REPEATED MILD TRAUMATIC BRAIN INJURY AND NEUROCOGNITIVE DEVELOPMENT

1. Meta Hypothesis

Repeated mild traumatic brain injury (rMTBI) has a cumulative adverse effect on neurocognitive development.

2. Specific Hypotheses

1. Although most patients with a single mild traumatic brain injury (MTBI) appear to recover completely and have no detectible brain abnormalities, they are susceptible to worse outcomes with subsequent rMTBIs. Specifically, with rMTBI there is dysfunction in neurocognitive development associated with brain pathology that progresses through time. These changes are more pronounced with each successive MTBI.

2. Those participants with a single MTBI are at greater risk for a subsequent or recurrent MTBI than those children who have yet to experience one (Swaine et al., 2007).

3. Background and Justification

MTBIs, also known as "concussions," are a silent epidemic, affecting 1.1 million patients each year in the United States (Centers for Disease Control and Prevention [CDC], National Center for Injury Prevention and Control, n.d.; Centers for Disease Control and Prevention [CDC], 2003; Langlois, Rutland-Brown, & Tomas, 2004). In current practice, a patient with a MTBI is defined as a person who has had a traumatically induced disruption of brain function as manifested by either a short loss of consciousness, memory dysfunction, or a Glasgow Coma Score (GCS) of 13-15 (Carroll, Cassidy, Holm, et al., 2004; Teasdale & Jennett, 1974). MTBI patients evaluated in hospital emergency departments are typically discharged to home after an unremarkable computerized tomography. However, approximately 15 percent of these patients are at risk of suffering persisting neurocognitive dysfunction such as memory dysfunction or difficulties with concentration (Anderson et al., 2001; Belanger et al., 2005; Carroll et al., 2004; Hawley et al., 2002; Karaus & McArthur, 1996; Langlois, Rutland-Brown, & Tomas, 2004; McAlllister et al., 1999). Furthermore, all MTBI patients may be at risk for a disproportionate degree of morbidity with a repeated MTBI in close temporal sequence. Notably, it is thought that a large percentage of these patients suffer persisting cognitive dysfunction (Cantu, 1998; Guskiewicz et al., 2003; Kelly & Rosenberg, 1998). Though the mechanisms behind "second impact syndrome" (Cantu, 1998) are not well understood, it raises questions about cumulative effects of rMTBIs, especially among children. The classic setting for a repeat TBI is athletic competition. For example, an estimated 20 percent of high school football players sustain at least one concussion each season (Cantu, 1998). College football players with more than one concussion have persisting cognitive dysfunction (Guskiewicz et al., 2003). Outside athletic competition, it is likely that some children sustain rMTBIs during normal activities of childhood. Indeed, although the cause is not clear, a history of TBIs is a risk factor for incurring a subsequent TBI (CDC, National Center for Injury Prevention and Control, n.d.; Centers for Disease Control and Prevention [CDC], 2000, 2003; Ashwal, Holshouser, & Tong, 2006; Taylor et al., 2002).

There is little research on the outcomes of rMTBIs in children. Most of the literature that addresses TBIs in the pediatric population focuses on the sequelae of an isolated moderate or severe TBI (Gordon, 2006; Salcido & Costich, 1992).

Characterization of the long-term outcome of children with rMTBIs would provide a platform to pursue preventive interventions, help guide patient management, and potentially reveal therapeutic targets.

3.1 Public Health Importance

Prevalence/incidence

According to the Centers for Disease Control (http://www.cdc.gov/ncipc/tbi/TBI.htm), there are 1.4 million patients of all ages who sustain TBIs in the United States each year. Approximately 1.1 million of these patients are MTBI patients who are typically treated and released from an emergency department (Kraus & McArthur, 1996; Langlois, Rutland-Brown, & Tomas, 2004; CDC, 2003; Thurman et al., 1999). Among children ages 0-14 years, it is estimated that TBIs result in 2,685 deaths, 37,000 hospitalizations, and 435,000 emergency department visits annually (CDC, National Center for Injury Prevention and Control, n.d.; CDC, 2003; Kraus & McArthur, 1996; Langlois, Rutland-Brown, & Tomas, 2004) Overall, these numbers are thought to vastly underestimate the prevalence of pediatric TBIs because many cases of MTBIs are not seen in an emergency department. The actual incidence of rMTBIs among children is not known. However, children and young adults make up the majority of TBI patients (CDC, 2003; Schneier et al., 2006) and patients with at least one TBI are at increased risk of subsequent injury (Anderson et al., 2000, 2001; Bijur, Haslum, & Golding, 1996; Cantu, 1998; Guskiewicz et al., 2003).

Economic and/or social burden

Direct medical costs and indirect costs such as lost productivity due to a TBI totaled an estimated $60 billion in the United States in 2000 (CDC, National Center for Injury Prevention and Control., n.d.). This figure is an underestimate because it does not include non-hospitalized persons, the costs of lost productivity, diminished quality of life, and the indirect costs borne by family members and friends who care for persons with a MTBI (CDC, 2003). For example, more than a third of prospective MTBI patients had not returned to work within three months after being injured (Boake et al., 2005; Levin et al., 1987, 2001, 2005; McAllister et al., 1999). No data exists for the impact of rMTBIs in children on society. Nonetheless, persistently reduced cognitive abilities and developmental problems in these patients would obviously represent a substantial emotional and financial burden.

3.2 Justification for a Large Prospective Longitudinal Study

The fact that little is known about the impact of rMTBIs in children is a compelling justification for this study. As above, many patients with a MTBI suffer persisting neurocognitive dysfunction and an initial MTBI predisposes patients to a worsened outcome with repeat exposures. For characterization of the epidemiology and impact of rMTBI, a large prospective longitudinal study is imperative. Success in this effort would guide preventive interventions, such as new guidelines for participation in sporting events. In addition, an enhanced understanding of rMTBI would help guide patient management such as diagnostic evaluations and rehabilitation. Finally, identification of pathologies associated with rMTBI could reveal therapeutic targets.

3.3 Scientific Merit

Numerous studies have documented the long term and often devastating consequences of severe TBIs (Anderson et al, 2000). More recent attention has focused on potential long-term sequelae of moderate and mild traumatic brain injuries and the effects of repetitive insults. Among the outcomes of MTBIs reported in adults are postconcussal syndrome (dizziness, nervousness, irritability, difficulty

concentrating) and information processing abilities (Carlsson, Svardsudd, & Welin, 1987). Some signs and symptoms may not appear until days to weeks following the concussion. At least two studies have suggested that the effects of multiple mild injuries in adults are cumulative (Jordan & Zimmerman, 1990; Gronwall, Wrightson, 1975). Furthermore, studies have documented a period of increased vulnerability following an initial insult. This "second impact syndrome" describes the catastrophic or even fatal outcomes that can occur when repeat brain injuries are sustained in a short time and may be related to metabolic changes in the brain and changes in brain blood flow that can persist for some time following an initial impact (Bergsneider et al., 2001). Some authors believe that the second impact syndrome is due to an un-diagnosed brain injury, which is then followed by another blow to the head. However, the effects of MTBIs on recurring head injuries in young children are not known. One of the reasons for this lack of information is that the signs of postconcussal syndrome may be difficult to detect in young children. In addition, few controlled studies have been done on MTBIs in children, and none have been done in children younger than age 5.

This lack of knowledge is of particular concern because mild head injuries are more common in children than in adults (Luerssen, 1988). Additionally, very young children may be more susceptible to persistent deficits secondary to TBIs than older children. Relative to their older counterparts, younger children had a poorer recovery of both IQ (Anderson et al., 2000) and of discourse function (Chapman & McKinnon, 2000) following a TBI. However, some animal studies have suggested that the immature brain may actually confer some protection (Bergsneider et al., 2001). What is clear is that outcomes depend both on the severity of the injury and on the maturational state of the brain (Bergsneider et al., 2001).

Studies have shown that persons who have had at least one TBI are at increased risk for a subsequent TBI (Salcido & Costich, 1992; Annegers, Grabow, Kurland, & Laws, 1980). Only a limited number of studies have examined the cumulative effects of mild or moderate head injuries in children (Bijur et al., 1996). Results of the study performed by Bijur et al. indicated that children who had sustained multiple mild head injuries did not differ in cognitive outcomes from matched children who had sustained multiple non-head injuries. In this study subjects were identified after the injury occurred, so pre-morbid assessment of their neurocognitive ability was unavailable for comparison. Instead, peers were used as controls for neuro-cognitive assessment. Further, the study had a small number (278) of children with more than one head injury, and the study also did not focus on very young children.

3.4 Potential for Innovative Research

It is anticipated that as the study progresses, the use of repeated standard neurocognitive outcome measures (including the potential use of surrogate biomarkers of injury) will allow elucidation of unknown features of rMTBI and the impact of rMTBI on trajectories of development. Elucidation of neuropathological mechanisms of brain injury from mild head trauma thorough neuroimaging techniques would enhance understanding of the pathophysiology of this exposure. Such measure are not feasible for the entire cohort but may be possible by internal adjunct studies on a sub-sample of individuals. In addition, these findings may reveal potential mechanisms that lead to a lowered threshold for morbidity with repeated injuries. Experimental confirmation of these mechanisms could lead to the development of novel therapeutic strategies to mitigate the exacerbated effects of rMTBI.

3.5 Feasibility

A standard battery of neuropsychological measures already exists that can detect neurocognitive dysfunction in single TBI and rMTBI. Collectively, several previous studies and a recent expert working group has provided a report to the CDC with detailed methodology for assessing

outcomes in children with TBI (CDC, 2000; Bijur et al., 1996; Gale et al., 2005; Gordon, 2006; Guskiewiz et al., 2003; Hawley et al., 2002; Inglese et al., 2005; Taylor et al., 1999, 2002).

Conventional brain imaging fails to identify changes in MTBI that are otherwise identified with histopathology (Adams et al., 1982; Ashwal et al., 2006; Bigler, 1999; Wallesch et al., 2001). New neuroimaging techniques have identified brain signal changes after MTBI suggestive of pathology, such as diffuse axonal injury and change in the volume of the brain (Adams et al., 1982; Arfanakis et al., 2002; Ashwal et al., 2006; Inglese et al., 2005; Wilde et al., 2005, 2006). It is anticipated that these changes will become more overt with repeated injuries. These advanced neuroimaging techniques include magnetization transfer imaging, diffusion-tensor imaging, susceptibility weighted imaging and brain volumetry (Adams et al., 1982; Arfanakis et al., 2002; Gale et al., 2005; Inglese et al., 2005; Levin et al., 2000; Tong et al., 2004; Wilde, Chu et al., 2006; Wilde, Hunter et al., 2005). Notably, most major pediatric centers have capabilities to perform these advanced neuroimaging techniques, and could be applied to an exposed sub-group as an internal adjunct study.

As a first diagnostic step, it would be ideal to have a simple blood test to rapidly identify brain pathology in rMTBI (Begaz et al., 2006; Qureshi, 2002; Rosen et al., 1998). Although there are no current conventional tests for surrogate markers of TBI in the serum, many promising approaches are currently in development and are anticipated to be available well within the study period (Begaz et al., 2006; Oureshi, 2002; Rosen et al., 1998).

Collectively, these measures can noninvasively detect the progression of neurocognitive and neuropathologic changes after rMTBI.

4. Exposure Measures

4.1 Individuals Targeted for Measurement

Primary/child

- Repeated TBI (to be compared to patients with a single TBI and patients with no history of TBI).

4.2 Methods

Primary/child

- Interviews/questionnaires
- Medical record review
- Advanced neuroimaging for a targeted sub-group as an adjunct study if possible
- Evaluation of serum surrogate markers of brain pathology
- Evaluation of behavioral, neurological and developmental surrogate markers

4.3 Life Stage

Primary/child

- After birth through 21 years

5. Outcome Measures

5.1 Outcomes Targeted for Measurement in Child

Primary

- Neurocognitive development: Behavioral, neurological and developmental outcomes.

5.2 Methods

Primary

- Examinations including neuropsychological, cognitive, and behavioral tests
- Interviews/questionnaires with parents on child behavior
- School records review (grades/performance/behavior)
- Medical record review
- Possible advanced neuroimaging for targeted subgroup as an adjunct study

5.3 Life Stage

Primary

- Periodically at all intervals after birth

6. Important Confounders, Mediators, and Effect Modifiers

- **Demographic variables:** Age, gender, and ethnicity may influence social acceptance of physical aggression of children or parental physical discipline of the child.
- **SES:** Children of disadvantaged backgrounds are at risk for poorer recovery from TBI (Taylor et al., 1999, 2002).
- **Risk-taking assessment:** Children with higher levels of risk-taking attitudes are more likely to sustain a second TBI. (Anderson et al., 2000)
- **Media influences:** Frequency and content of television viewing and video and computer use may impact a child's behavior and risk of injury.
- **Neighborhood characteristics:** Geographic area of residence as well as neighborhood characteristics and school environments put children at risk for poorer recovery from TBI. (Taylor, 2002)

- **Gene-environment interactions:** Parenting effects may be confounded with shared genetic tendencies toward risk taking and injury.

- **Parental IQ:** Parental IQ has been shown to affect parental depression, early parenting, a child's IQ, a child's behavior, and the interaction between parent and child behavior as well as home environment more globally and may have confounding effects on the prediction of head injury.

7. Power and Sample Size

All children with traumatic brain injury

According to the CDC, 7 of every 1,000 children under age 10 visit the emergency room for head trauma each year. Children with rMTBI would be expected to be more prevalent in this study in any given year. There will also be an opportunity to aggregate the subset of the study population with repeated head trauma events over the course of the study.

Power estimates are for analyses of variance including three matched groups of participants: those with repeated mild traumatic brain injuries; those with single mild traumatic brain injuries; and those with no brain injuries. Because CDC estimates that 0.7 percent of children seek medical attention for head trauma each year, the multiplicative probability of repeated head trauma prompting an emergency room visit is estimated at 0.000049 percent per year. In the National Children's Study (NCS), with a total sample of 100,000 and 20 years duration, this would result in a conservative estimate of 100 cases of repeated mild traumatic brain injury over the course of the Study. This is in fact a very conservative estimate, as the CDC statistics are based on emergency room visits and therefore do not include other forms of medical attention that might be sought for mild traumatic brain injuries such as visits to a primary care physician. If this group were matched to others with single mild traumatic brain injuries and no traumatic brain injuries, the analysis would entail three groups of 100 cases each.

Below are estimates of power for small, medium, and large effect sizes. Using the estimated sample of 100 per group, and an alpha of .05, power is sufficient for analyses with medium and large effect sizes.

Effect size	R^2	Power
Large	.14	.99+
Medium	.06	.98
Small	.01	.32

8. Other Design Issues

- Additional neuropsychological testing: Imaging for exposed sub-group if possible, and surrogate marker analysis would provide an additional burden to the participant and family but may be required for other aspects of the cohort study. More in-depth tests may be considered for the subsample of children suffering a single MTBI, and a non-injured control group, which would add additional burden to these subgroups and their families.

- Cost/complexity of data collection: Because this hypothesis will be assessed through ongoing data collection from subjects throughout the Study, response and retention rates of participants will be important.

- Ethical/burden considerations: Family privacy must be protected for the collection of sensitive information about injury and associated parenting variables. Detected instances of child abuse and/or neglect must be reported to authorities.

9. References

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BEHAVIORAL EXPOSURES, GENETICS, AND CHILDHOOD OR ADOLESCENT ONSET AGGRESSION

1. Meta Hypothesis

Biological, physical, and psychosocial components of the environment and their interactions with specific genetic variations are associated with and determine patterns of increased onset and maintenance of antisocial physical aggression.

2. Specific Hypotheses

1. Behavioral exposures of parenting styles and other psychosocial experiences (such as domestic violence, family conflict, parental criminality, and substance abuse) interact with specific genetic variations (gamma aminobutyric acid receptors, levels of monoamine oxidase, serotonin, and dopamine) to determine early onset and persistent chronic physical aggression.

2. Adolescent onset physical aggression is determined by a different pattern of interacting environmental and biological factors than for early onset persistent aggression. These exposure factors include poor parent-child relations, lack of parental/neighborhood supervision and family activities, high levels of family conflict, restricted opportunities to participate in adult-supervised conventional activities (sports, music, drama, etc.), access to weapons, exposure to antisocial peers, exposure to violence in the media (including video games), victimization by peers, and characteristics of the neighborhood environment.

3. The onset and extent of increased persistent chronic physical aggression and adolescent onset physical aggression, as distinguished from normative developmental patterns of physical aggression, can be individually predicted by the combination and pattern of interacting genetic, psychosocial, and contextual exposure factors.

3. Background and Justification

The use of physical aggression arises during childhood as a normative behavior with most individuals demonstrating some level of physical aggression at some point during childhood or adolescence (Alink et al., 2006; Brame, Nagin, & Tremblay, 2001; Cote, Vaillancourt, LeBlanc, Nagin & Tremblay, 2006). For most children, the use of physical aggression then declines with age. For some individuals, physical aggression then increases again during adolescence (Moffitt, 1993). Investigators have begun to tease out a limited number of developmental "trajectories," or longitudinal patterns, of aggressive behavior across childhood and adolescence that have been confirmed within a variety of populations (Broidy et al., 2003).

Two main developmental trajectories for aggressive antisocial behavior have been proposed: "life-course persistent" and "adolescence-onset" antisocial behavior (Moffitt, 1993). Life-course persistent, or early-onset, antisocial behavior is proposed to appear as early as preschool and to be characterized by severe persistent aggression accompanied by multiple problem behaviors including noncompliance, lying, stealing, poor academic performance, truancy, and excessive alcohol and drug use during adolescence. Adolescence-onset antisocial behavior is proposed to have little or no precursor in childhood behavior problems, and the antisocial behavior itself appears to be less severe, less frequent, and limited to adolescence.

The more serious early-onset aggression has been confirmed, particularly in boys, through research from several countries (Broidy et al., 2003; Cote et al., 2006; Eley, Lichtenstein, & Moffitt, 2003; Nagin & Tremblay, 2001; Van Lier & Crijnen, 2004). This developmental trajectory may include varying rates of physical aggression at different ages, but, those who are most aggressive as toddlers appear to be most likely to be aggressive through subsequent developmental stages (Brame et al, 2001; Cote et al., 2006; Lacourse, Nagin, Vitaro, Cote, Arseneault, & Tremblay, 2007).

Monoamine oxidase (MAOA), as a catabolic enzyme, regulates monoamine transmitter levels in the central nervous system. The activity of this enzyme is partly genetically regulated. The MAOA gene has several common polymorphisms, which Sabol et al (1998) was first to report in the promoter region of the MAOA gene. The nonpromoter MAOA gene polymorphisms have been implicated in mood disorders, aggression, and suicide. Some studies found that the certain polymorphisms of MAOA are associated with bipolar affective disorder (Rubinsztein, Leggo, Goodburn, Walsh, & Jain, 1996; Preisig et al, 2000). In addition, an association with bipolar disorder was found in one meta-analysis (Furlong et al, 1999). Current research is focusing on the possibility of MAOA influencing the risk for suicidal behavior by affecting aggressive/impulsive traits, mood disorders, or other factors. Studies that plan a developmental and longitudinal approach offer a more promising future in this area of research.

3.1 Public Health Importance

Prevalence/incidence

Mothers' reports indicate many children begin to use physical aggression before the end of their first year of life (Tremblay et al., 1999). The cumulative rate of physical aggression increases thereafter, reaching a peak between 18 and 24 months when almost 80 percent of children are reported to have been physically aggressive at some point (Tremblay et al., 2004; Keenan & Wakschlag, 2000; Hay, Castle, & Davies, 2000). About 29 percent of highly aggressive early childhood children persist in their aggressive behavior through adolescence, with 3-16 percent of children overall manifesting the life-course persistent pattern depending on the definition of aggression and the stage in childhood that is examined (Brame et al, 2001; Broidy et al., 2003; Cote et al., 2006; Nagin & Tremblay, 1999). Boys are much more likely to show the life-course persistent pattern than girls; research estimates the difference at 10:1 (Moffitt, & Caspi, 2001). Boys who demonstrate the highest levels of persistent aggressive behavior appear, from multiple studies, to be at highest risk for violent and criminal behavior as adults (Nagin & Tremblay, 1999; Fergusson & Horwood, 1995).

There is also evidence of aggression and general rule violations that emerge during adolescence. During adolescence, the prevalence of physical fighting appears to increase, with about one-third of high school students reporting being involved in a physical fight (Eaton et al., 2006). Research has estimated the prevalence of adolescent-limited aggression at 22 percent, with boys 1.5 times more likely to be in this group than girls (Moffitt, & Caspi, 2001).

Economic and social burden

It is estimated that 25 percent of the tangible costs associated with violent crime in the United States are attributable to juveniles (Miller, Fisher, & Cohen, 2001). Based on this assumption and a 1996 report estimating the tangible costs of violent crime in the United States, the estimated annual cost of juvenile violence in 2003 dollars was $24.3 billion (Miller, Cohen, & Wiersema, 1996).

Some early intervention efforts have been successful in reducing both economic and social burdens. One successful intervention was a randomized control group intervention with mothers and their

young children who were at risk for antisocial behavior. The intervention, which involved home visitation by a nurse from pregnancy to child age 2, reduced the incidence of arrests and conviction in the children in the home visitation group 15 years later, during adolescence (Olds et al., 1998). Preschool intervention has also been effective at reducing antisocial outcomes in children at risk for poor social outcomes with an estimated savings to society of $7-$16 for every dollar spent by the time the children reached age 40 (Nores, Belfield, Barnett, & Schweinhart, 2005). This indicates knowledge about causal factors can be translated into effective treatment modalities.

3.2 Justification for a Large Prospective Longitudinal Study

Although there are various prospective, longitudinal studies documenting physical aggression and violence and their risk factors, many confound physical aggression and verbal or indirect aggression, delinquency, hyperactivity, oppositional behavior, or other disruptive behaviors, lumping together disparate constructs. Some studies have small samples; none is based on a representative sample of the United States; few have prospectively collected data during pregnancy; few have collected data from birth; few have collected data on girls or examined differences among ethnic or racial groups; none has done so among Latinos; and each assessed only a subset of the potential risk factors, often singly or in small groups, not simultaneously and comprehensively.

While there are some existing longitudinal data on the trajectory of physical aggression through childhood and into adolescence, a compelling justification for the National Children's Study (NCS) to include outcomes related to physical aggression is the ability to link prenatal, genetic, familial, and environmental exposures as well as the interactions between exposures with membership in a particular trajectory group. A large longitudinal sample will be needed to identify the full range of trajectory groups. It is clear that a relatively consistent group uses physical aggression with higher-than-average frequency throughout childhood. There is variability even within this group (Brame et al., 2001; Cote et al, 2006; Tremblay et al., 2004) possibly indicating the presence of multiple subgroups. Only a large cohort study will suffice to answer questions about the etiology of aggression during childhood and its manifestations through adolescence.

Once the trajectories are identified, longitudinal observation will allow better understanding of the sequencing of influences. For example, it is not clear whether early coercive parenting leads to children who are more aggressive, whether children who are physiologically predisposed to be aggressive reinforce the use of more coercive parenting (Jaffee et al, 2004), or whether a shared genetic predisposition may predict parenting style and childhood aggressive behavior. The depth of longitudinal data from the NCS will help untangle these issues.

3.3 Scientific Merit

During the past decade, a series of cohort studies have collected longitudinal data on the frequency of use of physical aggression through childhood and adolescence. These studies identified three to five distinct developmental trajectories for physical aggression, depending on the country, sample, and size of the cohorts (Broidy et al, 2001). These trajectories include early appearance of normative aggression with a decline through childhood; life-course persistent aggression involving early-onset of high levels of aggression maintained over time; late-onset, adolescence-limited aggression; and other similar but slightly varied trajectories across studies.

Some differences in etiology of the early-onset and late-onset trajectories have been identified, but the actual pathways are still unclear. Most research has focused on etiology of the early-onset, life-course persistent pattern. Because the majority of children belong to the trajectory of early appearing low-level aggression that remits quickly, it has been hypothesized that physical aggression is a

normal part of early development, but a series of factors inhibit it (Brame et al., 2001; Nagin & Tremblay, 2001). These factors have been shown in at least one study (the gene for MAO-A in boys) to interact directly with the social environment to affect the life-course pattern of use of physical aggression (Caspi et al., 2002), although this interaction has not been replicated in more recent reports (Young et al., 2006). Research has also implicated an interaction between biological risk (e.g., perinatal and birth complications, maternal illness during pregnancy) and social risk (e.g., harsh or neglectful parenting) in the development of life-course persistent aggression (Brennan, Hall, Bor, Najman, & Williams, 2003). Increasing evidence suggests early adverse experiences such as maltreatment may affect children differently depending on their genotypes (Jaffee et al, 2004). This evidence leads to questions about the multigenic etiology of physical aggression. Other such interactions will likely be identified as more information is collected regarding general brain chemistry and its genetic associations and variations, and as the relationship of exposures to particular developmental trajectories is better elucidated (Moffitt, Caspi, & Rutter, 2005).

Late-onset, adolescence-limited physical aggression seems to be associated primarily with environmental factors, including harsh parenting, high levels of adolescent life stress, and association with deviant peers (Brennan et al., 2003; Aguilar, Sroufe, Egeland, & Carlson, 2000). The adolescent-onset trajectory also does not show the types of gender differences that life-course persistent trajectory does, with more girls engaging in adolescent physical aggression than in early-onset stable aggression (Moffitt, & Caspi, 2001). Late-onset physical aggression is not, however, benign. It is associated with higher levels of internalizing symptoms such as depression during adolescence (Aguilar et al., 2000), and with elevated mental health problems, substance use, and nonviolent crime during young adulthood (Moffitt, Caspi, Harrington, & Milne, 2002). More research can uncover the range of longitudinal correlates of this trajectory.

3.4 Potential for Innovative Research

No studies to date have had sufficient diversity and sample size to identify and analyze the range of trajectories of aggression. The NCS will provide the opportunity to not only identify the trajectories but also to develop subgroups of sufficient size to delve effectively into genetic, environmental, and social correlates and interactions among them.

The Study will also collect more information on maternal and paternal genetics and prenatal exposures than has ever been available previously. More thorough mapping of factors that influence the development of aggression should be possible. Targeted intervention for children at risk for antisocial behavior has been shown to work, so results from this research should allow for more effective targeting of those at risk.

Research has not uncovered clear exposures that differentiate adolescents with late-onset physical aggression from those who are at risk yet do not engage in physical aggression. Because this pattern is not fully transient and because even limited forays into physical aggression are costly to the individual and to society, the opportunity to elucidate the origins of this pattern will be important.

3.5 Feasibility

These studies are feasible because physical aggression has been the focus of substantial measurement at different ages. Repeated measures of aggression will be critical to permit tracking of the trajectories. Fortunately, there are valid and reliable measures of physical aggression easily administered and parsimonious, beginning in the toddler and extending well adulthood.

Such measures can be administered to a range of respondents (parents, teachers, and children) to permit the collection of a variety of perspectives and contexts. Longer, more detailed measures can be done through survey or interview, and brief measures can be administered by phone. For children, parent report is a standard measure in the field and would provide data to compare with other longitudinal studies. For school-aged children, teacher report and parent report have both been used and would be important to collect for comparability with past research. In addition, child self-report is possible among older children, and adolescents are often uniquely informative about their own, otherwise undetected, delinquent behavior.

4. Exposure Measures

4.1 Individuals Targeted for Measurement

Primary/maternal

- Alcohol, drug, tobacco use
- Nutrition
- Stress
- Age at child's birth

Primary/family

- Socioeconomic status (income, parental education, employment)
- Parenting (warmth, discipline, monitoring, maltreatment)
- Family stress
- Interparental conflict
- Domestic violence
- Neighborhood characteristics

Primary/child/adolescent

- Difficult temperament
- Cognitive development
- Congenital anomalies/birth complications
- Peer relationships/affiliations
- Substance use (alcohol, drug, tobacco)

4.2 Methods

Primary/maternal

- Interview
- Questionnaire
- Clinical events and ongoing health history

Primary/family

- Interview
- Questionnaire
- Direct observation of parent-child relationship

Primary/child/adolescent

- Interview (parent, child, teacher)
- Questionnaire (parent, child, teacher)
- Direct testing of children
- Clinical events and ongoing health history

4.3 Life Stage

Maternal

- Prenatal

Family

- Infancy, childhood, adolescence

Child/adolescent

- Infancy (parent, direct testing)
- Childhood (parent, child, teacher)
- Adolescence (parent, child, teacher)

5. Outcome Measures

5.1 Outcomes Targeted for Measurement in Child

- Physical aggression
- Criminal behavior

5.2 Methods

- Questionnaires (parent, child, teacher)
- Direct observation of parent-child interaction
- Public record

5.3 Life stage

- Questionnaires: Regularly beginning in the toddler period and through age 21
- Observation: Infancy, childhood, adolescence
- Criminal behavior: Age 21

6. Important Confounders, Mediators, and Effect Modifiers

- **Demographic variables:** Age, gender, and ethnicity may influence social acceptance of physical aggression of children or parental physical discipline of the child.
- **Media influences:** Frequency and content of television viewing and video and computer use may impact a child's aggressive behavior.
- **Neighborhood characteristics:** Geographic area of residence as well as neighborhood characteristics may affect a child's aggression.
- **Gene-environment interactions:** Parenting effects may be confounded with shared genetic tendencies toward aggression between parents and children.
- **Parental IQ:** Parental IQ has been shown to affect parental depression, early parenting, a child's IQ, a child's behavior, and the interaction between parent and child behavior as well as home environment more globally and may have confounding effects on the prediction of child aggression.

7. Power and Sample Size

Starting with the birth cohort of 100,000, the minimum odds ratio between measures of the child's physical aggression and hypothesized exposures will depend on the measure of physical aggression used, the prevalence of the exposure, and the age at which the assessment is completed. For this discussion, higher levels of exposure are assumed to contribute to higher levels of the outcome. The

calculations assume a target of 80 percent power using a two-sided 95 percent confidence interval and an intraclass correlation based on the study's sample design.

For the approximately 16 percent of children with high levels of physical aggression from infancy to age 12), the smallest reliably detectable odds ratio is 1.10 with an exposure prevalence of 25 percent. If the exposure used in the analysis has a prevalence of 5 percent, the minimum detectable odds ratio goes up to 1.21. If this same analysis is restricted to a subset of 10 percent of the population (possibly corresponding to the prevalence of a genetic marker), the minimum detectable odds ratio goes up to 1.54.

Assuming an assessment at age 20 when assessing the incidence of physical aggression in adolescence and still assuming 16 percent of children with high levels of physical aggression, the smallest reliably detectable odds ratio with an exposure prevalence of 25 percent is 1.11.

Assuming 4 percent of children have particularly high levels of aggressive behavior related to an exposure with a prevalence of only 5 percent, the minimum detectable odds ratio is 1.42. If this same analysis is restricted to a subset of 10 percent of the population (possibly corresponding to the prevalence of a genetic marker), the minimum detectable odds ratio goes up to 2.17. Thus, the power for testing these hypotheses in the Study is very good.

Considering interactions with genetic factors for aggression, a hypothesized gene (MAOA) and environment (child abuse) interaction was evaluated by considering the two most common variable number tandem repeat polymorphisms, the three-repeat variant with low activity and the four-repeat variant with high activity. These alleles have a population prevalence of about 33 percent and 62 percent, respectively (Brame et al., 2001). Child abuse was cited as 8 percent severe, 28 percent probable abuse and 64 percent with no abuse. Power analyses based on a prevalence of 5 percent in the unexposed population (conservative according to Caspi et al.) result in a required sample size of 31,650.

8. Other Design Issues

- **Ethical/burden considerations**: Family privacy must be protected for the collection of sensitive information about aggression and associated parenting variables. Detected instances of child abuse and/or neglect must be reported to authorities. Regarding burden, although regular assessment of aggression is required, there are brief measures that can be used for phone contact, which will reserve more in-depth measures for in-person contact.

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ANTECEDENTS AND RESILIENCY TO TRAUMATIC LIFE EVENTS IN CHILDHOOD

1. Meta Hypothesis

Antecedent factors such as genetic risk, family structure, neighborhood and community factors interact with traumatic life events to predict the risk of anxiety disorders.

2. Specific Hypotheses

1. The cumulative effects of repeated exposure to traumatic events (parental divorce, death of a family member) increase the risk of anxiety disorders in children.

2. A child's set of resiliency factors buffers the relationship between exposure to traumatic events and subsequent posttraumatic stress disorders.

3. Childhood intelligence is an antecedent for both risk of exposure to traumatic events and subsequent development of anxiety disorders.

4. A child's sensitivity to traumatic events has a strong genetic component, which interacts with the timing and magnitude of traumatic events to predict the risk for anxiety disorders.

5. The severity of a child's posttraumatic stress symptoms in reaction to potentially traumatic events increases the risk of negative physical health and functional outcomes.

6. Genetic variants implicated in neurobiological mechanisms central to the "fight-or-flight" response (dysregulation in the HPA axis, locus coeruleus/noradrenergic system, and limbic-frontal brain systems) influence the vulnerability to anxiety disorders after exposure to traumatic events.

3. Background and Justification

3.1 Public Health Importance

Prevalence/incidence

Anxiety disorders in children are a public health burden due to their economic costs, comorbid mental disorders, chronicity through life, and association with general medical conditions. As a general class, anxiety disorders are the most prevalent class of mental disorders (Kessler et al., 2005), with a cumulative prevalence of 9.9 percent by age 16 (Costello et al., 2003) lifetime prevalence of 28.8 percent (Kessler et al., 2005). Frequently occurring anxiety disorders include generalized anxiety disorder (GAD), phobias, panic disorders (PD), obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), and separation anxiety disorder (SAD). The median age of onset for the class of anxiety disorders using retrospective recall is age 11 (Kessler et al., 2005), making this especially relevant for the young participants of the Study. Specific and social phobias have a median age of onset of 7 to 13 years, respectively. SAD and PTSD have a median age of onset of 7 to 23 years, respectively.

Mortality/morbidity/quality

Anxiety disorder subtypes are linked. Each subtype has a potentially different underlying multifactorial etiology; however, anxiety disorder subtypes frequently co-occur. As an example, as many as 83 percent of individuals with GAD also have another active anxiety disorder (Dyck et al., 2001). The presence of a pre-existing anxiety disorder also increases the subsequent risk of developing another anxiety disorder subtype. A four-year longitudinal study found that adolescents with SAD had an increased risk of developing subsequent PD with agoraphobia (hazards ratio [HR] = 18.1), specific phobia (HR = 2.7), GAD (HR = 9.4), and OCD (HR = 10.7) (Bruckl et al., 2007). Anxiety disorders also have an extremely high comorbidity with major depression, which is among the top five leading causes of disability and disease burden in the world (Murray et al. 1997; Wang et al., 2003; Sartorius 2001). This comorbidity is estimated to be as high at 70 percent (Kessler et al., 1999), which provides further evidence that anxiety disorders are extremely costly for society.

Individuals with anxiety disorders are at higher risk, compared to nonaffected individuals, for adverse cardiovascular events (Kubzansky et al., 1997) and suicide attempts or ideations (Allgulander, 1994; Sareen et al., 2005). Medical illnesses are frequently associated with anxiety as in the case of diabetes for which GAD occurs in 14 percent of cases (Grigsby et al., 2002). Anxiety symptoms, and specifically GAD symptoms, both predicted greater risk for coronary heart disease, which was independent and in excess of the risk associated with major depression (Barger & Sydeman, 2005).

Economic and/or social burden

Child data on economic costs are limited. In the adult population, the economic burden of anxiety disorders is estimated to be $42.3 billion to $46.6 billion annually in the United States (Dupont et al., 1996; Greenberg et al., 1999). Health costs directly associated with treatment of anxiety disorders are substantial. Average estimated total costs for individuals diagnosed with an anxiety disorder are $6,475, and having a diagnosis of PTSD increases that cost by $3,940 (Marciniak et al., 2005). Individuals with the highest health costs are anxious patients with depression, individuals with PTSD or GAD, and patients diagnosed with anxiety and a comorbid medical condition such as diabetes (Marciniak et al., 2005).

Preventability/malleability

Whereas pharmacological treatments for anxiety disorders continue to be modified for efficacy, the prevention of anxiety symptoms has not been as commonly addressed. The focus of targeted prevention programs should aim to understand what factors increase risk of exposure to traumatic events and to reduce the incidence of anxiety disorders like PTSD, GAD, and PD in individuals who have been exposed to trauma by boosting factors related to resiliency.

3.2 Justification for a Large Prospective Longitudinal Study

Because of the dearth of longitudinal studies on early antecedents of trauma, previous research has not been successful in clearly outlining causal mechanisms underlying exposure to trauma, identifying critical periods of vulnerability during development, and targeting opportunities for intervention. The longitudinal nature of the Study would allow prospective assessment of variables that have not been incorporated in studies of childhood traumatic stress, its antecedents, and consequences. These include genetic risk factors and prebirth parental variables (such as parent history of trauma exposure and anxiety disorders). The Study will advance the current understanding of risk associated with trauma exposure by elucidating causal pathways in which exposure to trauma is influenced by antecedent factors, exposure to trauma confers risk for anxiety disorders, and associations between traumatic exposure and anxiety outcomes are buffered by resiliency.

It is also essential to acknowledge the risk of anxiety disorder subtypes differs by exposure type and differing periods of vulnerability. Whereas the majority of previously published studies focuses on the risk for a specific disorder (e.g., PTSD), the Study will be able to identify how risk factors and the chronicity (relapse and recurrence) of anxiety disorder subtypes change during development.

3.3 Scientific Merit

Traumatic events and anxiety disorders

Exposure to physical or emotional trauma is a commonly suspected risk factor for anxiety disorders such as GAD, PD, and PTSD (Brantley, Mehan, Ames, & Jones, 1999; Brown et al., 2000). Many of the larger epidemiological studies of trauma exposure and anxiety symptoms in youth have focused on abuse, violence, and victimization (Boney-McCoy & Finkelhor 1995, Hanson et al., 2006). Only recently have studies begun to focus on children or youth assessed exposure to the full range of potentially traumatic events (PTEs) both high and low in magnitude (Breslau et al., 2004; Breslau, Lucia, & Alvarado, 2006; Costello, Erkanli, Fairbank, & Angold, 2002; Giaconia et al., 1995, Storr, Ialongo, Anthony, & Breslau, 2007). Breslau et al. (2004) and Storr et al. (2007) reported on a community-based prospective study that followed a group of 2,311 urban children enrolled at ages 6-7 and into young adulthood. By age 20-23, 82 percent of this sample had experienced at least one PTE, and 7 percent had PTSD at some point in the observation period. Across child/youth community-based studies on PTSD, the conditional probability of PTSD given exposure to any PTE ranged from 8.3 percent to 14.5 percent (Breslau et al., 2004, 2006; Storr et al., 2007). Several types of PTEs (most notably sexual assault and other assaultive violence) were found to confer a much higher risk of developing PTSD.

Many studies on the direct exposure to mass traumatic events focus only on posttraumatic stress symptoms in children (Goenjian et al., 2001; Smith, Perrin, Yule, & Rabe-Hesketh, 2001). PTEs are not only associated with PTSD. PTEs have been linked with greater risk of numerous mental disorders, including GAD or generalized anxiety disorder syndrome (defined as GAD for at least 2-weeks), PD (Bandelow et al., 2002), and major depression (Blazer, Hughes, & George, 1987; Angst & Vollrath, 1991; Newman & Bland, 1994; Kendler et al., 2003). Very few studies on the effects of PTEs have incorporated the broader range of anxiety disorders. Despite increasing awareness of PTSD onset after natural disasters and war, responses to traumatic events such as these are not limited to PTSD. As an extreme example, children in New York City public schools who were interviewed six months after September 11, 2001, were screened for elevated mental disorders in addition to PTSD. The most prevalent disorders identified were probable agoraphobia (14.8 percent), SAD (12.3 percent), followed by PTSD (10.6 percent), and GAD (10.3 percent) (Hoven et al., 2005).

PTEs in the form of alterations in family structure or environment have also been implicated in the risk for anxiety disorders. In addition to family history of GAD, an adverse family environment during childhood was associated with risk of GAD but was not a shared risk factor during childhood for major depression (Moffitt et al., 2007). Therefore, although there is high comorbidity between these two disorders, this suggests they have different etiological pathways. Traumatic stressors such as parental conflict, childhood physical abuse by a father figure, and the absence of a parent or adult confidant during childhood have also been associated with an increased risk of developing social phobia (DeWit et al., 2005). Two recent longitudinal studies provide evidence that trauma in the form of injuries may be associated with anxiety disorders. Unintentional injuries were associated with subsequent childhood separation anxiety symptoms (Rowe, Simonoff, & Silberg, 2007). Injury events in which adolescents perceived a threat to their life or having lack of control over the event were also strongly associated with PTSD risk (Holbrook et al., 2005).

Neurobiology of trauma exposure

When humans are exposed to stress or trauma, a complex activation of behavioral, autonomic, sensory-motor, cognitive, and neuroendocrine systems is elicited (Sanchez, Ladd, & Plotsky, 2001). The most commonly linked system to the stress response is the limbic-hypothalamic-pituitary-adrenal (LHPA) axis. Activation of the LHPA axis results in the downstream secretion of glucocorticoids (e.g., cortisol) and is an adaptive, critical mechanism by which humans cope with exposure to challenges. Although the stress response can be a protective function (McEwen, 1998), chronic exposure to stress can be damaging to neurons. Hypersecretion or hyposecretion of glucorticoids leads to neuronal atrophy, neurotoxicity, and neuroendangerment. Neuroendangerment occurs when the vulnerability of neurons alters their capacity to deal with subsequent neurologic insults (Sapolsky, 1996). Structural imaging studies on adults with exposure to stress and subsequent PTSD support these biological findings (e.g., reduced hippocampal volumes were found in adults and combat veterans with PTSD [DeBellis et al., 1999]). The association between hippocampal volumes and childhood PTSD is not as consistent (DeBellis et al., 1999; Bremner et al., 1995; Carrion et al., 2001; Carrion, Weems, & Reiss, 2007; Tupler & DeBellis, 2006). These conflicting findings are likely to be due to developmental differences in the biological mechanisms behind stress exposure, the continued maturation of the hippocampus throughout childhood and adolescence, and possible differences in the vulnerability of the LHPA system during the developmental period (Cicchett & Walke, 2001).

Childhood resiliency

Some children appear to be resistant to tremendous trauma whereas other children struggle after a stressful event. Resiliency refers to the concept of individual variations in response to comparable experiences. Resiliency also accounts for evidence that exposures to stress can increase resistance to later stress (Rutter et al., 2006). Thus, it is important to recognize that the type, timing, and magnitude of traumatic exposures during childhood may play a role in accumulating resiliency against later stress.

The resiliency concept purports that a host of factors, both proximal and distal, contribute to the variability in stress response. Prenatal factors, genetic makeup, developmental stage, prior exposures to stress, and economic hardship may act together to determine the different ways in which humans' neural systems react to a stressful event (McEwen et al., 1994; Sapolsky et al., 1994).

Genetic risk for traumatic exposure and anxiety disorders

There is evidence for a genetic influence on the exposure to certain forms of trauma and susceptibility to trauma and stress. Twin data suggest that certain forms (e.g., violent or assaultive) of trauma and stressful events have a genetic influence (Stein, Jang, et al., 2002; Kendler et al., 1993; Foley, Neale, & Kendler, 1996). This observation may be mediated through personality traits, such as neuroticism, which predispose a person to certain traumatic events and consequent anxiety disorders (Kendler, Myers, & Prescott, 2002; Stein, Jang, et al., 2002; Hettema, Prescott, & Kendler, 2004). Additionally, research by Yehuda, Halligan, & Bierer (2001) has documented an increased susceptibility to PTSD following exposure to traumatic events in the adult offspring of Holocaust survivors with PTSD compared to offspring of survivors without PTSD. The relative and overlapping contributions of genetic susceptibility to both exposure and anxiety require further research.

Family and twin studies suggest the familial aggregation of many types of anxiety disorders is high (Hettema, Neale, & Kendler, 2001). Individuals with PD have higher rates of psychiatric disorders in their families in general, especially PD and GAD (Bandelow et al., 2002). Summary odds ratios associated with family history range from 4.0 to 6.0 for PD, GAD, phobias, and OCD (Hettema et al., 2001).

Evidence for a genetic influence on PTSD risk has come from adult twin studies (Lyons et al., 1993, True et al., 1993, Stein, Jang, et al. 2002) which demonstrate an elevated risk of PTSD in the monozygotic (MZ) co-twin of a PTSD proband, compared to dizygotic (DZ) co-twins. Studies of veteran and community twin samples suggest that genetic influences account for about one-third of the variance in PTSD risk. The heritabilities for anxiety disorders range from 30-40 percent, denoting that the vast proportion of variance in risk may be explained by environmental factors (Hettema et al., 2001).

A growing number of studies have attempted to pinpoint candidate genes for anxiety disorders. One study found that polymorphisms in the GAD1 (glutamic acid decarboxylase) region were significantly over-represented in cases with a variety of anxiety disorders (Hettema et al., 2006). Association studies on PTSD and candidate genes involving in the dopaminergic system are conflicting, but Segman et al. (2002) present the strongest evidence for an association (Koenen, 2003). Further elucidation of the mechanisms through which genetic variants might influence PTSD risk comes from recent work by Koenen et al. (2005), who have demonstrated an association between polymorphisms in FKBP5 (posited to play a role in HPA axis regulation) and peritraumatic dissociation in children with burn injury. Despite the efforts of many studies to identify genes underlying anxiety disorders, concrete and adequately replicated evidence for specific genetic loci remains elusive (Merikangas & Low, 2005).

Physical health consequences of trauma exposure and anxiety disorders

There is evidence that both exposure to PTEs and the development of traumatic stress symptoms are each associated with poorer health and functional outcomes. For example, the Adverse Childhood Experiences study (retrospective adult report of adverse childhood experiences) has documented links between the degree of exposure to adverse childhood experiences (many of which would fit the definition of potentially traumatic event) and a wide range of physical health outcomes in adulthood (Dube et al., 2003; Dong et al., 2004). Child data is more limited, but suggests a similar link between trauma exposure and/or PTSD and adverse physical health and functional outcomes. Cross-sectional evidence to date also suggests, but cannot yet establish conclusively, that PTSD may serve as a mediator for the effect of traumatic exposure and adverse physical health outcomes such as circulatory, endocrine, and musculoskeletal conditions (Seng et al., 2005). In a preschool-age Head Start sample, exposure to violence and PTSD symptoms were also each associated with greater health problems such as asthma and gastro-intestinal problems (Graham-Bermann & Seng, 2005). Few longitudinal analyses have been conducted to support PTSD and other anxiety disorders as having a mediating effect in the causal pathway from PTEs to physical health outcomes. Only one study with a 24-month follow-up interval reported that injured adolescents had an increased risk for PTSD and that prolonged PTSD symptoms were associated with lower health-related quality of life (Holbrook et al., 2005).

Advancement of scientific understanding

The prospective data available to date regarding antecedents or predictors of exposure to PTEs, antecedents of anxiety disorders, and of the impact on child health and functioning, suggest that there are likely to be complex interactions among individual, family, and community factors. None of the existing prospective studies can shed light on etiological pathways that begin in early childhood and carry forward into adolescence or adulthood, and none include factors such as genetic risk, parental trauma, or history of psychiatric disorders. The National Children's Study (NCS) offers an ideal opportunity to tease apart these interactions and understand pathways to risk and how resilience buffers against children's all-too-common exposures to stressful or difficult events.

Capturing a broader range of exposures can provide a better estimate of the public health impact of exposure to trauma. Studying traumatic events requires examination of the continuum of events from high to low magnitude. Lower magnitude events occur more frequently throughout the lifespan compared to high magnitude events. While some experiences (such as sexual assault) may lead to a higher conditional probability of anxiety disorders, others (such as motor vehicle crashes) can potentially produce more cases in the population because of their frequency (Norris, 1992). By assessing the continuum of exposures, the field can move forward in its understanding of the circumstances by which the magnitude, timing, and chronicity of events contribute to the risk of childhood anxiety disorders. Increased understanding and awareness of PTEs may ultimately lead to improved preventive and treatment options for the occurrence and impact of traumatic events in childhood.

Directly addressing the lack of research on what factors contribute to resiliency, and whether these same factors contribute to risk of exposure to PTEs, will aid future efforts to prevent exposure, potentially alter factors to boost resiliency, and identify critical periods of vulnerability to intervene against the negative consequences of traumatic exposures.

3.4 Potential for Innovative Research

The NCS offers a unique opportunity to address the limitations of existing studies and to add significantly to our understanding of the scope and impact of exposure to PTEs in childhood. There has been no nationally representative study of the prevalence or consequences of exposure to the full range of PTEs in children and adolescents.

The literature to date suggests there are antecedent factors that affect underlying neuronal processes which control the stress response. These may be genetic, prenatal, behavioral, or cognitive in origin. However, these factors may also influence the likelihood that a child will encounter stressful or traumatic events. Furthermore, the same factors could determine the extent to which a child will respond with adverse psychopathology in the form of PTSD, GAD, or PD. There are complex relationships between biological processes involving the stress response, exposure to stressors or trauma, and the development of anxiety disorders. Only sophisticated longitudinal studies employing a developmental approach will be able to disentangle these intricate processes. There has not been a study of child and youth trauma exposure or anxiety disorders that is nationally representative, covers a broad range of traumatic event types repeatedly across childhood development, and provides sufficient prospective longitudinal data to trace relationships through time among family and genetic risk factors, trauma exposure, anxiety symptoms, and physical or functional health.

3.5 Feasibility

The longitudinal nature of the NCS makes it highly feasible to address the proposed hypotheses. The NCS assessment schedule targets critical periods of development to assess exposures and outcomes. Valid and reliable measures are available to assess 1) exposures across the full range of PTEs, 2) anxiety symptoms on a continuum (symptom) and categorically (diagnosis), 3) physical and functional health outcomes, and 4) a host of antecedent factors to risk of exposures.

Addressing this hypothesis is feasible given the structure of the study. Assessment of children's and parents' exposure to PTEs will be required to tackle the significant questions and hypotheses described here. Empirical data on the impact of traumatic stress interviews on research participants indicates high degrees of acceptance of these topics in research interviews.

4. Exposure Measures

4.1 Individuals Targeted for Measurement

Primary/maternal

- Exposure to potentially traumatic events
- Lifetime history of psychiatric disorders (e.g., depressive or anxiety disorders)
- Family history of psychiatric disorders (e.g., depressive or anxiety disorders)
- Genotyping for genetic risk factors
- Behavioral problems (e.g., antisocial, violent or criminal behaviors)
- Parenting style
- Parent-child interactions
- Community resources, social capital, etc.
- Socioeconomic status (income, wealth, education)

Primary/paternal

- Exposure to potentially traumatic events
- Lifetime history of psychiatric disorders (e.g., depressive or anxiety disorders)
- Family history of psychiatric disorders (e.g., depressive or anxiety disorders)
- Genotyping for genetic risk factors
- Behavioral problems (e.g., antisocial, violent, or criminal behaviors)
- Parenting style
- Parent-child interaction

Primary/child

- Exposure to potentially traumatic events (e.g., maltreatment, neglect, abuse, family conflict, serious illness, injury, witnessing/learning of trauma to a loved one, romantic break-up, or loss of a friend)
- Cognitive and intelligence measures
- Genotyping for genetic risk factors
- Behavioral problems (e.g., antisocial, violent or criminal behaviors)

- Parent-child interactions
- Cortisol levels

Secondary/maternal, teacher proxy report

- When a child is too young for self-reported exposures, a mother can report her child's exposure to potentially traumatic events and stressful life events
- Behavioral problems (e.g., disruptive, aggressive, antisocial, violent, or criminal behaviors)

4.2 Methods

- Blood samples for genotyping
- Salivary cortisol
- Interview/questionnaires for exposures to traumatic or stressful events (e.g., Life Events Interview section of the Child and Adolescent Psychiatric Assessment, alternatively, the NIMH Diagnostic Interview Schedule)
- Parent-child interaction task
- Family environment (e.g., HOME)
- Cognitive and intelligence testing (e.g., Wechsler Intelligence Scale for Children-Revised or Woodcock-Johnson subtests)
- Behavioral problems (e.g., Child Behavior Checklist, or Strengths and Difficulties Questionnaire)

4.3 Life Stage

Primary/maternal

- Repeated assessments throughout the study

Primary/paternal

- Repeated assessments throughout the study

Primary/child

- Repeated assessments from early childhood through the study. Self-reported exposures can be assessed after approximately age 7

Secondary/maternal, teacher proxy report

- Repeated assessments of exposures during early childhood until the child is age 7
- Behavioral problems can be assessed by mothers and/or teachers at the study visit that falls closest to when child enters first grade

5. Outcome Measures

5.1 Outcomes Targeted for Measurement in Child

- Anxiety symptoms or categorical (yes/no) diagnosis of an anxiety disorder
- Other comorbid psychiatric disorders or symptoms
- Physical health (e.g., chronic conditions such as diabetes, asthma, or those involving the circulatory, endocrine, gastrointestinal, or musculoskeletal systems)
- Functional health (e.g., quality of life)

5.2 Methods

- DSM-IV-based assessments for anxiety disorders (e.g., Child and Adolescent Psychiatric Assessment or the NIMH Diagnostic Interview Schedule for Children)
- Physical health outcomes via direct physical assessments or medical record reviews
- Functional outcomes via observational assessments and interviews

5.3 Life Stage

- Repeated assessments throughout the study. Relevant instruments will be administered where they are validated for specific age ranges

6. Important Confounders, Mediators, and Effect Modifiers

- **Gender:** Females are approximately twice as likely to have anxiety disorders such as GAD compared to males (Wittchen, Zhao, Kessler, & Eaton, 1994). Males are more likely to be exposed to a PTE, but females are more likely to develop PTSD given exposure. Gender may also influence the course of some anxiety disorders such as PD (Yonkers et al., 1998).
- **Age:** Age has differential effects on specific types of anxiety disorders. As one example, the prevalence rates of GAD are low in adolescence but increase substantially with age (Witttchen & Hoyer, 2001).
- **Race/ethnicity:** Anxiety disorders in general are found more commonly in racial/ethnic minorities (see Kessler & Wittchen, 2002 for review).

- **Socioeconomic status (SES):** In general, anxiety disorders occur more frequently in people with lower income and education (Wittchen et al., 1994; Brawman-Mintzer & Lydiard, 1996; see Kessler & Wittchen, 2002 for review). The extent of risk associated with SES is dependent upon the type of anxiety disorder.

- **Family history of anxiety and other psychiatric disorders:** Parental family history of major depression and anxiety disorders conveys the risk of anxiety disorders to their offspring (Biederman et al., 2001).

- **Family environment:** Costello et al. (2002) found that family environment factors increased exposure-specific risk. Having a parent with a criminal record or a disorganized family environment increased the likelihood of exposure to some PTEs (sexual abuse, traumatic events occurring to loved ones), but did not affect the likelihood of others (physical violence, serious accidents or illness).

- **Stressful life events:** Certain stressful life events (e.g. parental separation or divorce, moving, or changing schools) increase the chances of experiencing a later PTE (Costello et al. 2002).

- **Intelligence and cognitive ability:** Breslau et al.(2006) found that a lower IQ at age 6 predicted both greater trauma exposure and more PTSD symptoms by age 17. Youths who scored higher in reading readiness tests were also at lower risk for exposure to assaultive traumas (Storr et al., 2007).

- **Major depression:** Depression is often correlated with anxiety disorders and has a similar genetic component (Kendler et al., 2007). There is evidence that depression has different etiological pathways such that it is not the same underlying disorder and therefore must be considered an important confounder.

- **Pre-existing behavioral problems and other psychiatric symptoms/disorders:** Early aggressive/disruptive behavior problems have been found to predict greater exposure to assaultive violence but not other nonassaultive PTEs by late adolescence (Breslau et al., 2006, Storr et al., 2007). Additionally, anxiety and depressive problems at age 6 predicted greater conditional risk for PTSD, given exposure to a PTE, by late adolescence (Breslau et al., 2006, Storr et al., 2007). In adolescents ages 14-24, the presence of a pre-existing anxiety disorder at baseline predicted exposure to traumatic events during the follow-up period, possibly due to a tendency to report events as being particularly horrific (Stein, Hofler, et al., 2002). In adolescents with major trauma, the risk of PTSD was significantly and strongly associated with drug and alcohol abuse and other adolescent behavioral problems (Holbrook et al., 2005). In addition, the presence of illicit drug use in adolescents and young adulthood predicted later onset of traumatic events that were assaultive and sexual in nature (Stein, Hofler, et al., 2002).

- **Cigarette smoking:** Cigarette smoking is correlated with anxiety symptoms (Breslau, Kilbey, & Andreski, 1991; Amering et al., 1999). The direction of causality remains to be determined, but recent longitudinal analyses have suggested that cigarette smoking during adolescence may precede the onset of and increase risk for agoraphobia, GAD, or PD in early adulthood (Johnson et al., 2000).

7. Power and Sample Size

Given an exposure measure (such as a PTE) and a categorical outcome measure (i.e., the occurrence of an anxiety disorder), the relationship between exposure and outcome can be measured using an odds ratio. The following table shows the minimum odds ratio that can be reliably detected as a function of the age of assessment and assumptions about the prevalence of the outcome and exposure. The calculations assume a target of 80 percent power using a two-sided 95 percent confidence interval and an intraclass correlation based on the NCS sample design (0.04 for both the exposure and outcome). For the calculations, the assumed outcome is either the presence of anxiety disorder at age 16 (with a reported prevalence of 9.9 percent) and the presence of an unspecified anxiety disorder subtype as of age 7 (with as assumed prevalence of 1 percent). Three values for the exposure prevalence are assumed to illustrate how the minimum detectable odds ratio varies with exposure prevalence.

Table 1. Detectable Minimum Odds Ratios

Assumed outcome	Prevalence of the outcome	Age of assessment	Prevalence of the exposure	Minimum odds ratio that can be reliably detected
Anxiety disorder at age 16	9.9%	16	5%	1.26
			15%	1.16
			50%	1.11
Anxiety disorder subtype at age 7	1.0%	7	5%	1.82
			15%	1.49
			50%	1.37

Many of the hypothesized relationships between exposure and outcome involve interactions with other factors, such as demographic factors and the presence of a genetic risk factor. Calculating the minimum detectable odds ratio for an interaction requires additional assumptions. However, as a general rule, the minimum detectable odds ratio for an interaction involving exposure is roughly equal to or greater than the square of the minimum detectable odds ratio for the exposure. Thus, an example of the minimum detectable odds ratio for an interaction between exposure and gender, given the assumptions in the table above, ranges from roughly 1.23 (1.11 squared) to 3.31 (1.82 squared).

8. Other Design Issues

Lifetime history of psychiatric disorders is an important component of studying the risk for having an anxiety disorder(s). One method is to obtain self-reported, doctor-diagnosed psychiatric conditions, which often yields pertinent information about diagnosable conditions only for those who have available medical resources (access to psychiatric services, etc). It is beneficial to capture both continuous symptoms and/or categorical diagnoses for participants who may not have the benefit of being diagnosed by a clinician. Performing a full diagnostic interview with study participants may be time-consuming; however, several approaches exist to reduce participant burden and yield well-standardized information about psychiatric diagnoses. The NCS may choose to administer screening questions for specific psychiatric disorders. Participants who screen positive for psychiatric disorders of interest can be followed up at a later time by phone or self-administered interviews by which a full diagnosis can be obtained. This diagnostic process will be validated within the Study sample to determine the association between the diagnostic profiles after the positive screens vs. conducting a full diagnostic interview.

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