University of Pennsylvania

Annual Progress Report: 2007 Nonformula Grant

Reporting Period

July 1, 2011 – May 31, 2012

Nonformula Grant Overview

The University of Pennsylvania received $3,941,025 in nonformula funds for the grant award period June 1, 2008 through May 31, 2012. Accomplishments for the reporting period are described below.

Research Project: Project Title and Purpose

Biosocial Prediction and Intervention on Childhood Aggression - The purpose of this project is fivefold. First, it aims to identify the environmental, social, psychological, and neurobiological factors that raise the risk that a child will become seriously aggressive later in life. Second, it aims to test the effectiveness of two interventions for the treatment of childhood aggression both alone and in conjunction: cognitive-behavior therapy and nutritional supplements. Third, it aims to identify factors that protect some children who are predisposed to aggression from developing this outcome. Fourth, it uses animals exposed to environmental stress to assess the effectiveness of nutritional interventions in reducing aggression. Fifth, it attempts to understand how environmental factors interact with biological factors in giving rise to child aggression, and how these risk factors may affect treatment outcome.

Duration of Project

6/1/2008 - 5/31/2012

Project Overview

Understanding the joint neurobiological and social bases of aggression is critical to future attempts to tackle this major public health problem. The overarching goals are: (a) to conduct a systematic integration of biosocial risk factors for childhood aggression in order to predict later aggression, (b) to conduct one of the very few biosocial interventions on childhood aggression, (c) to predict and treat two fundamentally different manifestations of aggression – proactive and reactive aggression – which likely have different etiologies and responsiveness to treatment. The specific aims are: (1) to assess biological (genetic, neurocognitive, brain imaging, neuroendocrinological, neurotoxin, psychophysiological, nutritional), psychosocial (neighborhood, family, school, peer, psychological) and psychiatric (ADHD, CD, ODD, depression, anxiety, PTSD, schizophrenia-spectrum) risk factors for male and female aggression in order to better predict later aggression, (2) to improve prediction by identifying the genetic, neurocognitive, psychophysiological, and neuroendocrinological factors that protect children
socially at risk from violence outcome, (3) to develop a genetic mouse model of aggression to test the effectiveness of nutritional interventions in reducing aggression, (4) to begin to develop a new biosocial approach to the treatment and prevention of aggression, based on both cognitive-behavioral and nutrition treatments, (5) to assess the differential prediction and treatment of two fundamental variants of aggression in children: proactive and reactive aggression.

The human sample will consist of 500 male and female 11 and 12 year-old children drawn from high-risk communities in Philadelphia. Participants will engage in a baseline assessment for risk factors of aggression, and then be randomly assigned to one of four three-month treatment programs: nutrition supplementation only, cognitive-behavior therapy only, cognitive-behavior therapy + nutrition, and no-treatment controls. Aggression outcome will be assessed throughout treatment and post-treatment. The animal component experimentally tests risk factors (genotype, stress) and nutritional interventions (omega-3 fatty acids) on the development of aggression. It is believed that this biosocial interdisciplinary study offers a truly unique opportunity to identify the mechanisms and processes associated with two fundamental forms of childhood aggression that are the precursors to a major public health problem: serious adult violence.

Principal Investigator

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Other Participating Researchers

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Joel Fein, MD - employed by Children’s Hospital of Philadelphia
Douglas Granger, PhD - employed by Pennsylvania State University
Herbert Needleman, MD – employed by University of Pittsburgh

Expected Research Outcomes and Benefits

This research project tackles an enormously important issue in the Commonwealth of Pennsylvania in general, and Philadelphia in particular – violence. If we can predict future aggression and violence at a relatively early age before it starts, we will be in a much better position to apply intervention programs to take aggression-prone children off a life path to violent crime. This interdisciplinary study involving more than 9 departments across 4 Schools at the University of Pennsylvania and 5 additional institutions within Pennsylvania would be one of
the most comprehensive biosocial attempts ever to predict future aggression in children and to prevent future aggression in children. By examining a wide range of neighborhood, environmental, social, psychological, psychiatric, and neurobiological risk factors for aggression, we hope to be better able to predict later violence. By conducting experimental interventions to reduce aggression in children, we aim to provide novel ways of tackling this critically-important problem in growing children and adolescents. We anticipate that more effectively tackling aggression and violence early on in life will improve the health status of all children and adults in Pennsylvania and the country by cutting the enormous financial, physical, emotional, and psychological damage that violence perpetration creates in society. Because violence is a major public health problem in the country, more effective early prediction and treatment of aggression and violence will be of major benefit to society.

**Summary of Research Completed**

**Completion of risk assessment recruiting.**
Our first milestone was to complete risk assessments, interventions and follow-ups. We have been successful in recruiting 455 participants. This last year saw the largest-ever participant recruitment – a total of 145. Consequently we exceeded our revised target of 350 by 105.

**Completion of treatment interventions on 300 participants.**
Full details of our completion of treatment interventions are given in Table 1. We had a target goal of retaining 80% of the intervention participants. It can be seen that our retention at 3 months was 73.3%, at 6 months it was 92.6%, and at 12 months it was 87.8%. Overall therefore, we were successful in achieving our goal, even though the initial retention was the lowest of all three time-points. We saw 311 in the 3-month follow up, 348 in the 6-month follow-up, and 252 at the 12-month follow-up. Consequently in two of the three phases we exceeded our goal of assessing 300 participants, but fell short in the 12 month follow-up by 19%. Defining retention as seeing a subject at least once gave us a retention of 90.6%.

**Begin data analyses on aims 2, 3, and 5.**
Early analyses of the data reveal that on functional imaging, antisocial children showed *reduced* activation bilaterally in the fusiform gyrus, cerebellum, and the amygdala/hippocampus, and *increased* activation bilaterally in the inferior parietal cortex, the precuneus, the dorsolateral prefrontal cortex, and occipital cortex.

On structural imaging, higher scores on proactive (but not reactive) aggression were significantly associated with reduced volumes of both left and right amygdala in girls but not boys.

On psychophysiology, low heart rate was associated with higher APSD scores and proactive aggression, but not reactive aggression. Findings are among the first to document low heart rate in association with child psychopathy and demonstrate specificity to proactive aggression.

Data analyses are ongoing.
Completion of test of specific aim 4
Our fourth aim was concerned with the treatment of aggression. Specifically, we aimed to test whether a nutritional intervention could be effective in reducing aggression, both alone and in combination with more traditional interventions. A group (4 levels) x time (2 levels) repeated measures multivariate analysis of variance resulted in a trend for reactive aggression (p = .07), but not proactive aggression (p = .43). While in all four groups there was a reduction in aggression over time, there were steeper drops in the three treatment groups than in the controls. This trend was explored further by computing pre-treatment / post-treatment difference scores in reactive aggression and comparing the four groups. Group contrasts showed that both the nutrition only group (p = .024) and the nutrition + CBT group (p = .02) showed greater reductions post-treatment in reactive aggression compared to the no-treatment control group. The greatest decline in reactive aggression was marginally in the nutrition only group.

Reporting initial results at national conferences
Results from this project have been presented at:


Completion of minority institution pilot projects
While we have been working closely with our minority institution, pilot funds for pilot projects were cut when the grant was awarded after the original budget cut. Pilot studies were not specified in the original proposal.

Manuscripts submitted.
During the year we submitted three journal articles. Brief details of these are as follows:

Development of home cage social behaviors in BALB/cJ vs. C57BL/6J Mice (Fairless et al.) BALB/cJ and C57BL/6J inbred mouse strains are useful models of low and high levels of juvenile sociability, respectively, as measured in the Social Approach Test, which assays social approach of a test mouse toward an unfamiliar stimulus mouse in a novel environment. However, little is known about the generalizability of these results in the Social Choice Test to social behaviors in a familiar environment with a familiar social partner. We hypothesized that home cage social behaviors of BALB/cJ and C57BL/6J mice toward familiar littermates would show a similar pattern of strain differences in sociability across development as found in the Social Approach Test. We measured active and passive social behaviors in home cage environments by pairs of BALB/cJ or C57BL/6J littermates at 30-, 41-, and 69-days-of-age. The strains did not differ robustly in their active social behaviors in the home cage. C57BL/6J mice were more passively social than BALB/cJ mice as juveniles, and C57BL/6J levels of passive social behaviors declined to BALB/cJ levels by adulthood. These effects were primarily attributable to differences in huddling behavior. These results show a similar strain-difference pattern to that of
the Social Approach Test. They also show that differences in sociability can manifest in different behaviors in different social contexts: sniffing – an active social behavior – in the Social Approach Test, but huddling – a passive social behavior – in the home cage. An assessment of social behaviors in the home cage environment can provide a more complete profile of sociability in mouse models relevant to autism.

Recruitment of Community-residing Youth into Studies on Aggression (Richmond et al)
Recruitment of community-based youth into studies is challenging. We examined access issues (recruitment sources, referrals, gatekeepers), minority status, and personal costs of participants for a study of children with aggressive behaviors designed to identify which are at risk for future violent behaviors, to identify protective factors, and to test interventions to reduce aggression. Of 1038 contacts, 112 declined, 239 could not be re-contacted, and 124 were ineligible. 350 of 563 scheduled child-parent dyads completed intake assessment. Most were recruited through targeted mailings (33%) and community flyers (22%), 12% through regional news advertisements, 8% by Craigslist, and 5% through health care providers / clinics. Factors contributing to enrollment rates by zip code showed the % Black / zip code and targeted mailings positively contributed (Beta = .200 and .419 respectively) and estimated transit travel time negatively contributed (-.299) to enrollment rates (R² = 0.562). Targeted mailings proved to be the most efficient strategy in successful recruitment.

The Healthy Brains and Behavior Study: Objectives, Design, Recruitment, and Population Coverage (Liu et al.)
Violence is being increasingly viewed as a public health issue which is prefaced by genetic, neurobiological, psychological, and social risk factors which may be ameliorated by health-based interventions. The Healthy Brains and Behavior Study (HBBS) aims to both identify these risk factors in late childhood, and also to reduce aggression through psychological and nutritional treatment. Utilizing a cross-disciplinary collaborative research approach, HBBS has both animal and human components. The human component has two stages consisting of risk assessment followed by treatment. The risk assessment is based on 443 community-residing children aged 11-12 years and their caregivers, and entails the collection of genetic, brain imaging, neuroendocrinological, psychophysiological, environment toxicological, neurocognitive, nutritional, psychological, social and demographic risk variables. Children who met criteria for problematic aggressive behaviors were assigned to either cognitive-behavior therapy (CBT) alone, nutritional supplements alone, both CBT and nutrition, or treatment-as-usual. Treatment duration was three months with follow-ups at three, six, and 12 months. The animal project focused on the effects of dietary omega-3 fatty acids on the development of aggression. We utilized an interdisciplinary collaborative research approach involving scientists from multiple disciplines. This study aims to assess on how biological factors interact with social factors in shaping proactive and reactive aggression, and to assess whether the combination of psychological and nutritional approaches may more effectively reduce child aggression.

Hold final advisory meeting.
Advisory group members and community partners met in partnership with the Philadelphia Collaborative Violence Prevention Center. Partnering with this community participatory research group expanded interest in nutritional interventions, leading to a subsequent grant proposal to fund community-research translation of the findings beyond the term of our grant.
Bioethics meeting to discuss dissemination of scientific findings
The PI had a very productive meeting with Dr. Jonathan Moreno (Bioethics, University of Pennsylvania) and Dr. Martha Farah (Director of the Center for Neuroscience in Society, University of Pennsylvania) for several hours on Monday March 5 on the ethical history of biological research on violence, and current / future neuroethical issues in this field. We aim to continue this dialogue in the context of the monthly meetings of the Center for Neuroscience in Society and to potentially write an article on this topic for submission to a neuroethics journal.

Submit application for further extramural funding
One grant application entitled “Biosocial Prediction and Intervention on Youth Injury Risk Behaviors and Injury Events” has been submitted to the Center for Injury Prevention and Control of the CDC. Another entitled “Using CBPR to address health disparities in violence for urban African American Youth” has been submitted to NIH.

Table 1. Number of Completed Follow-ups on Those Originally Screened and Able to Participate in the Intervention.

<table>
<thead>
<tr>
<th>Follow-up Time</th>
<th>Participants Actually Seen</th>
<th>Participants Eligible to be Seen</th>
<th>Retention %</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 month</td>
<td>311</td>
<td>424</td>
<td>73.3%</td>
</tr>
<tr>
<td>6 month</td>
<td>348</td>
<td>376</td>
<td>92.6%</td>
</tr>
<tr>
<td>12 month</td>
<td>252</td>
<td>287</td>
<td>87.8%</td>
</tr>
<tr>
<td>Seen at least once†</td>
<td>384</td>
<td>424</td>
<td>90.6%</td>
</tr>
</tbody>
</table>

† This is asking the question “Of all subjects who were ready to be seen at least at the 3 month follow-up, how many were seen at least in one follow-up visit? Our retention was worse for the 3 month follow-up but improved at 6 and 12 month follow-ups. We felt it useful to see how many had at least one follow-up for the study. Consequently this captures if a subject was seen at least once out of 3 possible follow-up periods.