 31 weeks gestational age (Tramo et al., 2006). Numerous psychoacoustic studies have documented the surprising perceptual acuity of full-term infants have demonstrated preferences for theoretically consonant musical-intervals (major and minor thirds) over dissonant ones (minor seconds) by four months of age (Zentner and Kagan 2003).

In light of current knowledge about cortical development in primates and other animals and about auditory perceptual competence in human neonates, arguments traditionally advanced for early diagnosis and treatment of peripheral hearing loss (e.g., with hearing aids or cochlear implants) apply, in our opinion, to early prevention of incipient central auditory lesions wrought by abnormal sensory input.

Study Design

The proposed *Jeffrey Epstein Project for Infant Brain Development* encompasses three related multi-center, prospective, randomized-controlled clinical trials:

- The first two trials analyze the immediate effects of auditory stimulation on multiple outcome variables throughout infants' NICU stay.
- The third trial analyzes multiple outcome variables at multiple time points over a 3-21 month follow-up period after infants' discharge from the NICU and throughout the 2 year project period.

Informed, written consent will be obtained in accordance with Institutional Review Board guidelines at each of the hospitals — Massachusetts General Hospital, Boston Children's Hospital, and Beth Israel Deaconess Medical Center — where patients will be recruited for participation.

I. Effect of Auditory Enrichment on Infants' Physiological, Behavioral, and Biochemical Responses to Acute Pain and Stress

This first clinical trial employs a multiple-crossover design and the stimulus-response paradigm of Tramo et al. (2006, 2009; Appendix). We will measure the effects of different auditory stimuli (e.g., speech vs. song; song vs. instrumental music; familiar vs. unfamiliar songs) on physiologic responses (heart rate, respiratory rate, O₂ saturation), behavioral responses (crying, posturing), and endocrine responses (salivary cortisol levels) to acutely painful stimuli (heel-sticks) and stressful procedures (e.g., endotracheal suctioning). Our goals are:

- Extend our previous findings to a larger, sicker, and younger population of premature infants. Although our previous findings showed statistically significant decreases in heart rate, the population was small, the premature infants did not have illnesses requiring admission to a NICU; consequently, we know little about the prevalence of benefit in a population of premies, and whether those with altered levels of consciousness or other clinical conditions respond as well as those we studied. Also, we want to measure more endpoints. For example, we did not previously measure salivary cortisol pre- vs. post-procedure under different auditory stimulation conditions.
- Optimize the timing and type of auditory stimulation. No one knows what the best “dose duration and interdose interval” are when it comes to auditory enrichment or sensory enrichment for these sensory-deprived/disoriented NICU patients. In our preliminary studies, we used lullabies immediately after re-swaddling post-heelstick based on “common sense”, not empiricism. Would womb sounds have been better? Should we have started the lullabies randomly within a 5-15 min window before the heelstick instead of waiting until after re-swaddling? Here, we will take the first steps to empirical optimization. Interestingly, in light of observations about fetal activity during mother’s music listening, we will need to take into account cultural/experiential factors as well as acoustic features of auditory stimuli (Zimmer et al 1982). Our composer and producer colleagues at The Institute will help us explore auditory stimulus space.
- Publish the findings in a high-impact medical journal like *JAMA* (see Appendix), and develop protocols and built-in sound systems that are easy to use and safely deliver calibrated auditory stimuli to babies in isolettes.

II. Effect of Auditory Enrichment on Morbidity & Mortality in NICU Patients

The second clinical trial employs a prospective, randomized, case-control design. Auditory stimulation will be delivered via protocol by NICU nurses at regular intervals (4-6 times per day for 30-60 mins) during wakefulness or after somatic stimulation necessitated by tube feedings. This schedule was designed to avoid auditory stimulation that might otherwise disrupt sleep. Multiple outcome variables — cardiac, respiratory, and neurologic complications, dependence on mechanical ventilation and tube feedings, sleep-wake cycles, exposure to sedatives and other CNS-active drugs, and weight gain — will be monitored daily. Salivary cortisol and IgA will be analyzed at regular

intervals. At the time of discharge, BAEPs will be recorded for comparison with the admission BAEP, and NICU length-of-stay will be entered into the patient database. The total cost of NICU care will be determined in consultation with the billing office. Auditory stimulation will continue on a similar schedule on the ward after discharge from the NICU, and collection of data about medical complications, exposure to drugs with CNS activity, weight gain, length of acute-care hospital stay, and total acute-care costs will continue throughout the acute-care stay.

Our goals are:

- Demonstrate that certain types of controlled auditory stimulation are better than others — just like some drugs are better than others for certain indications — for the purposes of accelerating weight gain, decreasing cardiac, pulmonary, and neurological morbidity, decreasing mortality, and decreasing costs in NICU patients.
- As for the first arm of the trial, it follows that we want to take the important work of Als et al. and others on sensory manipulations to the next level — i.e., optimize the dose of auditory stimulation in order to maximize these very important benefits.
- And, as for the first arm, publish the findings in a high-impact medical journal, and to develop protocols and built-in sound systems that are easy to use and safely deliver calibrated auditory stimuli to babies in isolettes.

III. Effect of Auditory Enrichment on Cognitive Development at 3-30 Months

Infants enrolled in the third clinical trial will be eligible for enrollment in this long-term follow-up arm, which also has a case-control design.

After discharge from the hospital, parents in the test group will be given an audio CD and trained to administer 30 minutes of auditory stimulation 2-3 times per day. Compliance with auditory stimulation protocols will be encouraged via telephone contact and paid participation.

The Bayley Infant Neurodevelopmental Screener will be scored at follow-up in order to assess and compare cognitive development in the test and control groups. In addition, medical records of the patient's visits to her pediatrician and other physicians will be reviewed for information about development and intercurrent illnesses.

Brainstem auditory evoked potentials (BAEPs) will be obtained at yearly intervals in order to assess and compare developmental changes in waveform latency and amplitude within each subject in the case vs. control groups.

Study Population

All infants between 24 and 60 weeks gestational age who are admitted to the Newborn ICUs at Massachusetts General Hospital and Boston Children's Hospital will be considered for randomization in the pain and morbidity treatment trials in consultation with NICU staff. Separate subpopulations will be recruited for the pain trial and the morbidity trial to avoid confounding the effects of stimulation in one on the other. We estimate enrolling 300 patients over the two-year award period based on NICU admission rates of approximately 400/yr at each hospital (total ~2,400 admissions over two years) and an enrollment rate of approximately 15%.

All NICU patients routinely undergo auditory physiology testing — measurement of distortion product otoacoustic emissions (OAEs) — in order to assess the integrity of peripheral and lower brainstem systems. Patients with absent OAEs will be excluded from participation because their inclusion would increase the probability of Type I error (falsely accepting the null hypothesis). In a subpopulation of patients, we will explore the feasibility, cost, and utility of obtaining: 1) brainstem auditory-evoked potentials (BAEPs), which provide data on the integrity of the auditory midbrain and its inputs; and 2) cortical auditory-evoked optical signals (CAEOs), which can be obtained at our affiliated hospitals using novel optical imaging techniques that are presently only available for use in research studies.

At the time of discharge from the NICU, all families will be given the opportunity to enroll in the third clinical trial — the long-term follow-up study of cognitive and auditory development. The Bayley Scales of Infant Development are routinely administered during outpatient follow-up visits at both affiliated hospitals. In the subpopulation of patients studied with BAEPs and/or CAEOs, BAEPs will be obtained at six-month intervals and CAEOs will be obtained until closure of the anterior fontanelle (usually around age 2.5 years). Influences of patient-related variables, such as gestational age, sex, primary diagnosis, and neurologic status, on immediate- and short-term outcome measures will also be assessed.

Personnel, Facilities, and Resources

Nicholas Zervas MD and Mark Tramo MD PhD, founding members of the Executive Board of The Institute for Music & Brain Science, are responsible for: 1) administration of the grant by The Institute, including distribution of funds for personnel, equipment, and supplies to the two participating NICUs; and 2) ensuring adherence of all investigators to the design and methods of the clinical trials.

Dr. Tramo, Principal Investigator, Director of The Institute for Music & Brain Science, and Attending Neurologist at Massachusetts General Hospital (MGH), is responsible for: 1) setting up stimulus-response apparatuses and coordinating uniform data collection procedures at the MGH and Children's Hospital NICUs; 2) analyses of all behavioral and electrophysiological data; and 3) preparation of manuscripts, lectures, presentations, and webpages communicating the results to professional and general audiences.

Dr. Zervas, Co-Investigator and Attending Neurosurgeon at MGH, is responsible for: 1) analyses of clinical, endocrinological, immunological, demographic, and cost-of-care data; and 2) preparation of

manuscripts, lectures, presentations, and webpages communicating the results to professional and general audiences.

Margaret Settle RN MSc, Co-Investigator and Nurse Manager of the MGH NICU, is responsible for writing data collection protocols with Dr. Tramo that spell out the roles and procedures nurses at both participating NICUs will follow.

Jonathan Cronin MD, Co-Investigator and Chief of MGH Perinatology, oversees the medical care of MGH NICU patients. The MGH NICU has 18 single-bed rooms, including 14 Level III intensive care beds and 4 Level II special care beds. Approximately 3,500 babies are delivered per year at MGH. Dr. Cronin will assist Drs. Tramo and Zervas in the collection and analyses of clinical data, and will ensure adherence of MGH investigators and NICU staff to the protocols, policies, and procedures approved by MGH's Institutional Review Board.

Stella Kourembanas MD, Co-Investigator, Academic Chair of the Harvard Program in Neonatology, and Chief of Newborn Medicine at Boston Children's Hospital, oversees the medical care of patients at Children's NICU, a 24-bed Level III facility. Critically-ill infants are referred to Children's NICU from local, regional and international hospitals, including Brigham and Women's Hospital, where approximately 9,000 babies are delivered each year. Dr. Kourembanas will assist Drs. Tramo and Zervas in the collection and analyses of clinical data, and will ensure adherence of Children's Hospital investigators and NICU staff to the protocols, policies, and procedures approved by its Institutional Review Board.

Members of The Institute's Board available for expert advice and assistance in acoustics, audio engineering, and selection of sound recordings include Sir George Martin of AIR Studios, Professor Louis Braidia of the M.I.T. Research Laboratory of Electronics, Professor Robert Freeman of the University of Texas (Austin) School of Music, Dr. Bernie Krause of Wild Sanctuary Inc., Robbie Lee of I & Ear Records Ltd, and Caroline Bienstock of CarlinAmerica Music.

Data analysis and preparation of manuscripts and presentations will be carried out using equipment, supplies, telecommunication systems, and other support provided by The Institute for Music & Brain Science. Computer hardware includes two Macintosh G4 computers, one iMac, one IBM desktop computer, approximately one terabytes of hard disk storage, several portable storage drives, multiple DVD and CD drives, two high-resolution scanners, a color laser printer and a color inkjet printer. Computer software includes Mathworks MATLAB programming language for Mac OS and Windows OS, digital sound synthesis/editing/analysis applications (MacTheScope, Songwriter, Praat), and graphics, word processing, and web applications. Audio equipment includes a Larson-Davis CA250 calibrator, Larson-Davis 1/2- inch calibration microphone, Quest sound level meter, 2 Etymotic Research DPOAE probe assemblies, Yamaha MIDI-compatible keyboard, Tascam four-track tape recorder, JBL sound system, Marshall amplifier, and Les Paul electric guitar, and Grass oscilloscopes. Offices and labs are equipped with ethernet and wireless Internet and E-mail access, telephone/fax lines, standard furniture/storage items, and utilities.

Potential Impact for Infants and Young Children from Pre-Birth to Pre-School

Each year, about 500,000 of the 4 million or so babies born in the U.S. arrive before 37 weeks gestational age (March of Dimes 2005). Since 1981, the U.S. has witnessed a 30% increase in

premature births, an alarming statistic given: 1) premature infants have a high risk of congenital and acquired diseases that impede brain development and, consequently, delay or preclude achievement of cognitive and emotional milestones (Aylward 2005); 2) most premature infants spend the first weeks of their lives in incubators and isolettes that provide, on the one hand, a life-saving medical environment and, on the other, a sensory deprivation/disorientation environment in which random stimulation routinely evokes startle responses, sleep interruptions, and sudden increases in intracranial pressure (Caine 1991; Standley 1991); and 3) invasive procedures in the Neonatal ICU are frequent (e.g., approximately 60 procedures per Neonatal ICU infant, Barker & Rutter 1995) and result in acute, recurrent pain and chronic pain that may affect brain development in premature infants sufficient to result in cognitive and emotional complications (Huang et al. 2004). These problems also apply to the increasing number of full- and near-term infants being admitted to ICUs after elective C-sections (Makoha 2004).

Clearly, development of improved pain management and standardized protocols — non-pharmacological as well as pharmacological — in Neonatal ICUs is a priority (Halima, 2003; Larsson, 1999). To date, no randomized, controlled clinical trial on the medical, neurological, and developmental consequences of optimal auditory stimulation — i.e., auditory enrichment — has been conducted. The proposed research endeavors to transform the auditory deprivation/disorientation environment of premature infants into an enriched auditory environment that nurtures their developing auditory, linguistic, cognitive, and emotional systems using predictable, controlled stimulation with sounds they would normally be exposed to at home (e.g., familiar human voices, songs, instrumental music, and other environmental sounds). Through the proposed program, we anticipate improving outcome measures critical to improving the long-term development of this disadvantaged population. We would like to follow the patients out longer than two years and, pending the results of the first two years of the study, plan to seek additional funding that would allow us to continue to follow our patients through their early pre-school and elementary school years.

References

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ITEMIZED BUDGET

PERSONNEL	YEAR 1	YEAR 2
	Salary (% Effort)	
<i>Principal Investigator</i>		
Mark Jude Tramo, MD PhD Neurology/Neurophysiology/Acoustics Inst Music & Brain Science	\$80k (40%)	\$80k (40%)
<i>Co-Investigators</i>		
Nicholas Zervas, MD Neurosurgery/Neuroendocrine Inst Music & Brain Science	\$40k (20%)	\$40k (20%)
Margaret Settle, RN MSc Nurse Manager, Newborn ICU Mass General Hospital for Children	\$0 (10%)	\$0 (10%)
Jonathan Cronin, MD Chief, Perinatology & Newborn ICU Mass General Hosp for Children	\$0 (5%)	\$0 (5%)
Stella Kourembanas, MD Chief, Newborn Medicine Boston Children's Hospital	\$0 (5%)	\$0 (5%)
<i>Consultants</i>		
Barbara Hermann, PhD OAE & BAEP Consultant MGH/MEEI 75 pts/yr x 2 BAEPs/pt x \$50/BAEP	\$7.5k	\$7.5k
Ellen Grant, MD PhD Neuroradiology/CAEO Consultant Children's Hospital	\$0 (1-5%)	\$0 (1-5%)
Caitlin Fairmeny Biomedical Engineering Consultant MGH	\$0 (1-5%)	\$0 (1-5%)
Hang Lee, PhD Biostatistics Consultant MGH	\$0 (1-5%)	\$0 (1-5%)
<i>Research Assistants</i>		
MGH Children's Hospital	\$30k (100%) \$30k (100%)	\$30k (100%) \$30k (100%)

EQUIPMENTLaptop (MacBook Pro)
for Bedside Data Collection

MGH	\$2k	0
Children's Hospital	\$2k	0

Matlab Programming Software
License and Renewal

\$500	\$500
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Hard Drives for Storage (2)

\$400	0
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Sound delivery system (2)

\$400	0
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Video-audio recording system (2)

\$600	0
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SUPPLIES

Electronic/Computer

\$1k	\$1k
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Lab/Office

\$1k	\$1k
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Salivary Cortisol tests =
\$30/patient x 150 pts/yr =

\$4.5k	\$4.5k
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Salivary IgA tests =
\$30/patient x 150 pts/yr =

\$4.5k	\$4.5k
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Subject Fees =
\$50/pt x 150 patients/yr =

\$7.5k	\$7.5k
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TRAVEL

0	0
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DIRECT COSTS PER ANNUM

\$211,900	\$206,500
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INDIRECT COSTS PER ANNUM (20%)

\$42,380	\$41,300
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TOTAL COSTS PER ANNUM

\$254,280	\$247,800
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TOTAL FUNDS REQUESTED OVER 2-YEAR AWARD PERIOD = \$502,080