

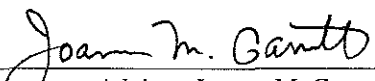
Are There Neuropsychiatric and Behavioral Sequelae of Group A, beta-hemolytic Streptococcus?: The First Ever Prospective Cohort Study to Examine PANDAS Symptomatology

A Research Plan

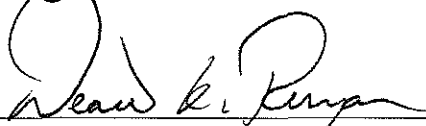
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Sample Abstract (hypothetical numbers used as the project is not yet complete):

Background: PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections) has been described in the literature to define a subset of children with Obsessive Compulsive Disease (OCD) and/or tic disorders whose neuropsychiatric symptoms begin following a streptococcal pharyngeal infection, most likely as a result of an auto-immune process. The existence of the entity remains controversial. Post-streptococcal neuropsychiatric sequelae have never been studied prospectively with a comparison group or in an outpatient pediatrics setting.

Aims: 1) To further assess the association between Group A beta-hemolytic strep (GABHS) and neuropsychiatric symptoms to determine if the exposure of “strep throat” confers a risk (not explained by stress itself) to the development of neuropsychiatric symptoms as described by parents and the children themselves. 2) If GABHS is found to be associated with neuropsychiatric sequelae, to determine the incidence of post-streptococcal neuropsychiatric and abnormal behavioral symptoms in an outpatient pediatrics practice and to categorize by symptom type the most common neuropsychiatric or behavioral sequelae.

Methods: Subjects were 796 sick and well children (age 4-11) without psychiatric or neurological disease from an outpatient pediatrics practice in upstate New York and their primary care takers. At time of enrollment: 1) all children received a throat culture testing for GABHS; 2) parents were administered a questionnaire that asked about demographics as well as the presence or absence of recent life stress for the child/family and presence or absence of recent symptoms of obsessive compulsive disease, tics, and other abnormal behavioral symptoms in their children; and 3) children who were able also completed a 10-item questionnaire about their own thoughts, obsessions, and compulsions. Children who cultured positive were treated with appropriate antibiotics. Two weeks and 11 weeks after enrollment, parents and children were sent the same

questionnaires. The final cohort included 370 children with strep throat (“exposed”), and 426 children without strep throat (“unexposed,” 205 of whom were healthy and 221 of whom presented with symptoms of illness). Two-sample t-tests were used to determine whether the mean number of survey question endorsements were different at time of enrollment and at time of follow-up in the exposed vs. the unexposed groups. Non-parametric testing was used for skewed samples. Risk ratios for individual symptoms were calculated to compare the risk of exposure versus non-exposure to GABHS. Pearson’s chi-square tests were performed to determine if the exposed versus the unexposed differed for each of the three groups of symptoms (OCD, tics, or abnormal behaviors not specified). The incidence of a PANDAS-like syndrome was calculated for this cohort based on a dichotomous outcome of a statistically significantly elevated number of symptoms present at follow up that were not present at enrollment.

Results: Parents whose children had throats that cultured positive for GABHS reported a higher mean number of neuropsychiatric and abnormal behavioral symptoms than parents whose children were strep negative ($p < 0.01$). RR of streptococcal exposure and three PANDAS symptoms are as follows: frequent hand-washing RR= 2.8 (95% CI 1.4-3.4); frequent checking RR=2.2 (95% CI 1.2-3.1); and unusual separation anxiety RR= 3.1 (95% CI 1.8-4.7). Post-streptococcal sequelae were most likely to represent the OCD-like spectrum and abnormal behaviors not specified ($p=0.01$, and $p=0.03$, respectively) with a trend toward tic-like disorders. The incidence of a PANDAS-like syndrome in this outpatient practice cohort was 10 cases per 370 exposed patients who were enrolled (2.7%).

Importance: The first prospective study of children to examine post-streptococcal neuropsychiatric and abnormal behavioral symptoms has shown that children exposed to GABHS do have increased symptoms when compared to both sick and well children without strep throat. This research adds strong support to a growing body of literature indicating a post-infectious pathophysiology for psychiatric symptomatology. Such findings may contribute to future abilities to curb disabling psychiatric symptoms in children.

Background:

PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections) describes a subset of children with Obsessive Compulsive Disease (OCD) and/or tic disorders, like Tourette's Syndrome (TS), whose symptoms begin following a streptococcal pharyngeal infection. It is important to note that much controversy surrounds PANDAS, and many notable researchers doubt that this newly described entity exists for reasons that will be discussed later in the manuscript. The research proposed in this manuscript plans to address the concerns of the PANDAS skeptics by using rigorous epidemiological methods to determine whether the exposure of "strep throat" increases risk of subsequent neuropsychiatric symptoms in a prospective cohort study. To understand the context of the research plan, a brief discussion of PANDAS and the literature describing its research context is necessary.

Though there is no definitive test, children may be diagnosed with PANDAS if they meet the following criteria for the illness¹:

1. Presence of OCD and/or tic disorder
2. Pediatric onset of symptoms (age 3 until puberty)
3. Episodic course of symptom severity (waxing and waning) and/or sudden onset of symptoms
4. Association with Group A beta-hemolytic streptococcal infection (determined by a positive throat culture for streptococcal infection and/or elevated anti-streptococcal antibody titer)

5. Association with adventitious movements (like chorea or hyperactivity)

Although the mechanism is largely unknown, PANDAS is believed to be an autoimmune disorder triggered by Group A beta-hemolytic streptococcal infection (GABHS). The pathogenic theory stems largely from that of rheumatic fever. In rheumatic fever the streptococcal infection causes the body to produce antigens, which then cross-react with heart valves, joints, and parts of the brain. As a result of this effect on the brain, children with rheumatic fever develop Sydenham's Chorea (SC), otherwise known as St. Vitus Dance. Sir William Osler actually originally observed the relationship between children with St. Vitus Dance and OCD when he described "a certain perseverativeness of behavior" in these patients¹. In the majority of patients with Sydenham's Chorea, there are new OCD symptoms at the time of the onset of SC that resolve when the chorea resolves². While there is much preliminary evidence of an association between streptococcal infection and OCD and/or tic disorder, there are many skeptics who doubt its existence^{3,4,5}. In 1978, the first probable case of PANDAS was reported in a Japanese boy whose Tourette's Syndrome evolved rapidly after a febrile illness and improved with prednisone⁶. Since that time, much has been published on this topic, including several more case reports^{7,8,9} and a recently published well described case series¹⁰. A systematic clinical evaluation of 50 children who met the working diagnostic criteria for PANDAS (outlined above) was published in the *American Journal of Psychiatry* in 1998, rendering PANDAS an established, if not particularly well-known, entity¹.

The natural history of PANDAS has not been well described. However, a typical case of PANDAS (to the extent that there is one) is that of a school-age child who gets strep throat followed in 1-12 weeks by sudden onset of tics or OCD behaviors, then gradual improvement, followed by sudden recurrence, etcetera. When symptoms flare, there is likely to be positive throat cultures or high antibody titers. When symptoms abate, there are often negative cultures and lower titers.

Some researchers, however, call into question the association between GABHS and neuropsychiatric disorders in children—suggesting PANDAS is merely an “epiphenomenon”^{3,4,5}. Indeed, the veracity of such an association between streptococcal infections and neuropsychiatric symptoms is suspect for two reasons. The first is that, given how common streptococcal throat is, new onset neuropsychiatric syndromes temporally following a strep diagnosis may be merely coincidental. One study found that GABHS infects the average child three times by the age of 13¹¹, and other studies have estimated the GABHS carrier state at between 2.5 %¹² and nearly 20%¹³. Second, “nay-sayers” postulate that since it is well known that Tourette’s and OCD symptoms worsen during periods of stress or illness, the noted exacerbations of these problems with streptococcal infections may simply be a non-specific reaction to the stress of illness⁴.

However, in making the case that the relationship between GABHS and neuropsychiatric disorders is causal as opposed to merely associative, one could refer to many of the Bradford-Hill criteria¹⁴ (the criteria are referred to here in quotation marks). First, there is “consistency” in the literature in the abundance

of case reports^{7,8,9,10}. The relationship is also “biologically plausible” because the disorder “behaves” as we know autoimmune processes do⁴. The “analogy” of Sydenham’s chorea as discussed above strengthens the evidence for a causal link. Finally, there is also some research with small n’s documenting “reversibility” using IVIG, steroids, and plasma exchange¹⁵. Contradictory results exist as to whether penicillin prophylaxis reduces the number of exacerbations of neuropsychiatric symptoms. In their research, Garvey and colleagues found that penicillin prophylaxis did not curb exacerbations of symptoms¹⁶ but a case series studied and published by Murphy and Pichichero indicated that many of the children with abnormal behaviors and neuropsychiatric symptoms improved after a course of antibiotics¹⁰. Evidence is more lacking in other Bradford-Hill criteria such as “temporality” (cause precedes effect), “dose response” (large exposures are associated with higher rates of disease), “specificity” (one cause leads to one effect) or “strength” (large relative risks)¹⁴.

The fact that GABHS occurs with such frequency in the population and the fact that many neuropsychiatric phenomena worsen during periods of acute stress, such as illness, underscore the importance of studies with appropriate comparison groups to examine the relationship between GABHS and neuropsychiatric sequelae. Given that PANDAS has only relatively recently been proposed as a diagnostic entity, there are actually few such studies that include comparison groups.

The first study on PANDAS to contain a comparison group occurred in 1993 after a GABHS outbreak in Providence, RI. Kiessling and colleagues noted a

temporal relationship between infection and abrupt onset of tics in some patients. They noted that in a sample of 50 children, those with movement disorders were significantly more likely than those without to have evidence of antineuronal antibodies in their sera¹⁷. Then, in 1997, Swedo and colleagues reported that the frequency of a serum trait marker for rheumatic fever susceptibility (labeled D8/17) was significantly higher in both children with PANDAS and children with Sydenham's chorea than it was in healthy controls¹⁸. In 1998, a study of 41 children with TS and 39 controls reported elevated anti-putamen (putamen is a brain structure) antibodies (though not elevated antibodies against GABHS) amongst the children with TS¹⁹.

Just last year three other case-control studies were reported. One determined that the sizes of certain brain structures (specifically, the caudate, putamen, and globus pallidum) were significantly greater in the group of children with PANDAS than in healthy controls²⁰. Another concluded, based on comparisons of antistreptococcal antibody titers and basal ganglia volumes in patients diagnosed with chronic tic disorder, OCD, and attention-deficit hyperactivity disorder (ADHD) versus community controls, that prior associations may have been confounded by the presence of ADHD²¹. Finally, a case-control study that investigated the clinical and laboratory evidence of GABHS infection in 150 children with tic disorders versus 150 controls without found that children with tics had statistically significantly higher mean ASO titers and higher rates of positive throat cultures than children without tics²².

Limitations of Previous Work:

While well controlled, these studies still have limitations. First, and most importantly, none prospectively followed a cohort of children to detect incidence of PANDAS or measured the relative risk that GABHS confers to such neuropsychiatric problems in children. In fact, none except the Peterson, et al, study even stated whether subjects were pre-selected for having had a recent, recurrent, or chronic infection with GABHS. Second, all included subjects with severe neuropsychiatric problems, and, therefore, may not serve the general physician as well. These studies may even underestimate the scope of the problem by not including transient or mild symptoms as opposed to full-blown illnesses that meet diagnostic criteria. Furthermore, the Peterson study used patients aged 7-55, so the study was not limited to children (one of the five criteria for PANDAS).

Another limitation of previous work is that no studies to date have used a comparison group to examine whether children with strep throat might be more likely to have abnormal behaviors not generally included in the OCD or Tourette's symptom spectrum. In their prospective case series of 12 school age children who met criteria for PANDAS, Murphy and Pichichero found that 7 of the 12 children displayed unusual urination behaviors (urgency and frequency and increased wiping without evidence of UTI), and 5 of the 12 displayed age-inappropriate separation anxiety¹⁰. Such findings underscore the need for further research to determine if symptoms like these should be considered part of PANDAS sequelae.

Though many PANDAS skeptics note that the stress of illness (rather than strep itself) may exacerbate tics and OCD symptoms, no studies to date have examined the potential inter-relationship between stressful life events, strep throat, and the development of neuropsychiatric sequelae despite a significant historical article in the literature that would indicate this as a plausible mechanism. A landmark 1962 study by Meyer and Haggerty found that in the 2 weeks preceding the onset of respiratory infections (including strep throat), the rate of stressful events (as reported by the mother) was 3-4 times higher than in weeks occurring not prior to onset of infections²³. Meyer and Haggerty found that chronic stress-- as well as acute stress-- was related to streptococcal infection rates. It seems possible, then, that neuropsychiatric sequelae to strep throat may be reactions to increased stress that we know from Meyer and Haggerty's work *precedes* streptococcal infection rather than an autoimmune *response* to the streptococcal antibodies themselves. Or, to propose a more biopsychosocial mechanism, it is possible that it is some combination of the preceding (psychosocial) stress and the (biological) autoimmune response that leads to PANDAS. In any case, any prospective examination of PANDAS should determine parental endorsement (or not) of a recent significant life event.

Specific Aims:

Some of the gaps in the causality chain between GABHS and neuropsychiatric symptoms come from the lack of prospective studies with comparison groups. As previously discussed, studies with comparison groups are

critical. Because PANDAS is thought to be a relatively rare phenomenon, large numbers of children would need to be followed to find the incidence of PANDAS. Under ordinary circumstances, a prospective cohort study to examine the relative risk of developing neuropsychiatric symptoms as a result of strep throat would be difficult both because of the large sample size required to document a difference and because of the usual inherent problems of follow-up. However, in a large, primary care practice where strong follow-up is the norm, this would be possible and valuable. Furthermore, using a large primary care pediatrician practice (as opposed to a neuropsychiatric clinic) as the source of patient recruitment and using surveys to query many types of unusual behaviors (as opposed to meeting formal diagnostic criteria for these illnesses) would enable us to find transient and/or mild illness that might otherwise go undetected.

Our **specific aims** are as follows:

1. To further assess the association between GABHS and neuropsychiatric symptoms and/or abnormal behaviors.

The subjects will form a cohort of both well and sick children who present to their primary care pediatrician's office from October to May (the well-documented strep season for this practice²⁴). The exposed group will be those with sore throat cultured positive for the presence of GABHS and the unexposed group will be a combination of those with sore throat that is not culture positive for GABHS as well as those who present for well-child care and are also GABHS negative (in order to address whether neuropsychiatric symptoms are a reaction to stress or,

more specifically, illness). We seek to determine if those with strep throat are more likely than those without strep throat to develop neuropsychiatric and abnormal behavioral symptoms as reported by the parents or the children themselves. We will administer surveys to parents asking them about the recent occurrence of neuropsychiatric and abnormal behavioral symptoms in their kids. We will also administer surveys to children themselves to determine if they report abnormal thoughts, anxieties, or compulsive actions.

Hypothesis:

Based on the data reported to date, we expect that patients with sore throat that is culture-positive for GABHS will have more neuropsychiatric and abnormal behavioral symptoms than those who are not culture positive, whether or not those in this latter group have a sore throat.

2. To assess the incidence of a PANDAS-like* syndrome in a primary care pediatrician's office in one strep season, well-documented to be September through May in Rochester, NY²⁴.

Hypothesis:

Because the incidence of PANDAS has never been tracked, it is impossible to know what incidence we will find. We can hypothesize that we will find a 10% increase in the number of positive responses to survey questions in the strep positive over the strep negative group and over baseline because we expect to find incident transient and mild abnormal behavior as well as previously

researched documented pathology (personal communication with John March and Sue Swedo, NIMH researchers on this topic). Since I will dichotomize the outcome in order to define a set of people who have a PANDAS-like syndrome versus not and since that outcome will likely represent a number of symptoms that is two standard deviations away from not, the true incidence of such a syndrome will likely be low (approximately 2-3%).

3. To assess whether: a) strep throat; b) parental endorsement of a significant life event; or c) a combination of a and b, are more associated with PANDAS-like symptoms.

Hypothesis:

Meyer and Haggerty's landmark 1962 study suggests that reports of significant life events increase immediately prior to onset of streptococcal infections, calling into question whether it is the strep infection or the preceding stress that leads to PANDAS²³. We expect that it will likely be a combination of endorsement of a significant life event and strep throat that result in PANDAS-like symptoms.

Secondary Aims:

1. To the extent that there are a greater number of neuropsychiatric or abnormal behavior symptoms in the strep positive as compared with the strep negative group, we will attempt to: 1) determine risk ratios for the individual

* Because we are not performing a structured clinical interview, nor are we using full validated surveys for OCD or Tourette's, we will not be able to diagnose these children with PANDAS, even according to PANDAS own criteria.

symptoms; and, 2) categorize the frequency of symptoms with the type of illness they might represent.

Hypothesis:

We expect GABHS to confer a high risk ratio to the following symptoms: unusual hand-washing, checking behaviors, and separation anxiety. Though overall we expect to find more abnormal behavioral symptoms in both groups derived from an outpatient population than we expect to find symptoms of OCD or Tourette's, we do expect that there will be more symptoms that fall along the Obsessive-Compulsive Disease-like category than the tic disorder or abnormal behavior, not specified, categories in those children from the strep positive group.

2. To assess the feasibility of conducting a prospective cohort study in a primary care pediatrics office which might then help to fund a larger-scale study such as a PROS (Pediatric Research in Office Settings) study.

Hypothesis:

We expect in this large practice well known for its clinical research and with excellent follow-up that we will be able to recruit and follow 800 patients.

This will provide evidence of feasibility for future cohort studies.

Methods:

Enrollment:

Our aim is to enroll 400 patients in each group in order to allow for some loss to follow-up and to make sure the study is powered to detect an appropriate difference (sample size calculations will be discussed later in the manuscript).

Patients will be recruited from two sites of Elmwood Pediatrics Group, a large, suburban practice in upstate, NY (at 125 Lattimore Road, Rochester, NY, 14620, and at 1000 Pittsford-Victor Road, Pittsford, New York, 14534). This practice cares for approximately 3000 patients with sore throat in a given strep season (September – May) (25% of whom usually have streptococcal infection) and approximately 1800 children for well-child care in the relevant age group. Patients will be recruited in three ways: 1) posters in the waiting rooms (see Appendix A); 2) by the nurse who is escorting them from the waiting room to the examination room prior to the doctor's evaluation (the nurse will be reminded of the study by a "Carolina blue" sticker on the patient's vitals sheet); and 3) by their primary care provider who will ask them to participate in the study. Providers will be informed of the study by an explanation at practice group meetings. Providers will be encouraged to invite all patients they identify with GABHS (strep throat) to enroll in the study as well as all patients they see for sore throat that is not strep positive and all patients they see in the time period of the study whose primary reason for the visit is routine well child care. Patients of both gender and all ethnicities will be recruited. Patients will need to be male and female children of the age group 4-11 (inclusive). Younger patients are excluded because the survey questions that will be used do not pertain to nor are they developmentally appropriate to use for children of a younger age group. Older patients are excluded because if patients are beyond the age of puberty, they do not meet one of the criteria for PANDAS.

Inclusion Criteria:

- *Seek their primary pediatrics care at Elmwood Pediatrics Group in upstate, NY
- *Be between the ages of 4 and 11 (explained above)
- *Have a positive culture for Group A beta-hemolytic strep (GABHS) for children in the exposed group
- *Have a negative culture for Group A beta-hemolytic strep for children in the unexposed group

Exclusion Criteria:

- *Have ever been diagnosed with a psychiatric or neurological abnormality, such as attention-deficit hyperactivity disorder (ADHD), obsessive compulsive disease (OCD), chorea, or tics (as this would make it difficult to detect incident rather than prevalent cases) or mental retardation (as survey questions might not be developmentally appropriate)
- *Have a history of seizures or closed head injury with loss of consciousness (as these might predispose to abnormal behavioral or neurological symptomatology)

Patients who are recruited from the population seeking well-child care and who have a positive culture for GABHS but no symptoms of strep throat (specifically lymphadenopathy, sore throat, or fever) will be regarded as carriers. They will be excluded to avoid misclassification bias.

In the unexposed group, developing strep throat during the duration of the study--within 12 weeks of initial culture--would cross patients over to the exposed group, but would not exclude them from the study altogether.

Study design: Prospective cohort study.

For patients in the exposed group, subjects will be those who have their throats cultured and have positive cultures. For patients in the unexposed group, subjects will be drawn from two groups – those that have sore throat who do not have positive throat cultures and those whose primary reason for visit is for routine well-child care.

Study Procedure: (see physician and nurse duties, APPENDIX B)

Consents: If a patient's parent agrees to participate in the study, the primary care provider will alert the study investigator. This person will decide if the patient meets eligibility criteria and will undergo the process of informed consent. This will be informed consent for adult parents of the children and assent for the children themselves. Non-English speaking subjects will not be enrolled. All subjects will sign an assent form (see APPENDIX C), and their parents will sign a consent form (See APPENDIX D) allowing participation in the study. This consent form will not only allow participation in the study detailed here, it will also ask parents if they would be willing to be contacted by the researchers for a separate study if their children's behavior appears to be abnormal based on the surveys they will be filling out. (This separate study would have its own protocol and consent. Participation in the separate study would be fully voluntary and have no bearing on their continued participation in this study. IRB protocol will be submitted separately).

Potential risks will be outlined in the consent forms. Potential risks are few and will occur equally in both the exposed and unexposed groups:

1. Emotional distress of the throat culture itself. For some children, this mildly invasive procedure can invoke some fear. However, someone will perform the culture that has experience and training.
2. Discomfort of the throat culture. For some children, the gag reflex that is triggered by culturing the back of the throat, stimulating vomiting, however helping children to “pant like a dog” minimizes the gag response.
3. Emotional distress of the survey questions. For some parents and children, answering questions about neuropsychiatric symptoms or unusual behaviors may be embarrassing or emotionally difficult. Participants will be allowed to withdraw from the study at any time and parents and children will be informed that some positive responses to questions are normal and do not necessarily indicate pathology.

We will try to maintain confidentiality but not anonymity. Of course, patients and their parents will be aware of this. All collected data will be kept in locked patient files, or on a database that is only accessible by the research investigators. All patients will be given a unique identification code. The linkage of the identification code and the patients’ names will be kept in a locked file and will be unavailable to persons not involved in the analysis. Since there is a separate study whose enrollment is dependent on results of this study, and since certain survey results may indicate the need for further pediatric attention, the code will be broken in the case of survey review that indicates abnormal behavior

potentially indicative of PANDAS pathology. Parents will be made aware of that linkage and the fact that their responses are confidential but not anonymous. Parents will be encouraged to discuss any unusual behavioral or medical symptoms with their pediatrician just as they would if they were not part of a study and will be informed that surveys will only be periodically—*and not immediately*-- reviewed.

Since we will not be diagnosing any neuropsychiatric illness as a result of this study, it seems unlikely that there will be any loss of insurability to the patients or their families as a result of this study's data collection or results.

Participants will be followed for 12 weeks following their initial throat culture. Participants will need to visit the pediatrics office only one time, the time of the initial culture, but they and their parents will be told they need to fill out 2 additional surveys. The initial, and only, office visit should last less than an hour beyond the standard amount of time the office visit would have normally lasted. The time to fill out additional surveys will be approximately 15 minutes for each of two additional surveys.

If patients' parents endorse certain abnormal psychiatric or behavioral symptoms of their children, the code will be broken and their primary care physician will be alerted to their need for further attention and for their participation in another study that would further evaluate the relationship between GABHS and their mental health. If this were to happen, patients would get appropriate care for a problem that might otherwise have never been treated or at least for which they might have received delayed care.

Consents will also discuss other benefits. Patients will be given a total of \$30 for participating in the research study. This will be prorated as follows: Patients will be given \$10 if they withdraw or are withdrawn after they and their parents have completed the throat culture and 1st questionnaire. Patients will be given \$20 if these events happen after they and their parents have completed the 2nd questionnaire. The amount will be \$30 if this happens after the 3rd questionnaire. If children are unable to complete the questionnaires because of reading difficulties, there will be no inducement penalty.

Patients will not incur any costs (other than time) for participating in this study beyond what they would have paid for their standard care (visit for sore throat, strep throat, or well child care). All clinic, diagnostic, professional, and laboratory fees related to the study will be covered, and no additional drugs, devices, or transportation costs will be necessary.

Procedural methods:

All subjects who have signed consents will have their throats cultured by health personnel at the practice. Positives will be those that grow GABHS within 72 hours according to plating techniques described in Pichichero, Hoeger, et al, 1999²⁵. Children will be treated for streptococcal infection with antibiotics and sore throat not attributed to GABHS according to standard practice in this pediatrics primary care group. If children derived from well-child care have cultures that are positive for GABHS but do not otherwise have symptoms of streptococcal infection (sore throat, fever, and lymphadenopathy), they will not be

treated for strep and they will be excluded from the study so as to avoid misclassification bias.

Parents of children in both the exposed and unexposed groups will fill out surveys that include demographic questions as well as questions about their children's behaviors (See APPENDIX E). These surveys will be completed at baseline (time of culture) and mailed to parents 3 weeks and 11 weeks following throat culture (initial presentation) to see if there are any endorsed tic, OCD, or other abnormal behaviors (including ADHD, separation anxiety, and unusual urinary behaviors). Questionnaires will also be given to children of reading age at all three time points asking them about unusual thought patterns characteristic of OCD of which parents may not be aware (See APPENDIX F). Researchers have found that it is important to ask children themselves since parents are often unaware of their children's symptoms²⁶. If children are not old enough to be able to read their survey, they may have an adult read the question and then they can answer "yes" or "no" on a separate sheet of paper (See APPENDIX G). Children at ages 4 or 5 may not be able to participate in this portion of the study. They will still be included in the study, and their parents' responses will still be used. Surveys will be piloted to at least 10 parents and children of varying ages to determine clarity and feasibility.

If surveys are not returned within 2 weeks of initial mailing, parents will be telephoned and encouraged to fill out the questionnaire. If needed, another mailing will be sent (with instructions not to complete if already completed).

Surveys will be counted as returned if they are completed within 4 weeks of first mailing or 2 weeks of the second mailing.

If patients who are strep negative and in the exposed group at the inception of the study develop GABHS, they will be “crossed over” to the exposed group.

See the following flow chart for a summary of the study protocol:

Enroll:

All children ages 4-11 who seek their care at Elmwood Pediatrics Group and visit for well or sick care between October, 2001 and May, 2002



Exclude those who:

1) Don't speak English or whose parents don't speak English; 2) children have ever had a diagnosis of ADHD, OCD, chorea, tics, mental retardation; 3) children have a history of seizures or closed head injury resulting in loss of consciousness; 4) don't agree to participate/sign consents or assents



At time of enrollment:

1) Parents sign consents and children sign assents
2) Child gets cultured for streptococcal infection
3) Parent answers survey
4) Child answers survey (if able)



Two weeks after enrollment:

1) Parent answers survey again
2) Child answers survey again (if able)



Eleven weeks after enrollment:

1) Parent answers survey again
2) Child answers survey again (if able)

Reliability of Measures

Some of the questions on the parents survey will be derived from the previously validated Yale Global Tic Severity Scale ²⁷, and the questions on the child version of the previously validated Yale-Brown Obsessive Compulsive Scale ²⁸. Other questions about abnormal child behaviors thought to be potentially related to PANDAS ^{1,10} will be included in the questionnaire in order

to determine if they occur more frequently after the exposure of strep throat. I will be working with Robert DeVellis, who authored *Scale Development: Theory and Applications*²⁹ to determine if the questionnaire can become a validated scale. Even if it cannot, however, this is unlikely to affect the quality of our results. The study does not attempt to identify children who meet diagnostic criteria for Obsessive-Compulsive Disease, tic disorders, or any other psychiatric illnesses. It merely seeks to determine whether streptococcal infection increases the risk for symptoms previously thought to be related to PANDAS. I have thus sought to capture symptomatology previously described in the PANDAS literature with my questionnaire and have therefore sought the advice of National Institute of Mental Health PANDAS researcher Susan Swedo whose work in large part brought PANDAS to the peer-reviewed literature scene (personal communication with Susan Swedo).

The reliability of the streptococcal culture is well documented. The Red Book 2000, the report of the Committee on Infectious Diseases³⁰, advises that throat culture on sheep blood agar can confirm Group A strep infection with a false negative culture rate of less than 10% of symptomatic patients when a throat swab specimen is obtained properly. Though recovery of GABHS from the pharynx does not distinguish patients with true infection from carriers, recent study indicates that the carrier rate of strep throat may be as low as 2% among healthy children and as low as 4% among children with apparent viral upper respiratory infections¹². We will collect data on whether the children who culture positive for strep were ill or well on presentation. Furthermore, we are also

including both sick and well children in our control (unexposed) group. Both of these plans should help to alleviate misclassification bias. Such bias would be in favor of the null hypothesis, anyway, so that if we are able to support out hypotheses over the null hypotheses, we can be confident in that assertion.

Statistical Analyses: (For the statistical analyses described here, only analysis of the parent- reported data will be described as the child-reported data may or may not be able to be analyzed depending on perceived reliability.)

Responses for all 3 surveys for both the exposed and the unexposed subjects will be collected and entered into a Microsoft Access database and then imported into a STATA 6.0 file (Stata Corporation, College Station, TX). One outcome measure, then, will be the continuous measure of number of symptoms endorsed by parents. I will calculate the mean number of symptoms for survey time points 2 and 3 for both the exposed and unexposed groups.

A baseline mean and standard deviation will be calculated for both the exposed and the unexposed groups. The responses for survey time points 2 and 3 will be combined into one number. Positives will be symptoms endorsed at either point. If a symptom is endorsed at both time points, it will count only once

Another outcome measure will be dichotomous—and will represent either a significant number of neuropsychiatric/behavioral symptoms or not. To define “significant,” I will use the number of symptoms above baseline endorsed on parent questionnaire that is two standard deviations away from the mean for both sick and well children.

Analysis for Specific Aim 1: To determine the association between GABHS and neuropsychiatric symptoms and/or abnormal behaviors.

For this aim, the continuous outcome of number of abnormal symptoms/behaviors will be assessed. I will use the 2-sample t-test of differences to answer the following 2 questions: 1) Are there baseline differences in the mean number of neuropsychiatric and abnormal behavior questions in both the exposed and unexposed groups? and, 2) Is there a difference between the change in number of symptoms from baseline in the exposed versus the unexposed groups?

Since the number of symptoms endorsed will likely be on the low end, with many in the 0-5 range, I may have to use non-parametric testing for skewed samples. Also, for people who do not complete both studies, I may either need to drop those persons from the study or I may need to use an alternative strategy that allows for repeated measures but counts each survey as an event. A sample table might look like the one below (though these numbers are hypothesized and not real and are present for demonstration purposes only):

Sample dummy table

	Non-exposed (n=400)	Exposed (n=400)	p value
Mean # positive endorsements At baseline	3.2	3.3	>0.05
Mean # positive endorsements Surveys 2 &3	3.6	6.4	<0.05

Analysis for Specific Aim #2: (To the extent that the exposure of GABHS is related to neuropsychiatric and abnormal behaviors), to assess the incidence of a PANDAS-like* syndrome in a primary care pediatrician's office in one strep season.

To answer this specific aim, I will use the dichotomous measure of significant number of symptoms (as described above) and calculate the incidence of this cohort. This calculation will be as follows: the number of people developed this outcome over the period of time that the cohort lasted divided by the number of people who were susceptible (exposed) at the outset.

* Because we are not performing a structured clinical interview, nor are we using full validated surveys for OCD or Tourette's, we will not be able to diagnose these children with PANDAS, even according to PANDAS own criteria.

Analysis for Specific Aim #3: To assess whether: a) strep throat; b) parental endorsement of a significant life event; or c) a combination of a and b, are more associated with PANDAS-like symptoms.

To address this specific aim, the dichotomous outcome of a significant number of symptoms or not will be used (as described above). I will use logistic regression analysis to determine whether the endorsement of a significant life event, streptococcal infection, or the two in combination are predictors of getting a significant number of neuropsychiatric/behavioral symptoms or not. Such analysis will also determine whether streptococcal infection adjusted for potential confounders is related to neuropsychiatric sequelae.

Analysis for Secondary Aim #1: To the extent that there are a greater number of neuropsychiatric or abnormal behavior symptoms in the strep positive as compared with the strep negative group, we will attempt to: 1) determine a risk ratio for the individual symptoms; and, 2) categorize the frequency of symptoms with the type of illness they might represent.

To address the first part of this aim, risk ratios will be calculated with 95% confidence intervals.

To address the second part of this aim, I will use individual Pearson's chi square tests to answer the question: Are the people in the exposed group different from people in the unexposed group with respect to each category of symptom of symptom endorsed ("OCD-like," "tic-like," or "abnormal behavior-like")? A category will count as endorsed if any symptom in that category is endorsed that was not endorsed at baseline. The table below shows hypothesized values.

% With Positive Endorsements Above Baseline

	Non exposed	Exposed	p value
OCD-like	1	10	<0.05
Tic-like	2	6	>0.05
Abnormal behavior	2	9	<0.05

Sample Size Estimations:

Sample size estimation was determined using STATA 6.0 (Stata Corporation, College Station, TX). For our dichotomous outcome, we estimate a needed sample size of at least 286 patients in each of the exposed and unexposed groups to provide 90% power, with a two-tailed alpha of 0.05 to detect a conservative difference 10% difference in proportions (of “PANDAS-like syndrome” rate). We assumed that the rate of abnormal behavioral symptoms among controls would be 10% and the rate of abnormal behavioral symptoms among those exposed to strep throat would be 20%. We hope to enroll 400 to allow for loss-to-follow-up and to ensure adequate power to appropriately determine results. With 286 in each group (accounting for loss to follow up), we will have 90% power to

detect a 10% difference in rate of abnormal behavioral symptoms. With 80% power we could detect a statistically significant difference in proportion of behavioral symptoms as small as 9% between exposed and unexposed with only 286 in each group.

Our continuous outcome is based on number of symptoms endorsed. If we use mean parent-rated symptom score and assume that controls will have a mean of 2 abnormal symptoms (where as those exposed will have a mean of 4 abnormal symptoms), and we assume the standard deviation will be a conservative 4, then the sample size needed to detect this difference is only 85. If we enroll 250 in each group, we'll be able to say with 99% power that we have detected a difference.

Feasibility of Achieving this Sample Size:

Since this practice sees approximately 3000 patients with sore throat in a given strep season (September – May) (25% of whom usually have streptococcal infection) and approximately 1800 children for well-child care in the relevant age group and parents are used to participating in studies at this practice (which has published over 70 research articles based on studies conducted at the practice), patient recruitment at the numbers needed should not be difficult. I will likely have adequate power to address my key study question.

Joanne Garrett, Ph.D., biostatistician and epidemiologist will be helping me with the statistical analysis here at UNC-CH.

Funding Sources:

My Robert Wood Johnson Fellowship comes with research support to pay research assistants for data entry and to provide supplies such as address labels and serial number labels. To pay for throat cultures, a study nurse coordinator full-time employed in Rochester, envelopes, postage, and patient incentives, I have received intramural funding in the amount of approximately \$114,000 from the budget of Dr. Sue Swedo, NIMH researcher in the Pediatrics and Developmental Neuropsychiatry Branch.

IRB Approval: IRB Approvals from both UNC and NIHM have already been secured.

Potential significance:

OCD and tic disorders are not rare illnesses in childhood. One-year prevalence rates of OCD have been reported to be as high as 4% in the pediatric/adolescent population³¹ and tics may be present in up to 6% of school age children⁴. If PANDAS defines a meaningful subset of this population of disturbed children (and it is possible that “mild” PANDAS is much more common than this even), then it is common enough to warrant further investigation. My study will lend further support to the following: 1) the association between Group A beta-hemolytic streptococcal infections and their neuropsychiatric sequelae through a prospective approach, an approach that many skeptics find critically warranted at this point^{3,4,5}; 2) the theory of an auto-immune pathogenesis, which

might suggest that these children could benefit from “immune-modifying treatment”⁴; 3) the biopsychosocial determinants of health; 4) the idea of a spectrum of illness; and, 5) the idea of using primary care pediatric practices as research settings.

In short, we hope this study will lend further support to the association between GABHS and neuropsychiatric symptoms and will lend credence to the theory of an autoimmune pathogenesis. As an investigation with a comparison group, this study will contribute to a growing body of knowledge on autoimmune diseases and the role of infectious precursors as well as the growing body of evidence that supports the biopsychosocial determinants of illness theory. Autoimmune phenomena, of which PANDAS is a postulated example, have a known cause, so it would seem likely, then, that the treatments might then be specifically targeted toward reducing the infection (antimicrobials) or the body’s inflammatory response (steroids). The future of gene therapy might also hold promise for preventive techniques since D8/17 markers are those of genetic predisposition toward PANDAS. Teasing apart the relationship between this infection and these neuropsychiatric sequelae might potentially serve as a model for other such phenomena.

With frequent surveys of an outpatient population, we hope to find mild and transient symptoms —symptoms that might otherwise never come to health professional attention. While such symptoms obviously have no long-term or diagnostic significance, they might lend further support to a post-infectious etiology of psychiatric sequelae.

Perceived Limitations:

- 1) Limited time (only one strep season in which to collect data)
- 2) Need a large sample size
- 3) Incidence of PANDAS is unknown
- 4) Any neuropsychiatric sequelae of strep throat that are found can only be said to be “PANDAS-like” since we will not be using formal diagnostic criteria.
- 5) The exposure status will not be the only difference between groups (i.e. the strep exposed group will also be receiving antibiotics)
- 6) There may be some misclassification bias. However, this should bias toward the null hypothesis.
- 7) Patients will not be blinded to whether they have strep or not. Though the investigators will not mention PANDAS, some parents may already be aware of PANDAS and the potential association of strep with behavioral symptoms and therefore may observe them more in their children, leading to bias.

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Andrew J. Perrin, PhD

Michael E. Pichichero, MD

David Ransohoff, MD

Desmond K. Runyan, MD, DrPH

Susan Swedo, MD

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APPENDIX A

Is your child age 4 -11?

Is your child here today for either a well-child check-up or a sore throat?

If the answer to these questions is “yes,” we would appreciate your participation in a study about children’s thoughts, behaviors, and movements.

As part of the study, your child would get a throat culture, and you and your child would fill out 3 questionnaires.

Children who participate will receive \$30.

If you’re interested, please take one of these “flags” with you and give it to the doctor so we can see if you are eligible to participate.

APPENDIX B- Physician and Nurse Duties

Enrollment

Doctor Role

Be thinking every time you see a patient this fall, winter, and spring for a well-child checkup or a sore throat (ESPECIALLY STREP THROAT) that you could enroll them in the study (see inclusion/exclusion sheet). We need lots of subjects for this study to work.

Refer these patients to a study nurse at the time of the patient visit
For those children whom you are swabbing for a rapid strep, do a formal throat culture as well

Study Nurse Role

Formal inclusion/exclusion questions of parent- see inclusion/exclusion sheet

Explanation of study to parent and child- see nurse coordinator sheet

Consent of parent and assent of child

Base line surveys for adults and children

Throat cultures of children who have not already received one (sore throats thought not to be strep and well children)

Database entry of patient information

Survey # 2

Doctor Role - None

Study Nurse Role

Send out surveys

Log in database whether returned to or not (I will give this information)

Reminder phone calls for those not returned

My role

Enter into database responses

Let study nurse know which have been returned and which have not

Survey #3

Doctor Role- None

Study Nurse Role

Send out surveys

Log in database whether returned or not (I will give this information)

Reminder phone calls for those not returned

My role

Enter into database responses

Let study nurse know which have been returned and which have not

Analysis

Doctor Role- None

Study Nurse Role- None

My role

Analyze and write up results

Before the patients start being enrolled:

Put study packets together. A study packet should contain the following items: 1) A patient information sheet; 2) A parent consent form; 3) A child assent form; 4) A baseline parent survey (COLOR); 5) A baseline child survey; 6) Parent survey #2; 7) Child survey #2; 8) Parent survey #3; 9) Child survey #3; 10) 2 large envelopes with EPG's return address and space for parent to fill out his/her address; 11) 2 small envelopes with Eliana's address and place for parent to fill out his/her own address; 12) two parent letters

Prepare envelopes now, except for parent's addresses, which they will do themselves (see #11 below). Make sure that the envelopes have appropriate postage on them for the number of pages that will be in them.

Put labels with the same serial number on all items in the packet (INCLUDING ENVELOPES) #1-11. Item # 12 (two parent letters) do not need serial numbers on them.

For each patient:

1. Make sure each patient meets inclusion criteria and does not meet exclusion criteria
If a patient meets any one of the exclusion criteria, he/she cannot be a part of the study and will not receive his/her own serial number
2. If patient is to be enrolled, explain to him/her the following:
Elmwood Pediatrics Group and a researcher from the University of North Carolina are conducting a study to determine why some children have different behaviors, thoughts, or body movements. If you decide to partake in this study, you and your child will each answer 3 brief surveys (they should take no more than 5-10 minutes each) asking about the behaviors, thoughts, and body movements of your child as well as a few questions about medications and demographic information. If your child cannot read, you will read the questions to him/her so that he/she can answer them. Your child will also receive a throat culture if he or she hasn't already. Your child will be paid \$30 for his/her participation in the study with your help. Please read the following consent form.
3. Have the parent read and sign the consent form. Make sure that he/she checks the two boxes at the end (or at least the one that gives permission for this study). Make sure that he or she knows that if there is any problem with the child's behavior throughout the study that he or she would otherwise bring the child in for, that they should certainly do that (i.e. explain that we researchers will not be looking at the survey forms immediately).
4. Have the child read and sign the assent form. If the child cannot read well enough, read it to him or her yourself, showing the parent how you are doing this so that the parent can assist the child for survey #s 2 and 3.

5. Once the parent is consented and the child is assented, give them each copies of their consents/assents (these do not need to be signed and may simply be taken from a stack). Put the paper work you are not using today (follow-up surveys #2 and #3 for both adult and child) into the child's file to be kept in a locked cabinet.

6. After putting the serial number on the information sheet that corresponds to the serial number on all of the pages of the study packet, have the parent begin filling out the information sheet.

7. Have the parent start filling out the survey.

8. If the child is of reading age, have the child start working on his/her survey. If the child is not of reading age, read the questions to the child and have the child circle "yes" or "no" appropriately. Meanwhile, show the parent how to help the child fill out this form because it will be the exact same form for the next two follow-ups. If the child is unable to answer, indicate this on the information sheet, so that the children will not be mailed this survey in follow-up. Show the child how he/she can fold the survey and put it in the envelope for confidentiality.

9. As soon as possible, enter the information on the information sheet into the database, and put aside the information sheet and consent/assent for safe-keeping in the patient's file in a locked cabinet.

10. Once the parent and child are each done with their respective surveys, make sure that all questions are answered and put them in a secure envelope. Compile these envelopes in a pile for xeroxing. Once xeroxed, put the original forms in one of the large envelopes that is addressed to me. Make sure items stay stapled during xeroxing. You will be sending me a large envelope each week at the end of the week.

11. Ask if the child has had a throat culture yet. If the child has, make sure that it was done as a regular culture—not a rapid strep test. If the child has not had a throat culture, culture the child's throat with a regular culture—not a rapid.

12. Have the parent write his/her address on 2 large envelopes for the 2nd and 3rd survey mailings (These envelopes should have EPG's return address on them). Have the parent also write his/her name as the RETURN address on two smaller envelopes (these will be the envelopes that contain the COMPLETED surveys – once they have filled them out—that will be sent to me). These two smaller envelopes should have been previously addressed (see at the top of this page) to me (Eliana Perrin at UNC).

13. Tell the parent and child upon leaving the following:

Thank you very much for enrolling in this study. Remember that we will be mailing you surveys just like the one(s) you filled out today on two more occasions. One will be mailed to you in 2-3 weeks. Another will be mailed to you in 2-3 months. Please take the short time it takes to fill them out promptly (within a week) and return them in the addressed and stamped envelope that will be provided. They will be addressed to a

researcher at the University of North Carolina. Don't send them here. And again, if you have any concerns about your child, let your pediatrician know.

14. As soon as possible, enter the information on the information sheet into the database, and put aside the information sheet and consent/assent for safe-keeping in the patient's file in a locked cabinet.

15. At the end of each week throughout the study:

Figure out how many patients enrolled that week. E-mail me that number.

Figure out strep status on each of the children cultured that week (NOTE: for children cultured at the end of the week, save their strep status for the following week when it will have been growing at least 48 hours)

Enter strep status into the computer database

Back up the database file

Make a hard copy of the file (put it in locked storage)

Send me a copy of the back up

Send me the large envelope addressed to me and stamped that contains Xeroxed patient surveys.

Assess which patients need to be sent out their second round of surveys (see #13).

Assess which patients need to be sent out their third round of surveys (see #13).

Assess which patients have not returned surveys within 2 weeks of having been mailed them and make a telephone reminder call (See # 14).

Note, the data base has many of these items in its reminder "Task list"

16. For those patients who need to be sent out second or third batch surveys: Enclose the cover letter to the parent. Enclose the adult survey and the child survey (or just the adult survey if the child was not able to complete the child survey on the baseline attempt) in an envelope. Both should be marked with correct serial numbers for the patient. Also put one return stamped envelope addressed to me (with the patient's return address on this as well) in the envelope. Make sure the appropriate parent address is on the outside envelope and make sure the envelope has appropriate postage. Then send it out and indicate on the database that you have done so.

17. I will send you a list each week of the serial numbers of the surveys that have been sent back to me. Please enter into the database that they have been returned. If a survey has not been returned within 2 weeks of the date it was sent out, please make a note of it for the telephone reminder calls.

18. Make sure that patients receive their incentive (\$30) if they completed all 3 surveys. Once they have received incentive, mark this in the database.

APPENDIX C

University of North Carolina-Chapel Hill
Assent to Participate in a Research Study
Minor Subjects

This consent form should be signed only
between 7/13/01 and 7/13/02

Approved by School of Medicine IRB

Medical IRB Study # 01-MED-375

Consent Form Version Date: 07/07/01

Title of Study: Behavior, Thoughts, and Movement Study

Principal Investigator: Eliana Miller Perrin, M.D.

UNC-CH Department: Robert Wood Johnson Clinical Scholars Program & Community
Pediatrics

Phone number: 919-966-3776

Co-Investigators: Marie Lynd Murphy, M.D., Michael Pichichero, M.D., Janet Casey, M.D.,
Anne Francis, M.D., Carolyn Cleary, M.D., Correne Curtin, M.D., Steven Marsocci, M.D.,
William Hoeger, M.D., Anne Sorrento, PNP, Alice Loveys, M.D., Sue Swedo, M.D. Lisa Snider,
MD, Joanne Garrett, Ph.D., Desmond Runyan, M.D., Ph.D.

Sponsor: Robert Wood Johnson Foundation and National Institute of Health

The researchers named above are doing a research study.

These are some things we want you to know about research studies:

You do not have to be in this study if you don't want to.

You may stop being in the study at any time. If you decide to stop, no one will be angry or upset with you.

Sometimes good things happen to people who take part in studies, and sometimes bad things happen. We will tell you more about these things below.

Why are you being asked to be in this research study?

Because we would like you to be able to help other kids who might have behavior problems or have trouble with unusual thoughts or movements of their body.

Why are they doing this research study?

Because they think that the answers to the questions we are going to ask your parents and the throat culture we are going to do on you might help us to better care for children who have behavior problems and unusual thoughts or movements of their body.

What will happen during this study?

This study will take place at Elmwood Pediatrics, which is where you go to the doctor. During this study you will have a throat culture and you will answer some questions about your thoughts. Your parents will also answer questions about you and ways you have been acting.

Only the doctors doing this study will know your answers and they will not be mad at you for any of your answers.

What are the bad things that might happen?

Sometimes things happen to people in research studies that may make them feel bad. These are called "risks." These are the risks of this study:

You may gag on the throat culture. Some children do. No one will be mad at you if you do. The doctor will try to do the throat culture as quickly as possible and teach you some tricks that help some kids not gag on the throat culture.

You may feel embarrassed about some of the questions that are asked of you or about you, but nobody is trying to embarrass you. Many normal children answer these questions in many different ways. None of your doctors will be mad at you for answering the way that you do.

Both these things may happen to you or neither of them may happen. Or things may happen that the doctors don't know about yet.

What are the good things that might happen?

People also may have good things happen to them because they are in research studies. These are called "benefits." The benefits to you of being in this study may be:

You might be able to help other children because you have participated.

If you have serious worries, behaviors, or body movements, someone may be better able to help you get better.

Will you get any money for being in this research?

You will be paid \$30 for being in this study.

Who should you ask if you have any questions?

If you have any questions about this study, you may ask the research coordinator who is the person who gave you this form. You may also ask your doctor.

If you sign your name below, it means that you agree to take part in this research study.

Signature of Research Subject

Date

Signature of Person Obtaining Assent

Date

APPENDIX D

University of North Carolina-Chapel Hill
Consent to Participate in a Research Study
Parents of Minor Subjects

This consent form should be signed on
between 7/13/01 and 7/13/02
Approved by School of Medicine IRB

Medical IRB Study # 01-MED-375
Consent Form Version Date: 07/07/01
Title of Study: Behavior, Thoughts, and Movement Study
Principal Investigator: Eliana Miller Perrin, M.D.
UNC-CH Department: Community Pediatrics & Robert Wood Johnson Clinical Scholars
Program
Phone number: 919-966-1274.
Co-Investigators: Marie Lynd Murphy, M.D., Michael Pichichero, M.D., Janet Casey, M.D.,
Anne Francis, M.D., Carolyn Cleary, M.D., Correne Curtin, M.D., Steven Marsocci, M.D.,
William Hoeger, M.D., Anne Sorrento, PNP, Alice Loveys, M.D., Sue Swedo, M.D. Lisa Snider,
MD, Joanne Garrett, Ph.D., Desmond Runyan, M.D., Dr. PH.
Sponsor: Robert Wood Johnson Foundation and National Institute of Mental Health

You are being asked to allow your child to take part in a research study. The investigators listed above are in charge of the study; other professional persons may help them or act for them.

What are some general things you should know about research studies?

Research studies are designed to gain scientific knowledge that may help other people in the future. Your child may not receive any direct benefit from participating. There may also be risks associated with participating in research studies.

Your child's participation is voluntary. You may refuse to allow this participation, or may withdraw your consent at any time, and for any reason, without jeopardizing your family's future care at this institution or your relationship with your doctor. If your child is a patient with an illness, your child does not have to participate in research in order to receive treatment.

Details about this particular study are discussed below. It is important that you understand this information so that you can decide in a free and informed manner whether you want your child to participate. You will be given a copy of this consent form. You are urged to ask the investigators named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?

The purpose of this research study is to determine why some children have different behaviors, thoughts, or body movements.

How many subjects will participate in this study?

Your child will be one of approximately 800 subjects in this research study.

How long will your child's participation last?

Your child's participation in this study will last for approximately 12 weeks. If your child's behavior or movements are especially different from average, you may be asked to have your child participate in another study. That study is separate from this one and you may refuse or accept participation in that study for your child at that time.

What will happen if your child takes part in the study?

During the course of this study, the following will occur:

If he or she hasn't already, your child will receive a throat culture today. If your child has symptoms of strep throat and the throat culture is positive (meaning your child has strep throat) he or she will receive antibiotics and appropriate medical care for his/her strep throat. No child will be given placebos or sugar pills for any reason. No child will be given any medication for strep throat or sore throat that he or she would not otherwise be given if he or she were not in the study, and all medications prescribed will be with your full knowledge.

Whether or not your child has strep throat, you will be given a questionnaire to fill out asking brief demographic questions and 20-30 questions about his/her behavior, thoughts, and body movements. If your child is able to read well, he or she will also be given a questionnaire asking him/her about thoughts, fears, and movements. If your child is unable to read well, we may ask you to read the questions to him or her but not watch him or her fill out the answers. The first of these questionnaires will need to be completed by you and your child today before you leave. Then, in 3-4 weeks, the same questionnaires will be mailed to you and your child in 3-4 weeks. Finally, in 11-12 weeks (about 3 months), third questionnaires will be mailed to you and your child. The first questionnaire may take 15 minutes to fill out, but the second and third should take only about 10 minutes because you will be familiar with them.

We are asking you the same questions over and over because children's behaviors, thoughts, and movements may change over the course of 12 weeks and we want to know if that happens. You will need to send back the second and third surveys within a week in order to make sure the surveys all get done in the same range of time. You will be given a stamped envelope for that purpose so there will be no out of pocket expenses. If you do not mail back the survey on time, another survey will be sent to you and possibly one of our research coordinators will call you to remind you to fill out the survey.

You should know that answering "yes" to some of the questions may be entirely normal. Surveys will be periodically, BUT NOT IMMEDIATELY, reviewed. If you have answered "yes" to certain questions or to many of the questions, your child may have unusual behaviors, thoughts or movements that require further treatment. If this is true, you will be contacted by your doctor's office for appropriate follow-up. Also, if you answer "yes" to certain questions or to many of the questions, you may be asked on behalf of your child to participate in another

study. That study is separate from this one and you may refuse or accept participation in that study for your child at that time.

Your doctor will remain the same during this time, and, as always, if you have any questions about your child's behavior, thoughts, or movements, you should contact him or her **JUST AS YOU WOULD IF YOUR CHILD WERE NOT IN THIS STUDY.**

Are there any reasons your child should not participate?

Your child should not participate in this study if he or she has ever been diagnosed with obsessive compulsive disease, a problem with tics (repetitive, unusual movements), attention-deficit hyperactivity disorder (ADHD), chorea, mental retardation, depression, rheumatic fever, or a seizure disorder.

Your child should not participate in this study if he or she has ever had a head injury with loss of consciousness.

What are the possible risks or discomforts?

This study might involve the following risks and/or discomforts to your child:

Occasionally children gag with a throat culture. The throat cultures will be done by health personnel at Elmwood pediatrics who are used to doing throat cultures in children. He or she will do it as quickly as possible.

You may feel embarrassed about some of the questions that are asked of you about your child, but nobody is trying to embarrass you or your child. Many parents of normal children answer these questions in many different ways. Your doctors will not reduce the level of care they provide your child based on your answers.

In addition, there may be uncommon or previously unrecognized risks that might occur that we are not aware of yet.

What are the possible benefits?

The benefits to your child of participating in this study may be that he or she will help other children with unusual behaviors or body movements. You and s/he may help researchers discover the cause of unusual behaviors or body movements.

It is possible that if your child does have certain unusual behaviors or movements, he or she might be able to get care whereas otherwise, these behaviors or movements might be thought to be normal and not receive a physician's attention.

If your child came to the doctor today for a well-child check-up, it is possible that as a result of participating in this study, you will determine whether your child is a carrier of strep throat. If your child is a carrier, he or she will not be able to participate further in the study, but you would be informed of this.

What if we learn about new risks during the study?

You will be given any new information gained during the course of the study that might affect your willingness to continue your child's participation.

How will your family's privacy be protected?

No subjects will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, the University of North Carolina at Chapel Hill will take all steps allowable by law to protect the privacy of personal information.

We will try to maintain confidentiality but not anonymity. What this means is that the researchers will be able to know which parent and child filled out which questionnaire, but this information will not be told to anyone outside of the research project. All collected data will be kept in locked patient files, or on a database that is only accessible by the research investigators. All patients will be given a unique identification code that is destroyed once the analysis is complete. The linkage of the identification code and the patients' names will be kept in a locked file and will be unavailable to persons not involved in the analysis.

However, if your answers to surveys or your child's answers to surveys indicate to us the need to contact you to bring your child in for further investigation of any problems, we will do so. Additionally, if you agree, we may contact you about your child's participation in another study that may help to determine why your child is having unusual behaviors or movements.

Because the National Institute of Health is sponsoring this study, as a government agency, it has the right to review all records.

Because this study involves the treatment of a medical condition, a copy of this consent form will be placed in your child's medical record. This will allow the doctors caring for your child to

obtain information about what procedures he/she is receiving in the study and treat him/her appropriately, if he/she has other health problems or needs during the study.

Will you or your child be paid for participating?

Your child will receive \$30 for participating in this study. If you withdraw at any time or if you are excluded from the study, your child will still be paid for the time invested so far. For example, if your child withdraws after completion of the throat culture and first questionnaire, your child will still receive \$10. If your child withdraws after completion of the second questionnaire, your child will still receive \$20. If you and your child participate until the end of the study, the full amount of \$30 will be paid to your child.

Will it cost you anything if your child participates? There will be no out-of-pocket expenses for you or your family for the throat culture, mailings, or surveys. All of these items will be paid for by the sponsors of this research.

Who is sponsoring this study?

This research is funded by the National Institute of Health and the Robert Wood Johnson Foundation. The research team is being compensated by the sponsor for conducting the study. The researchers do not, however, hold a direct financial interest in the sponsor or in the product being studied.

What will happen if your child is injured by this research?

In the event of personal injury resulting directly from the research procedures, financial compensation cannot be provided by The University of North Carolina at Chapel Hill. In spite of all precautions, your child might develop medical complications from participating in this study. If such complications arise, the researchers will assist you in obtaining appropriate medical treatment but The University of North Carolina at Chapel Hill does not provide financial assistance for medical or other costs. You do not waive any liability rights for personal injury by signing this form.

What if you want to stop before your child's part in the study is complete?

You can withdraw your child from this study at any time. The investigators also have the right to stop your child's participation at any time. This could be because you failed to follow instructions, or because the entire study has been stopped. No matter how or by whom the study is stopped, your child will be paid according to the parts you and he or she have completed as above.

What if you have questions about this study?

You and your child have the right to ask, and have answered, any questions you may have about this research. If you have further questions, or if a research-related injury occurs, you should call the study nurse at 716-244-9720.

What if you have questions about your child's rights as a subject?

This research has been reviewed and approved by the Committee on the Protection of the Rights of Human Subjects (Medical IRB) at the University of North Carolina at Chapel Hill. If you have any questions or concerns regarding your child's rights as a research subject, you may contact the Chairman of the Committee at (919) 966-1344.

Parent's Agreement:

I have read the information provided above. I voluntarily agree to allow my child to participate in this study. (By checking the box, you indicate your agreement with these statements.)

I also voluntarily agree to be contacted to participate in another study, depending on my child's and my answers to the questionnaires in this study. (By checking the box, you indicate your agreement with this statement.)

Printed Name of Research Subject (Child)

Signature of Parent

Date

Printed Name of Parent

Signature of Person Obtaining Consent

Date

Printed Name of Person Obtaining Consent

APPENDIX E- INSTRUCTIONS

Dear Parent or Caregiver-

Enclosed is a questionnaire you have agreed to fill out in participation of the Behavior, Thoughts, and Movement Study. You will recognize the questionnaire as one you have completed before. It's important that the entire questionnaire be completed again, as we are interested to see if answers stay the same or change at the 3 time points the questionnaire is completed by you (on the day of enrollment, 2-3 weeks following enrollment, and 2-3 months following enrollment).

Also enclosed is a questionnaire for your child to fill out. Please help your child to fill out this questionnaire as you were shown on the day of enrollment (do not look at his/her answers and, once finished, fold up the questionnaire without looking at it). If your child was unable to fill out this questionnaire even with help on the day of enrollment, then it is not included here.

Once finished with the questionnaire(s), put it (or them) in the stamped, addressed envelope provided. Note that the envelope is addressed to Eliana Perrin, M.D, who is working on the study along with members of the Elmwood Pediatric Group. She is located at University of North Carolina, Chapel Hill, CB #7105, Room 5034 Old Clinic Building, Chapel Hill, NC, 27599 (the address should already be on the envelope).

Please return these as soon as possible. Your timely response ensures the most accurate information for our study and really helps us.

If you have any questions about the study, please call the study nurse at Elmwood Pediatric Group 716-244-9720.

Thank you very much for your participation!!

Your Name: _____

Child's Name: _____

Child's birth date (mo/day/year): _____

Address _____ (Street and Apt#)

_____ (City, State, zip)

Phone Number (____) - ____ - ____

Why is your child here today? (circle one of the following):

a. Sore throat

b. Well-child check-up

For Study Nurse to Fill Out:

Patient MR # _____

S# _____

Child able to answer questions at least with help (circle one)? Yes No

APPENDIX E

Have the behaviors listed below been true of your child RECENTLY? Check YES only if your child has had the behavior for 2 weeks or less.	YES	NO
1. Do you believe your child has a much harder time paying attention recently?		
2. Do you believe your child has been more fidgety or restless lately?		
3. Does your child seem unusually clingy or have a much harder time being separated from you recently?		
4. Has your child recently been more sick with worry recently?		
5. Has your child had unusual fears (such as fear of AIDS or earthquakes or something else unlikely to happen) recently?		
6. Has your child recently asked you more for reassurance? (such as, "Is it okay that ___?" "Does this mean that something bad is going to happen?")		
7. Has your child recently had unusual muscle twitches or jerks, sometimes called tics, such as eye blinking or shoulder shrugs that he or she can't stop?		
8. Has your child recently made unusual noises or sounds over and over again, such as throat clearing or barking noises?		
9. Has your child recently been checking the same thing over and over again (such as whether the door is locked or the oven is off)?		
10. Has your child wiped herself with toilet paper over and over again recently or had any other unusual bathroom routine recently?		
11. Has he or she recently needed to dress a certain way every day?		
12. Has he or she recently needed to wash his or her hands or body a certain way every day?		
13. Have you recently heard your child say he or she is still dirty even after washing or seem overly worried about germs?		
14. Has your child recently hoarded things (kept too many things that should be thrown out or at least not be kept where your child wants to keep them)?		
15. Have you recently tried to stop a behavior that your child repeats constantly?		
16. Has your child recently needed to arrange things so they are just right or put things in a certain order?		
17. Has your child recently prayed more than other members of the family?		
18. To your knowledge has your child recently had upsetting thoughts that he or she can't make go away?		
19. Has your child had unusual urinary problems recently, such as needing go to the bathroom urgently, wetting the bed, or having daytime accidents?		
20. Does your child seem more negative about various aspects of life than he or she used to be?		

Which of the following statements represents your feelings about your child's behaviors:

- a) My child's recent behaviors have not been a problem.
- b) My child's recent behaviors have been a little bit of a problem
- c) My child's recent behaviors have been a moderate problem
- d) My child's recent behaviors have been a severe problem and have meant that we have had to change our routine at school or home to compensate.

Which of the following statements is true (CIRCLE ONE)?

- a) My child and/or our family has had a significant life event RECENTLY (examples include death of a family member, friend, or pet; divorce or separation of parents; abuse; recent move; recent change of schools; recent change in care arrangements)
- b) My child and/or our family has NOT had a significant life event RECENTLY

(PLEASE TURN THE PAGE OVER AND ANSWER QUESTIONS ON THE OTHER SIDE)

Please answer the following questions about your child (If you have more than one child, please answer these and all following questions just about the child that is enrolled in this research study at Elmwood Pediatrics):

How old is your child?
_____ years old

Is your child (circle one)?

- a) Male
- b) Female

Is your child of Hispanic origin?

- a) Yes
- b) No

What is your child's race?

- a) White
- b) Black/African American
- c) Asian (eg. Chinese, Japanese, South Asian, and South East Asian)
- d) Native Hawaiian/other Pacific Islander
- e) American Indian/Alaska Native
- f) Other, specify _____

Has your child had strep throat 3 or more times in his or her life?

- a) Yes
- b) No

To your knowledge, which of the following medicines has your child had in the last 2 weeks? (CIRCLE ALL THAT APPLY).

- | | |
|------------------------------|---------------------------------------|
| a) Acetaminophen (Tylenol) | g) Tylenol Sinus |
| b) Ibuprofen (Motrin, Advil) | h) Theraflu |
| c) Dimetapp | i) Alkaseltzer Cold |
| d) Sudafed | j) Cough medicine (Robitussin, Vicks) |
| e) Pediacare | k) Nyquil |
| f) Tylenol Cold | l) Benadryl |

Now, please answer some questions about you:

Are you?

- a) Single, never married
- b) Single, separated or divorced
- c) Single, widowed
- d) Married

What is your highest level of education?

- a) Grade school
- b) High school degree
- c) Some college
- d) College degree
- e) At least some graduate school

What is the highest level of education for your spouse or significant other?

- a) I do not have a spouse or significant other
- b) Grade school
- c) High school degree
- d) Some college
- e) College degree
- f) At least some graduate school

To your knowledge, have you or anyone in your family (parents, spouse, siblings, or children) ever had rheumatic fever?

- a) Yes
If yes, list relationship to you _____
- b) No

THANK YOU!

APPENDIX F

PLEASE CHECK YES OR NO TO THE QUESTIONS BELOW.	YES	NO
1) Do you worry that you are not clean enough?		
2) Do you think that you have to say certain things over and over again or pray a lot to keep bad things from happening?		
3) Do you have to check things over and over again?		
4) Do you feel you have to go to the bathroom all the time?		
5) Do you like to save things (like food or pieces of paper) that other people don't think you need to save?		
6) Do you have to count things over and over again?		
7) Do you have to do your homework many times until it is just right?		
8) Do you have to get dressed in a certain way every day or put your clothes on in a certain order every day?		
9) Do you put things in a certain order or arrange them until they are just right?		
10) Do you worry a lot that you or someone you love will die if you do something wrong?		

If children are not able to read well enough, parents may read the chart above and children will circle yes or no on a separate paper as follows.

APPENDIX G

1.)	YES	NO
2.)	YES	NO
3.)	YES	NO
4.)	YES	NO
5.)	YES	NO
6.)	YES	NO
7.)	YES	NO
8.)	YES	NO
9.)	YES	NO
10.)	YES	NO