

# University of Pennsylvania

## Annual Progress Report: 2007 Nonformula Grant

### Reporting Period

July 1, 2010 – June 30, 2011

### 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.

### Anticipated 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.

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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**

Nutrition and Antisocial Behavior: We have begun initial pilot analyses on data collected to date to explore possible relationships between nutritional status and antisocial behavior. A total of 276 of our participants (150 males and 126 females) aged 11-12 years were assessed on the Antisocial Process Screening Device (APSD), as well as serum concentrations of 25-hydroxyvitamin D2 and D3 (25-OHVITD). Correlational analyses indicated that higher scores on antisocial personality were associated with lower levels of vitamin D ( $r = -.194$ ,  $p = .021$ ). Group analyses indicated that those with low vitamin D had higher antisocial scores than those with high vitamin D levels ( $t = 2.18$ ,  $df = 139$ ,  $p = .031$ ) – see Figure 1. As low vitamin D status has been associated with abnormal brain and reduced cortical thickness, results of these initial data suggest that an important environmental factor, vitamin D, may in part explain the cortical brain deficits observed in antisocial children.

Pilot Analyses on Treatment of Aggression: Although we are only part-way through the treatment study, we have conducted initial, pilot analyses on the effectiveness of nutritional supplements and cognitive behavioral therapy in reducing reactive and proactive aggressive behavior (specific aim # 5). The four groups consist of: (1) treatment-as-usual ( $N = 25$ ), (2) nutritional supplements only ( $N = 31$ ), (3) cognitive behavioral therapy (CBT) only ( $N = 25$ ), (4) both CBT and nutrition ( $N = 27$ ). Reactive and proactive aggression was measured at baseline (month 0) just before treatment, and three months later immediately post-treatment.

A group (4 levels) x time (2 levels) repeated measures multivariate analysis of variance resulted in a trend for a group x time interaction for total aggression ( $p = .22$ ), reactive aggression ( $p = .17$ ), and proactive aggression ( $p = .23$ ). Results are outlined in Figure 2. It can be seen that 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 using paired t-tests. The control group failed to show a significant reduction in total, reactive, and proactive aggression over time ( $p = .14$ ,  $.12$ ,  $.68$  respectively). In contrast, significant reductions were observed for all three outcomes for the nutrition only group ( $p = .001$ ,  $.0001$ ,  $.02$  respectively), and the CBT only group ( $.002$ ,  $.007$ ,  $.005$  respectively). The combined CBT + nutrition group showed significant reduction on total aggression ( $p = .001$ ) and reactive aggression ( $p = .0001$ ), but not proactive aggression ( $p = .20$ ).

These pilot results should be treated with caution. Nevertheless, the results of the paired t-tests that show significant improvements in all three treatment groups - but not in controls - indicate some promising trends. Notably, nutritional supplementation alone appears to be just as effective as either CBT alone, or the combination of CBT and nutritional supplementation.

Aggression in Mice: As noted in last year's progress report, levels of fertility of mice and survival of pups whose mothers were maintained on the high omega-3 fatty acid diet are strikingly low. This has greatly slowed the rate of breeding of mice, despite multiple measures that we have taken to try to keep breeding rates up, such as setting up very large numbers of mouse breeding pairs, and ensuring that breeding males and females are at an age of peak fertility. Given the unexpectedly extremely low fertility and survival rates of mice on special diets, we conclude that it will not be possible to generate an additional set of C57BL/6J and BALB/cJ mice that are bred on (exposed from earliest prenatal development to) the high and low omega-3 fatty acid diets and that are exposed to chronic variable stress within the time frame of the award.

We are therefore now beginning a study of a new set of C57BL/6J and BALB/cJ mice that are maintained on a standard mouse diet (moderate level of omega-3 fatty acids) until 4-weeks-of-age (shortly before the onset of puberty), and then are maintained on either a high-omega-3 fatty acid diet or a low omega-3 fatty acid diet continuously through adulthood. Then, we will measure the effects of this dietary assignment during postnatal development on aggressive behaviors across puberty and during adulthood. This will enable us to compare the effects of different developmental timing (prenatal vs. postnatal) of high omega-3 fatty acid diets on development and aggressive behaviors. We believe that this is the most scientifically feasible and important question to address, because the mice will be more easily bred on a standard mouse diet within the remaining time frame of the award (i.e. higher feasibility), and we can further assess whether there are potentially adverse effects of prenatal exposure to high omega-3 levels that could be avoided by high omega-3 fatty acid diets during the *postnatal* period.

Recruitment: Figure 3 identifies recruitment status and the number of participants at each point in the study flow. To date, 310 children and parents have been recruited into the study. As reported previously to the Health Research Advisory Committee on 12/8/2010, one concern we have had is that our population is over-represented in terms of African-Americans (84%). We have been making strenuous efforts to increase participation of other ethnic groups by sending our recruiters into the outer suburbs to post flyers in pools, recreation centers, stores, offices, libraries, religious centers, and mailing flyers to parents in these more distant suburbs using addresses provided by USA Data (a company that has provided us with names and addresses of parents who have 11-12 year old children, which they obtain through surveys). Inevitably the location of our institution near predominantly African-American communities is a key source of the African-American over-representation.

Risk Assessments: Three hundred and ten children and parents have completed the initial risk assessments. Two hundred and nine of these children have had MRI scans.

Data are entered into SPSS within one-two days after completion of the risk day assessment. Data cleaning is ongoing and up-to-date. We have started SPSS syntax for variable computation.

Intervention: The intervention consists of four groups: cognitive behavioral therapy only, nutritional supplements only, cognitive behavioral therapy and nutritional supplements, and usual care. Of the 310 who have completed risk day assessment, 219 have been randomized to one of the 4 treatment groups. One hundred and nine are in one of the two treatment groups that involve cognitive behavioral therapy. Ninety-four have completed the entire CBT intervention. Fifty-three are randomized into the nutrition only group, 54 are randomized into the nutrition and CBT group, and 57 are in the control condition. As can be seen, once enrolled in the CBT arms, most subjects complete the intervention. We have increased incentives to facilitate completion and provide a bonus upon completion of the CBT intervention.

Fidelity Monitoring: As recommended by the site visitors, we have added additional therapists (3) to our full-time lead interventionist for the CBT arm. We routinely conduct fidelity monitoring of randomly-selected sessions with all interventionists to assure that the manualized CBT is being delivered. Sessions are randomly selected for fidelity monitoring, such that the interventionist is unaware of which sessions are being monitored.

Children randomized to either of the nutrition groups are called weekly to monitor intake of the nutritional supplements and to encourage taking the supplements at the study dosage. Twenty-nine subjects out of the 40 who have completed the nutrition intervention took the supplements on a regular basis (only missed 1 week or less of the 12 week intervention), 1 person stopped taking the supplements because he had an allergic reaction (but it was not related to the supplements), 5 subjects could not be reached after they started the intervention, 1 person declined to participate, 9 subjects did not take the supplements on a regular basis. Because of import issues with our primary mode of Omega-3 delivery (Smartfish juice), we have had to use an alternative product, Coromega, that has similar levels of Omega-3. We will return to using the Smartfish juice as soon as the import issue is cleared up.

Follow-Up: Of the 296 subjects followed-up, 16 have withdrawn or are lost for all three time points at the 12 month follow-up (16/296, 5.4%). Ninety-seven of 113 subjects who should have completed the 12 month follow-up did so (86%), although we should note that there are missing data from some of the follow-up points (e.g. missing 3 month, but complete 6 & 12 month data). Please see Table 1 for the breakdown by each time point (3, 6, and 12 month follow-up).

Minority Institutions and Community-Penn Preceptor Teams: Students from AchieveAbility and from the Institute for the Development of African American Youth (IDAAY) continue to work with their study team members on the assessment, intervention, and follow-up parts of the study.

Project-Wide Grand Rounds: On April 22, 2011, the Healthy Brains and Behavior Grand Rounds featured the work of Dr. Dustin Pardini, University of Pittsburgh, on brain function abnormalities associated with divergent criminal careers in men.

Public Health Translation: In order to build a foundation for sustainable replication of our intervention findings, we continue to communicate with local youth serving organizations. As

part of the recruitment process we connect with and provide information to recreation programs, nutritional services, faith-based programs, primary health care offices, pediatric/dental clinics, charter schools, and school counselors. We have mailed interested parents and organizations a seasonal newsletter that provides parent tips and resources. This will provide a method for disseminating information on the study's findings to interested members of the community.

Figure 1. Scores on antisocial personality in low and high vitamin D groups.

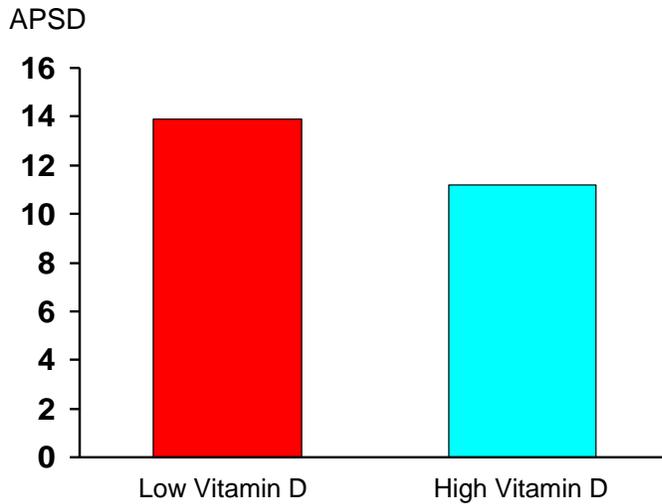


Figure 2. Pre- and post-treatment changes in total aggression scores in the treatment-as-usual control group and the three treatment groups, together with p values for paired t-tests assessing within-group changes in aggression over time.

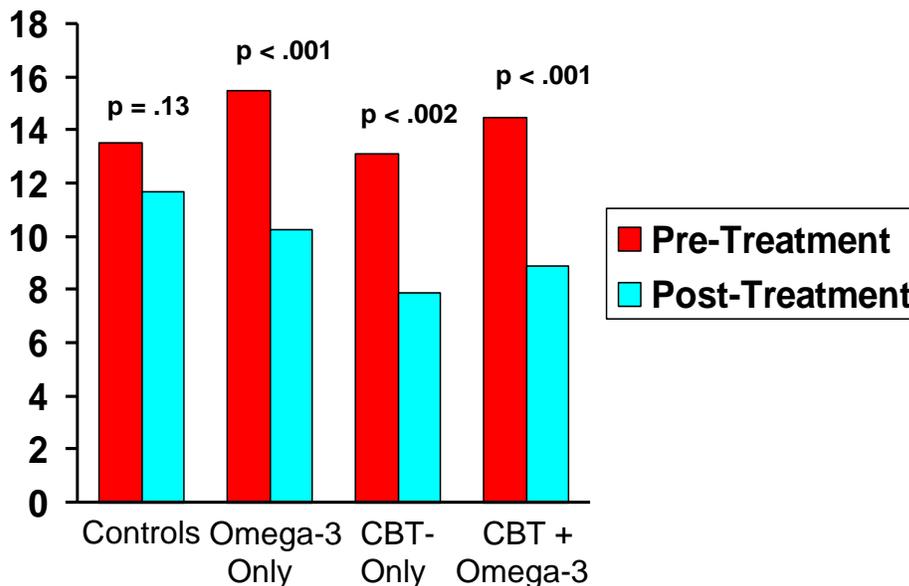


Figure 3. Participant Flow

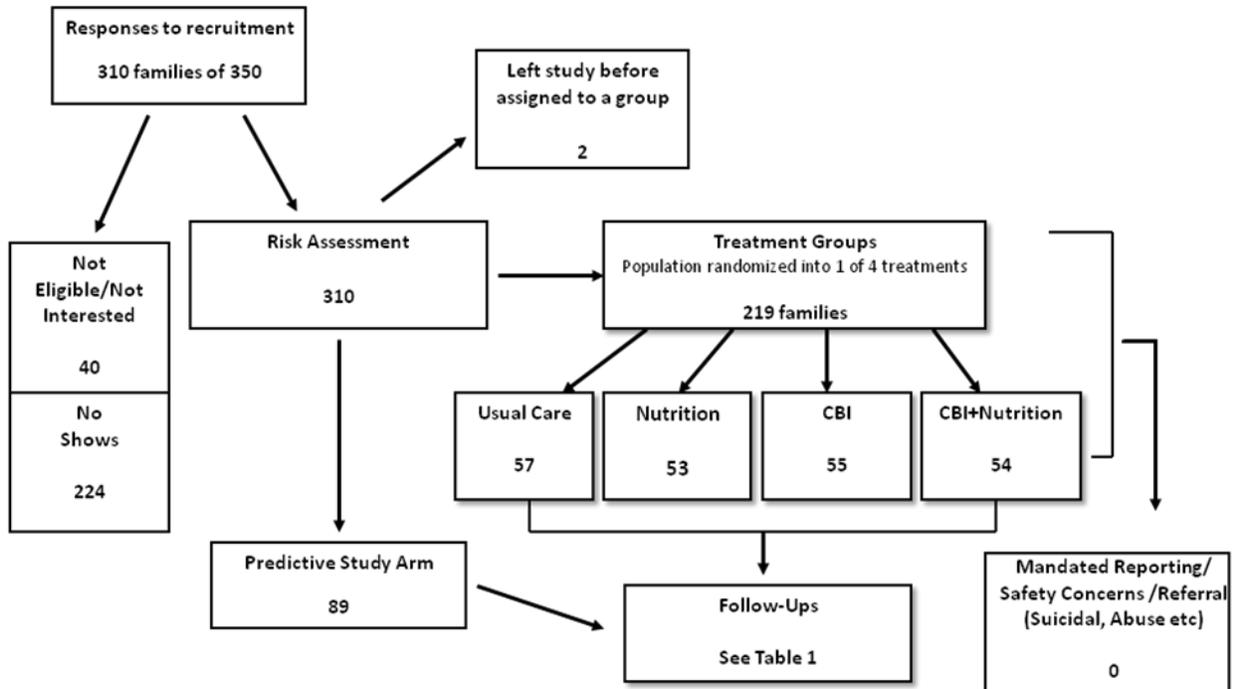


Table 1. Number of Completed Follow-ups

12 Month Follow-up: 113 should have completed 12 month f/u.

Status	N (%)
Completed at least 1-2 f/u visits	97 (86%)
Missed/withdrawn	16 (14%)

6 Month Follow-up: 91 have reached 6 month follow-up data collection point

Status	N (%)
Completed at least 1 f/u visit	84 (92%)
Missed	7 (8%)

3 Month Follow-up: 38 should have completed 3 month follow-up

Status	N (%)
Completed	34 (90%)
Missed	4 (10%)

An additional 54 are not yet ready to be seen for their 3 month follow-up visits

Note: As can be seen from the data above, our attrition rate is below the 20% that we factored into the study. That said, it is important to note that our study protocol is for three follow-up time-points (3, 6, 12 months) and that not all subjects made it to all three follow-up visits. Thus, for our 12 month completed group who are retained in the study, 54/97 (56%) have completed data sets and 44% are missing data from one or more follow-up visits.