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Autonomic nervous system function in children and adolescents with primary headache disorders

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Boston University
AUTONOMIC NERVOUS SYSTEM FUNCTION IN CHILDREN AND ADOLESCENTS WITH PRIMARY HEADACHE DISORDERS

by

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The relationship between autonomic dysfunction and primary headache disorders has been established in the adult population. The aim of this retrospective study was to elucidate if there was a similar association in the pediatric primary headache population. Three groups were compared – migraine patients, tension-type headache patients and idiopathic scoliosis patients as a control group. Utilizing clinical data collected during patients’ initial visits, prevalence of autonomic dysfunction symptoms were quantified. The headache groups also filled out the Functional Disability Index (FDI) as well as the Children’s Depression Inventory (CDI) to help elucidate if there was a relationship between function disability, psychiatric state and primary headaches and/or autonomic dysfunction symptoms. It was found that the headache groups had significantly greater dysautonomia as compared to the control group. Only slight differences were found between the migraine and tension-type patients in regards to dysautonomia. No significant differences were found in total FDI or CDI scores. These results illuminate a relationship between autonomic nervous system dysfunction and primary headache disorders in the pediatric population studied. Prospective studies and the development of standardized dysautonomia questionnaires will allow a more detailed autonomic dysfunction profile to be built for this population.
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<tr>
<td>ANS</td>
<td>Autonomic Nervous System</td>
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<td>CDI</td>
<td>Children’s Depression Inventory</td>
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<td>CGRP</td>
<td>Calcitonin Gene-Related Peptide</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<td>CSD</td>
<td>Cortical Spreading Depression</td>
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<td>FDI</td>
<td>Functional Disability Index</td>
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<tr>
<td>fMRI</td>
<td>functional-Magnetic Resonance Imaging</td>
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<td>HRV</td>
<td>Heart Rate Variability</td>
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<td>ICHD-2</td>
<td>International Classification of Headache Disorders, Second Edition</td>
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<tr>
<td>IS</td>
<td>Idiopathic Scoliosis</td>
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<tr>
<td>M</td>
<td>Migraine</td>
</tr>
<tr>
<td>NO</td>
<td>Nitric Oxide</td>
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<td>PHP</td>
<td>Pediatric Headache Program</td>
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<td>POTS</td>
<td>Postural Orthostatic Tachycardia Syndrome</td>
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<td>PSNS</td>
<td>Parasympathetic Nervous System</td>
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<tr>
<td>SDB</td>
<td>Sleep Disordered Breathing</td>
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<tr>
<td>SNS</td>
<td>Sympathetic Nervous System</td>
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<td>TTH</td>
<td>Tension Type Headache</td>
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INTRODUCTION

Headaches are one of the most common complaints in the general population. Estimates of prevalence vary widely depending on the study, definition of headaches, measures used, population involved, and time period monitored. In a meta-analysis of a variety of international studies, Karli et al. (2006) reported that prevalence rates for all diagnoses of headaches in children and adolescents ranged from 19.5% - 93.3%. Females in this population are also more likely to suffer from headaches than males. The majority of the headaches seen in emergency rooms and doctors’ offices are primary headache disorders. Primary headache disorders refer to headaches with a lack of a clear underlying pathophysiology, trauma, or systemic disease. The two most predominant primary headaches diagnosed are tension-type headache (TTH) and migraines (M).

Significant headaches are often associated with emotional distress, sleep impairments, gastrointestinal complaints, neck and shoulder pain and disturbances in school behavior and performance as compared to those children without chronic illnesses. The 2010 Global Burden of Disease, released in December 2012, ranked migraine as the foremost disabling neurological disease. During childhood and adolescence, many hormonally-driven psychological and physiological changes occur. Some researchers suggest that chronic pain may affect these changes negatively and hinder proper development. Many studies have examined the impact and relationship of various life-stressors on the presence of headaches. Straube et al. (2013) concluded that certain critical events at school, socially and academically, and at home may contribute to
the development of somatic problems. The negative impact of chronic headache pain has been likened to the negative impact of other chronic conditions, such as arthritis or cancer. Both have been found to adversely affect the lives of children and adolescents to a similar degree \(^{10,14}\).

Researchers have also found certain co-morbidities that are frequently present in children and adolescents with chronic headaches – gastrointestinal problems, inflammatory conditions such as asthma and allergies, and psychiatric issues such as depression and anxiety may provide important information regarding the clinical and pathological development of these headaches \(^{1,10}\). These pediatric issues may prolong headache-related disability into adulthood. A five-year follow up study by Camarda et al. (2002) reported that 56.2% of children who had migraines continued to suffer through adolescence \(^{15}\). Knook et al. (2012) found that children with chronic pain and related psychiatric disorders had an increased prevalence of psychiatric disorders continuing through late-adolescence and into adulthood \(^{16}\). There is a higher incidence of both types of headaches predicted in adulthood when a childhood diagnosis of primary headaches, M or TTH, is made \(^1\). It is also important to note the socioeconomic impact of living with a chronic pain condition extending throughout adulthood. In the U.S., it has been estimated that medical costs, and the consequential loss of productivity (a reduction of 3.5 hours per week) result in an economic impact of approximately $61.2 billion per year \(^{17–20}\). Comprehensive and early treatment of pediatric headaches may be able to prevent this future economic, social, and emotional burden.
A. The Autonomic Nervous System

The autonomic nervous system (ANS) is the branch of the peripheral nervous system that acts as the control system for physiological activities necessary for daily living. Generally functioning involuntarily, the ANS regulates the respiratory, cardiovascular, digestive and endocrine systems. It can be affected by exogenous stressors originating from outside the body, such as temperature or social factors, as well as endogenous stressors arising from inside the body, such as hormones. The ANS has two branches – the parasympathetic and the sympathetic nervous systems (PSNS and SNS, respectively) which operate independently as well as in coordination with each other. The balance of interactions between the two branches is very important in maintaining proper function of the organs they innervate. Numerous studies using functional-Magnetic Resonance Imaging (fMRI) and other imaging techniques have identified specific brain regions responsible for various autonomic functions. Within the brain, the ANS is located in the medulla oblongata in the lower brainstem. The hypothalamus, located directly above the brainstem, is important as it is the location for the integration and regulation for all autonomic functions \textsuperscript{21–23}.

Due to the autonomic nervous system’s intimate involvement in many day-to-day activities, dysfunction in the ANS can have widespread negative effects. Any problem affecting the sympathetic or parasympathetic branch or an imbalance between the two, an inhibition or hyper-activation, results in dysautonomia. Examples of dysautonomic symptoms include abnormal blood pressure, gastric stasis, vertigo, nausea, disordered sleep and pulse rate variation. Diseases can develop as a result of autonomic dysfunction,
or autonomic dysfunction may be a symptom of certain diseases. Measuring these symptoms via standardized autonomic function testing protocols cannot discern the cause or source of the disease, but may be useful in monitoring its severity and for modifying treatment ²⁴–²⁷.

Stress is a variable that is coordinated in part by the autonomic system. In a group of young children, it was found that heart rate variability (HRV), a function controlled by the ANS, was a valid indicator of the child’s stress levels. A lower HRV, indicated an imbalance between the PSNS and SNS branches, and correlated with a higher level of reported-stress and abnormal cortisol levels ²⁸. Juvenile patients with Chronic Widespread Pain Syndrome, Postural Orthostatic Tachycardia Syndrome (POTS), and Small-Fiber Polyneuropathy also present autonomic dysfunction symptoms ²⁹,³⁰. In these cases, autonomic testing has proven to be a valid tool to monitor and identify variances and severity of condition, resulting in better treatments for the patients.

Postural Orthostatic Tachycardia Syndrome (POTS) is caused by decreased cerebral perfusion and increased sympathetic activation, causing an imbalance in the autonomic system. Autonomic dysfunction criteria for this condition have been identified in the adult-population and recently, a pediatric profile has been defined ³⁰,³¹ Nisbet et al. (2013) pursued a similar goal within the adult-Sleep Disordered Breathing (SDB) population. Using autonomic testing measures, they identified dysautonomic symptoms in the pediatric-SDB population ³¹. In these conditions, it was found that the adult profiles, though similar, did not accurately represent the presentation in children and adolescents.
B. Chronic Headache Etiology

Primary headaches are central nervous system disorders involving the activation of the trigeminovascular system and its connections to regions of pain transmission. As the stimulation is passed through the brain, further connections are made to the entire autonomic system. The then deregulated autonomic system results in a variety of symptoms that disrupt everyday life, including irregular heart rate, dizziness, or gastric irregularity.

Migraine is a complex neurovascular disorder that initiates via an unspecified-trigger in the central nervous system with spread to the trigeminal vascular pathway. There has been evidence linking these triggers with the release of calcitonin gene-related peptide (CGRP), which closely links the trigeminovascular system to migraine pain. Many other triggers may play a role in the initiation of the event, such as stress, fatigue, and illnesses. Recent neuroimaging has elucidated a migraine active region within the brainstem. There are strong indications for a hereditary component as genomic regions linked to migraine prevalence have been identified in neurological, vascular, and hormonal pathways.

Migraines are diagnosed via medical history and examinations and rarely require neuroimaging. Migraine pain is characterized by recurrent pulsating, unilateral headaches accompanied by sensory sensitivity made worse by physical activity. Migraines present with or without an aura, a transient sensory disturbance directly before or during the headache. The aura has been attributed to an electrophysiological event termed cortical spreading depression (CSD) caused by a wave of neuronal activity followed by inhibition.
slowly spreading over the cortical regions of the brain. Many researchers have found that migraines without aura are more common than those that present with aura \(^1,39,40\).

Tension-type headaches are also associated with a disorder in the central nervous system, specifically, the sympathetic nervous system, and results in a secondary sensitization of the trigeminal neuronal pain pathway \(^4,35,42\). TTH is the most common type of headache though it is generally less disabling and therefore less diagnosed \(^5\). TTH present with bilateral, non-pulsatile pain without sensory sensitivity and can occur with or without muscle tenderness \(^4\). The etiology of TTH is not well understood. Some theories predict the same stressors involved in the development of migraine play a role, but to a lesser degree. Another hypothesis states a possible role of excess Nitric Oxide (NO) generation causing central sensitization and therefore resulting in an increased sensitivity to the impulses \(^5,43\). Recent research has postulated that the sensitization may occur via chronic pericranial myofacial tenderness and nociceptive input \(^44,45\).

**C. Evidence of ANS Dysfunction in Headache Patients**

Autonomic function testing protocols have been validated for both the adult and pediatric populations \(^24,25,27\). These studies have shown the positive impact autonomic testing may have on the treatment of certain autonomic-driven diseases. Multiple reports in adult-headache literature have used validated autonomic dysfunction measures to analyze ANS function in that population \(^24,42,46\). As compared to non-headache controls or to non-chronic headache patients, chronic M and chronic TTH patients were found to have greater autonomic dysfunction – lowered parasympathetic NS activity and elevated
sympathetic NS activity. In the pediatric population, ANS dysfunction is now commonly reported in studies of Postural Orthostatic Tachycardia Syndrome, Diabetic Peripheral Neuropathy, Complex Regional Pain Syndrome, and a predominantly pediatric headache syndrome – Cyclic Vomiting Syndrome. Due to the fact headaches are common symptoms in many of these syndromes and the overwhelming evidence found in the adult-research, headaches are likely linked to autonomic dysfunction. Recently, Straube et al. (2013) indicated a few key differences in the presentation of pediatric migraine as compared to in the adult population. Recurrent nausea, episodes of abdominal pain, introverted behavior, and recurrent attacks of vertigo are predominantly pediatric presentations. As per the findings in other autonomic dysfunction-related disorders, such as POTS and SDB, it may be possible to develop a specific pediatric-migraine and TTH profile in order to better identify and treat these patients.

D. Classifying and Diagnosing Chronic Headaches and Associated Issues

a. Headaches

The diagnosis of headaches is hierarchical; the more information that can be provided about the onset, duration, and location of the pain allows for a more specific classification. A primary headache diagnosis is a first-digit level diagnosis. That group includes migraines, tension-type headaches and cluster headaches. Identifying one of those three is called a second-digit classification. A standardized, generally accepted classification system has been established by The International Classification of Headache Disorders, now on its second edition (ICHD-2).
Figure 1. Diagnosis of Pediatric Migraine With and Without Aura as Defined in the ICHD, 2nd Edition.

**Diagnosis of Pediatric Migraine With and Without Aura as defined in the ICHD, 2nd edition**

A. At least 5 attacks fulfilling criteria B–D

B. Headache attacks lasting 1-72 hours

C. Headache has at least 2 of the following characteristics:
   1. Either bilateral or unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravated by routine physical activities

D. During headache at least 1 of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia (may be inferred by behavior)

E. At least one of the 2 following:
   1. History and physical and neurological examinations do not suggest that an organic disorder, including head trauma and vascular disorders, non-vascular intracranial disorders, substances or their withdrawal, non-cephalic infection metabolic disorders, disorders of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures
   2. History and/or physical and/or neurological examinations do suggest an organic disorder, but migraine attacks do not occur for the first time in temporal relation to the disorder

These are the criteria for diagnosis pediatric of migraine with or without aura. A pediatrician or neurologist would obtain this information through a clinical visit and a thorough medical history.
Figure 2. Diagnosis of Pediatric Tension-Type Headache as Defined in the ICHD, 2nd Edition.

These are the criteria for diagnosis of pediatric tension-type headache. A pediatrician or neurologist would obtain this information through a clinical visit and a thorough medical history.

b. Functional Disability Index (FDI)

The Functional Disability Index (FDI) was developed to assess illness-related disability in children and adolescents. The various measures of disability gauge the impact on everyday functioning and the extent to which the illness affects the family. The FDI has been validated in the assessment of acute and chronic pediatric pain. The FDI scores have been validated as demonstrating stability over a three month period in chronic patients. The pediatric 15-item instrument asks the rater’s perception of their ease of activity over the past two weeks. Each question is answered on a Likert-scale of difficulty – “No trouble” = 0, “A little trouble” = 1, “Some trouble” = 2, “A lot of
trouble” = 3, and “Impossible” = 4. A sum score of zero indicates that the rater finds none of the activities difficult and can complete them all with ease. A parallel parent form which asks parents to rate the extent of their child’s disability over the past two weeks has also been validated and standardized $^{50,51}$.

c. Children’s Depression Inventory (CDI)

The Children’s Depression Inventory (CDI) is a self-report, symptom-oriented, 27-item questionnaire that helps assess cognitive and behavioral signs of depression. The scale is suitable for children and adolescents ages 7-17 years old. This scale is sensitive to changes in depressive symptomology over time and can also be used to assess severity of symptoms. A total score is calculated of which a T-score over 65 indicates potential clinical depression. The CDI also calculates scaled scores for Negative mood, Interpersonal Problems, Ineffectiveness, Anhedonia, and Negative Self-esteem. A parallel parent form directs the parent(s) to rate the extent of their child’s depressive symptoms. Authors suggest incorporating these results with other information gathered from a comprehensive medical and psychological evaluation of the patient before drawing any conclusions $^{52}$. In this study, patients were administered the first edition of the CDI questionnaire.
GOALS

A. The Pediatric Headache Program

The Pediatric Headache Program (PHP) at Boston Children’s Hospital in Waltham is a unique collaboration between the Neurology and Anesthesia departments. Here, children and adolescents with chronic or intractable headaches are seen by neurologists and psychologists and are provided with a multidisciplinary evaluation. During the initial visit, each member of the team meets with the family to fully understand the problems and identify any specific triggers, both medical and psychological. Families are then provided comprehensive information on a wide variety of treatment options including medications, cognitive-behavioral therapies, psychological counseling, or alternative therapies such as acupuncture. Due to the strong evidence linking the autonomic system and the trigeminovascular system, the clinic hopes to quantify autonomic dysfunction in its patients. Such information has the potential to improve targeted-therapies and treatments.

B. Aims

Compared with data in the adult-headache population, there are few reports that describe the presentation of autonomic dysfunction in pediatric-headache patients. The main goal of this project is to develop an autonomic dysfunction profile for the pediatric primary headache population. If dysautonomia symptoms are prevalent at these patients’ first visit to the PHP, monitoring their autonomic system function throughout treatment
will prove to be an important clinical tool. This study will look at the following objectives:

1. To determine if the autonomic nervous system has a relationship with pediatric primary headache disorders by comparing the prevalence of autonomic dysfunction symptoms in a headache group versus a control non-headache group
   a. Symptoms: constipation, insomnia, dizziness/orthostasis, blurry vision, hyperhidrosis/ excessive cold in hands or feet, and abnormal blood pressure

2. To determine if prevalence of dysautonomia in pediatric primary headache patients is related to a higher reported functional disability via the Functional Disability Index questionnaire

3. To determine if pediatric migraine patients have more prevalent autonomic dysfunction symptoms and/or higher reported functional disability than pediatric tension-type headache patients
METHODS

A. Study Design

This retrospective study reviewed the records of patients seen at Boston Children’s Hospital between 2009 and 2013. The patients in the migraine and tension-type headache groups were diagnosed either by neurologists at the PHP or by a local (Boston-area) neurologist and then referred to the PHP. Headache classifications were made using the ICHD-2. The presence of autonomic dysfunction symptoms was extracted from the patient’s clinical data recorded during their initial evaluation at the PHP. This clinical data was obtained via a patient-doctor interview in which all of the bodily systems, including the autonomic nervous system, are reviewed. During their first visit to the PHP, patients also filled out questionnaires, including the FDI and CDI.

Patients in the control group all had a diagnosis of “Idiopathic Scoliosis” (IS) and were seen in the Orthopedic Clinic at Boston Children’s Hospital. It was important to pick a control group with no autonomic nervous system dysfunction but which also had medical records that could be queried. Idiopathic scoliosis is diagnosed only if the neurological exam is normal and there are no unusual presentation symptoms. Juvenile idiopathic scoliosis is diagnosed in those patients aged 3 – 10 years old while adolescent idiopathic scoliosis, the most common type of IS, is found in those patients older than 10 years old. This group also rarely presents with other comorbidities or pathologies, making them a fairly uncomplicated medical group and long-term follow up shows little-to-no functional impairment. This population was chosen as the control group due to
the fact that they are a clinically-simple non-headache presenting group that there are medical records for.

Exclusionary criteria were based on disorders with known involvement of the autonomic system. Patients were excluded from all groups for the following conditions:

- Primary headache diagnosis other than migraine or tension-type headache
- Major Anxiety or Major Depressive Disorder diagnosis
- Diabetes diagnosis
- Inherited peripheral neuropathy
- Familial Dysautonomia diagnosis
- Congenital Heart Disease diagnosis
- History of uremia
- History of vitamin deficiency
- History of Lyme Disease
- HIV diagnosis
- History of Celiac Disease, Lupus or Arthritis
- Inflammatory Bowel Disease diagnosis

B. Statistical Analysis

Statistical analysis included univariate comparisons based on Student T-Test for age and Fisher’s Exact Tests for comparing binomial proportions as well as logistic regression to identify the symptoms independently associated with headache (to control
for possible confounding). Symptoms that are found to differentiate pediatric headache and scoliosis groups were summarized using odds ratios and 95% Confidence Intervals (CI). Functional disability was assessed using physical and social activities obtained from the Functional Disability Index questionnaire. Headache and scoliosis groups were compared using Fisher’s Exact Test to assess whether presence and type of headache interfere with lifestyle activities (as a surrogate for quality of life). Statistical analysis was performed using IBM SPSS Statistics (version 21.0, IBM, Armonk, NY). Two-tailed P < 0.05 was considered statistically significant.

Power analysis indicated that a sample size of 100 patients with headache (50 migraine, 50 tension-type) and 100 age-and gender-matched scoliosis controls would provide 80 power to detect a difference of 25% in each of the following symptoms - constipation, insomnia, dizziness/orthostasis, blurry vision, hyperhidrosis/ excessive cold in hands or feet, and abnormal blood pressure, between the groups using Pearson Chi-Square (overall test) and Fisher’s Exact Test for pairwise comparisons using a two-tailed alpha level of 0.05 (version 7.0, nQuery Advisor, Statistical Solutions, Saugus, MA).
RESULTS

The headache group contained 125 individuals (54 males, 71 females, mean age 13.9) and the control/IS group contained 106 individuals (33 males, 73 females, mean age 12.6). Of the headache group, 68 individuals were diagnosed with M (37 males, 31 females, mean age 13.1, st. dev. 3.0) and 57 were diagnosed with TTH (17 males, 40 females, mean age 14.7, st. dev. 2.6).

Table 1 shows the mean ages and standard deviations for each group. During post-hoc analysis using the statistical Bonferroni method, the TTH group was significantly older than the M group \(p=0.002\) and the control group \(p<0.001\). This correlates with the information found in the literature regarding TTH, M and IS ages.

Table 1 also shows the gender frequency within each group. There was no significant gender differences found between the groups.

<table>
<thead>
<tr>
<th>Group (mean age ± st. dev)</th>
<th>Male (%)</th>
<th>Female (%)</th>
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<tbody>
<tr>
<td>Migraine (13.1 ± 3.0)</td>
<td>54.40%</td>
<td>45.60%</td>
</tr>
<tr>
<td>Tension-type (14.7 ± 2.6)</td>
<td>29.80%</td>
<td>70.20%</td>
</tr>
<tr>
<td>Control (12.6 ± 2.5)</td>
<td>31.10%</td>
<td>68.90%</td>
</tr>
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</table>
The ANS dysfunction symptoms collected were tabulated and their prevalence compared group-wise. For most of the symptoms investigated, the headache group (M and TTH combined) presented with significantly more dysautonomia than the control group. Those symptoms were “constipation,” “insomnia,” “dizziness/orthostasis,” and “hyperhidrosis/excessive cold in extremities” (Figure 3). Within the headache group (M and TTH combined), “hyperhidrosis/excessive cold in hands and feet” was the most endorsed symptom and “abnormal BP” was the least endorsed symptom.

Comparing the two headache groups individually (M and TTH separately) against the control group yielded more specific differences. The TTH group presented with significantly more dysautonomia as compared to the control group in five of the symptoms except for “abnormal blood pressure.” The M group presented with significantly more dysautonomic symptoms only in regards to “insomnia,” “dizziness/orthostasis,” and “hyperhidrosis/excessive cold in extremities” were significantly different. When comparing within the headache group (M versus TTH), TTH presented with significantly greater dysautonomia in regards to “blurry vision” and “hyperhidrosis/excessive cold in extremities.”
Figure 3. The prevalence of ANS dysfunction symptoms across all three patient groups.

The black bar in this graph represents the percent of patients in the migraine group, the grey bar represents the percent of patients in the tension-type group, and the vertical striped bar represents the percent of patients in the control group with the specified ANS dysfunction symptom. All of these symptoms were collected via doctor-patient interview. * = significantly greater dysautonomia in the specified group as compared to the control group ($p \leq 0.006$) 
\textdag = significantly greater dysautonomia in the TTH group as compared to the M group ($p \leq 0.03$)
Within the 125 headache patients, 94 (75.2%) completed the Functional Disability Index questionnaire (45 M, 49 TTH) and 88 (70.4%) completed the Children’s Depression Inventory questionnaire (47 M, 41 TTH).

Table 2 presents data from the FDI questionnaire given to all headache patients during their first visit to the PHP. The sum score is out of 15 questions with a score of 0-4 possible points each. The highest possible sum score on the FDI is 60. The functional disability between the M and TTH groups were found not be significantly different.

Table 2. The mean FDI sum score, st. dev. and ranges for both the M and TTH groups.
This table presents the mean FDI sum score, standard deviation, and range for the M and TTH groups.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>St. Dev.</th>
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<tbody>
<tr>
<td>Migraine</td>
<td>20</td>
<td>14</td>
<td>0-48</td>
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<tr>
<td>Tension-type</td>
<td>17</td>
<td>10</td>
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</tbody>
</table>
Looking at each FDI item individually can provide interesting information on the difficulty of these various activities. Each item can be scored on a scale between 0 and 4 (0 signifying the patient can complete the activity with “no trouble”, 4 signifying the activity is “Impossible” for the patient to do). Analysis showed that the mean score of each item fell in the range of 0 – 2 for both the M and TTH patients. Using this range to map the each mean item score on a scale from 0 (representing activities that were easier for the patients to do, specifically a mean score of 0-0.5) to 2 (representing activities that were harder for the patients to do, specifically a mean score of 1.5-2) we can see which activities/items were harder for these patients than others. By separating these scores by primary headache diagnosis, we can identify which items were easy/hard for both groups or for a particular group over the other (Figure 4, A).

Forty percent of the items/activities were difficult for both the M and TTH groups as their mean scores were greater or equal to 1.5. These harder items/activities were “being up all day,” “being at school all day,” “doing activities in gym/sports,” “reading or doing homework,” “running the length of a football field,” “getting to sleep at night and staying asleep.” One item/activity was found to be easier for both groups with its mean score of less than or equal to 0.5 – “walking to the bathroom.” The map also shows us that there are some activities that are endorsed differently between the two groups. For example, “doing something for a friend” is harder for the M group (mean score = 1.6) than it is for the TTH group (mean score = 1.2). Also, the TTH group finds “walking up the stairs” (mean score = 0.5) and “walking the length of a football field” (mean score = 0.5) easier than the M group (mean scores = 0.8, 0.9, respectively).
Figure 4. The mean FDI scores for each item for both the M and TTH groups.

The X axis represents each FDI item. The Y axis represents the mean score for that item. Though each item could be scored from 0 ("No trouble") to 4 ("Impossible"), the mean scores of the M and TTH groups had a range of mean values from 0-2. The lower scores, 0-0.5, indicated the activities that were easier for these patients to do while the higher scores, 1.5-2, indicated the activities that were harder for these patients to do. By plotting both the M and TTH item scores on the same chart, the items/activities that were easier/more difficult for the groups are elucidated.

Figure 5. A and B indicate visually indicate that the M group found less items easier (mean score of ≤ 0.5) than the TTH group did – one item/activity versus three items/activities, respectively. The M group also found more items/activities difficult (mean score of ≥ 1.5) than the TTH group did – seven items/activities versus six items/activities, respectively.
Figure 5. The ratio of harder, easier and moderate items/activities for both the M and TTH groups.

These figures represent ratio of harder, easier and moderate items/activities asked on the FDI per primary headache diagnosis. Harder items were items that had a mean score of 1.5-2. Easier items/activities had a mean score of 0-0.5. Moderate items/activities had a mean score between 0.5-1.5.
Table 3 presents data from the CDI questionnaire given to all headache patients during their first visit to the PHP. There are five sub-scale totals, Negative Mood, Interpersonal Problems, Ineffectiveness, Anhedonia, and Negative Self Esteem which provide specific information on the patient’s psychological state. The M group’s median Interpersonal Problems sub-total score was significantly greater than the TTH group’s median score. In all the other sub-total scores as well as in the total CDI score, the M and TTH groups did not score significantly differently. It is interesting to note though that the range of scores in the TTH group for Negative Mood, Ineffectiveness, Anhedonia, Negative Self Esteem and total CDI score were wider than in the M group.

Table 3. The median CDI sub-total scores, total score and ranges for both the M and TTH groups.

This table presents the sub-total scores, total CDI score as well as their individual ranges for both the M and TTH groups.

<table>
<thead>
<tr>
<th></th>
<th>Negative Mood</th>
<th>Interpersonal Problems</th>
<th>Ineffectiveness</th>
<th>Anhedonia</th>
<th>Negative Self Esteem</th>
<th>Total CDI Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>1 (0-8)</td>
<td>1 (0-3)</td>
<td>2 (0-4)</td>
<td>4 (0-7)</td>
<td>0 (0-5)</td>
<td>7 (0-22)</td>
</tr>
<tr>
<td>Tension-type</td>
<td>2 (0-10)</td>
<td>0 (0-2)</td>
<td>2 (0-6)</td>
<td>4 (0-11)</td>
<td>1 (0-7)</td>
<td>9 (1-32)</td>
</tr>
</tbody>
</table>
DISCUSSION

Finding a specific pathophysiological etiology for primary headaches has been at the forefront of chronic pain research for many years. In the adult population, autonomic dysfunction has been confirmed to have a relationship with primary headaches, such as migraines and tension-type headaches. Unfortunately, there is limited pediatric primary headache research regarding autonomic dysfunction. This project was designed to elucidate a relationship between dysautonomia and primary headaches retrospectively. If significant autonomic dysfunction is found in children and adolescents with migraine and tension-type headaches, it may be beneficial to measure these symptoms prospectively as clinical tools.

As a combined headache group (M and TTH), most symptoms were significantly different than the control group, except for “blurry vision” and “abnormal blood pressure.” When investigated separately, the TTH group had a significantly higher prevalence of dysautonomia as compared to the control group in all symptoms except “abnormal blood pressure.” The M group only showed significantly greater prevalence of “insomnia,” “dizziness/orthostasis” and hyperhidrosis/excessive cold in extremities.” The headache group’s higher overall prevalence of dysautonomia lends support to the hypothesis that the ANS plays a role in primary headache disorders.

Contingent upon this retrospective review’s detection of significant dysautonomia symptoms among headache patients, another aim of this study was to define an ANS dysfunction profile for pediatric migraine and tension-type headache patients. Only slight
differences were found between these two groups. The TTH group presented with significantly more dysautonomic features in only two out of the six symptoms, specifically “blurry vision” and hyperhidrosis/excessive cold in extremities.” Autonomic dysfunction is reported for patients with primary headaches, but further investigation is needed to elucidate a more specific profile of dysfunction for each headache subtype.

Another aim of this study was to associate level of functional disability with level of autonomic dysfunction. Prior research on chronic pain conditions have shown that living with these symptoms may affect one’s mental, emotional, and physical well-being and may be especially harmful to younger patients. Quantifying the level of ANS dysfunction and headache may have a positive impact on these patients’ daily lives. This variable was measured by the Functional Disability Index (FDI); a self-reported questionnaire where the subject rates how difficult it is for them to complete certain activities or tasks. The FDI was given to the headache patients on their first visit to the PHP, the same day their nervous system function interview was conducted.

The mean FDI sum score of the two headache groups was not significantly different, meaning that their average functional disability is roughly at the same level. Out of a total high sum score of 60, the mean sum score within the headache group was 18.49. By mapping the individual mean scores of each item/activity one may find the items/activities that are most disabling within the M and/or TTH groups. Many of the items/activities were endorsed at the same or similar levels by the M and TTH groups. Six out of a total 15 items (40%) were endorsed on the more difficult side of the spectrum, meaning that these activities are found to be challenging by the pediatric-
primary headache population, regardless of specific diagnosis. For example, “being up all day,” “being at school all day,” “doing activities in gym/sports,” “reading or doing homework,” “running the length of a football field,” and “getting to sleep at night and staying asleep” were endorsed on the more difficult side of the spectrum for both groups. There were also some activities that were endorsed differently by the two groups. For example, “walking the length of a football field” was scored as more difficult for the M group than it was in the TTH group. This information may be useful for clinicians as a measure of treatment efficacy. The FDI questions discuss common, everyday activities, and if therapies or treatments can target these endpoints, the quality of life of these children and adolescents may improve.

Along with functionality, the psychological concerns of these patients are also important. Mood was measured via the Children’s Depression Inventory (CDI) which asks about various thoughts the patient might have had about him or herself. This data provides information on levels of Negative Mood, Interpersonal Problems, Ineffectiveness, Anhedonia, and Negative Self Esteem. Those patients with a diagnosis of Major Depression or Major Anxiety were excluded from this study due to potential ANS involvement in those conditions.

There was no significant difference between the two headache groups in regards to their total CDI scores. Out of a total high score of 54, the mean score of both groups was not higher than ten. It is interesting to note, however, that in the TTH group, the range of total scores was wider than in the M group, by ten points. One explanation for this finding might be due to the TTH group having a more variable depression profile. An
extended period of this low level of chronic depression may lead to a variety of negative outcomes when initiated at a young age. These problems may manifest themselves socially and via self-perception, ultimately affecting mental and social development. In the adult headache population, a high rate of depression is prevalent. One explanation may be due to the fact that younger children and adolescents may have a more difficult time quantifying their emotional state for a questionnaire. Due to the low level of depression found throughout this population and the prevalence of depression found in the adult population, the mental state of these patients should be carefully monitored throughout their treatments to better determine when and why this change occurs.

Retrospectively quantifying dysautonomia symptoms is limited by patient interpretation and physician report. For example, it is difficult to standardize a definition of “blurry vision” in an interview format. In other areas of pediatric autonomic dysfunction research, such as in POTS and Diabetes research, autonomic dysfunction measuring protocols have shown clinical utility, such as tilt-table testing, HRV measurements, the Valsalva maneuver, and sudomotor testing. Even though this retrospective method of data collection may have limitations, a significant relationship between the presence of autonomic dysfunction symptoms and pediatric primary headaches were found. It is valid to further explore the prevalence of these symptoms by measuring them in a prospective study.

Due to the autonomic nervous system’s involvement in many different bodily systems, there are many ways dysfunction may present itself. For example, there can be
an imbalance in the signal to the heart causing an elevated or lowered heart rate, the
innervations to the lungs may be affected causing disordered breathing patterns, or the GI
system can be affected resulting in delayed gastric emptying or excessive emptying. The autonomic dysfunction symptoms collected are only a small subset of the many
symptoms possible. The symptoms chosen were decided based upon their prevalence in
the adult-headache population literature, as well as their ability to be measured
prospectively. One possible reason for minimal difference between the migraine and
tension-type headache groups may be attributed to the particular symptoms selected for
study. Measuring patients’ levels of dysautonomia, and utilizing validated autonomic
function protocols, would allow a more comprehensive collection of symptoms, thus
leading to a more specific ANS dysfunction profile for both migraine and tension-type
headache patients.

Careful review of these patient histories and self-reported symptoms highlighted
the intrinsic complexity of the ANS. Along with prospectively measuring these
symptoms with validated measures, developing a standardized clinical questionnaire for
physicians would help synthesize information. A consistent method for quantifying self-
reported data would give more clinical meaning to that information.

The autonomic nervous system’s integrated involvement throughout the body
caused another limitation when selecting a control group for this study. This study
required a control group with non-headache symptoms, no possible autonomic nervous
system involvement and a full clinical evaluation. These requirements ruled out many of
the most prevalent pediatric conditions for example, asthma and allergies. Patients
with a diagnosis of idiopathic scoliosis commonly present with no other comorbidities. Though a comparison group of healthy controls is ideal; due to the retrospective, clinical evaluation-requirement of this study, the IS group was a thoroughly investigated alternative.

During this retrospective review, some additional findings requiring future investigation were found. For example, the level of “insomnia” was significantly elevated in both M and TTH groups. As insomnia is a complex diagnosis in itself, it would be valuable to investigate that relationship further.
CONCLUSION

There is very little information published regarding the role of the autonomic system in pediatric-primary headache disorders. This project is an initial step towards confirming a relationship. It suggests that development of an autonomic dysfunction profile for this population utilizing validated measures, such as HRV, tilt table testing, and sudomotor testing, may be clinically relevant. By collecting this information we will also be able to more specifically define ANS dysfunction in patients suffering from migraines versus tension-type headaches. This information will not only help clinicians monitor treatment effectiveness, it will also bring us closer to elucidating the underlying mechanisms causing primary headaches.
Functional Disability Index (FDI)

When people are sick or not feeling well it is sometimes difficult for them to do their regular activities. In the last few days, would you have had any physical trouble or difficulty doing these activities?

<table>
<thead>
<tr>
<th>Activity</th>
<th>No Trouble</th>
<th>A Little Trouble</th>
<th>Some Trouble</th>
<th>A Lot of Trouble</th>
<th>Impossible</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Walking to the bathroom</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>2. Walking up the stairs</td>
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</tr>
<tr>
<td>3. Doing something with a friend (for example, playing a game)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>4. Doing chores at home</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Eating regular meals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Being up all day without a nap or rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Riding the school bus or traveling in the car</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Being at school all day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Doing the activities in gym class (or playing sports)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Reading or doing homework</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Watching TV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Walking the length of a football field</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Running the length of a football field</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Going shopping</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Getting to sleep at night and staying asleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Children’s Depression Inventory (CDI)

Kids sometimes have different feelings and ideas. This form lists the feelings and ideas in groups. From each group of three sentences, pick one sentence that describes you best for the past two weeks. After you pick a sentence from the first group, go on to the next group.

There is no right or wrong answer. Just pick the sentence that best describes the way you have been recently. Put a mark like this □ next to your answer. Put the mark in the box next to the sentence that you pick.

Here is an example of how this form works. Try it. Put a mark next to the sentence that describes you best.

Example:
□ I read books all the time.
□ I read books once in a while.
□ I never read books.

Remember, pick out the sentences that describe you best in the PAST TWO WEEKS.

**Item 1**
□ I am sad once in a while.
□ I am sad many times.
□ I am sad all the time.

**Item 2**
□ Nothing will ever work out for me.
□ I am not sure if things will work out for me.
□ Things will work out for me O.K.

**Item 3**
□ I do most things O.K.
□ I do many things wrong.
□ I do everything wrong.

**Item 4**
□ I have fun in many things.
□ I have fun in some things.
□ Nothing is fun at all.

**Item 5**
□ I am sad all the time.
□ I am sad many times.
□ I am sad once in a while.

**Item 6**
□ I think about bad things happening to me once in a while.
□ I worry that bad things will happen to me.
□ I am sure that terrible things will happen to me.

**Item 7**
□ I hate myself.
□ I do not like myself.
□ I like myself.

**Item 8**
□ All bad things are my fault.
□ Many bad things are my fault.
□ Bad things are not usually my fault.

**Item 9**
□ I do not think about killing myself.
□ I think about killing myself but I would not do it.
□ I want to kill myself.

Turn over and fill out the other side.
<table>
<thead>
<tr>
<th>Item</th>
<th>Sentences</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>- I feel like crying every day.</td>
</tr>
<tr>
<td></td>
<td>- I feel like crying many days.</td>
</tr>
<tr>
<td></td>
<td>- I feel like crying once in a while.</td>
</tr>
<tr>
<td>11</td>
<td>- Things bother me all the time.</td>
</tr>
<tr>
<td></td>
<td>- Things bother me many times.</td>
</tr>
<tr>
<td></td>
<td>- Things bother me once in a while.</td>
</tr>
<tr>
<td>12</td>
<td>- I like being with people.</td>
</tr>
<tr>
<td></td>
<td>- I do not like being with people many times.</td>
</tr>
<tr>
<td></td>
<td>- I do not want to be with people at all.</td>
</tr>
<tr>
<td>13</td>
<td>- I cannot make up my mind about things.</td>
</tr>
<tr>
<td></td>
<td>- It is hard to make up my mind about things.</td>
</tr>
<tr>
<td></td>
<td>- I make up my mind about things easily.</td>
</tr>
<tr>
<td>14</td>
<td>- I look O.K.</td>
</tr>
<tr>
<td></td>
<td>- There are some bad things about my looks.</td>
</tr>
<tr>
<td></td>
<td>- I look ugly.</td>
</tr>
<tr>
<td>15</td>
<td>- I have to push myself all the time to do my schoolwork.</td>
</tr>
<tr>
<td></td>
<td>- I have to push myself many times to do my schoolwork.</td>
</tr>
<tr>
<td></td>
<td>- Doing schoolwork is not a big problem.</td>
</tr>
<tr>
<td>16</td>
<td>- I have trouble sleeping every night.</td>
</tr>
<tr>
<td></td>
<td>- I have trouble sleeping many nights.</td>
</tr>
<tr>
<td></td>
<td>- I sleep pretty well.</td>
</tr>
<tr>
<td>17</td>
<td>- I am tired once in a while.</td>
</tr>
<tr>
<td></td>
<td>- I am tired many days.</td>
</tr>
<tr>
<td></td>
<td>- I am tired all the time.</td>
</tr>
<tr>
<td>18</td>
<td>- Most days I do not feel like eating.</td>
</tr>
<tr>
<td></td>
<td>- Many days I do not feel like eating.</td>
</tr>
<tr>
<td></td>
<td>- I eat pretty well.</td>
</tr>
<tr>
<td>19</td>
<td>- I do not worry about aches and pains.</td>
</tr>
<tr>
<td></td>
<td>- I worry about aches and pains many times.</td>
</tr>
<tr>
<td></td>
<td>- I worry about aches and pains all the time.</td>
</tr>
<tr>
<td>20</td>
<td>- I do not feel alone.</td>
</tr>
<tr>
<td></td>
<td>- I feel alone many times.</td>
</tr>
<tr>
<td></td>
<td>- I feel alone all the time.</td>
</tr>
<tr>
<td>21</td>
<td>- I never have fun at school.</td>
</tr>
<tr>
<td></td>
<td>- I have fun at school only once in a while.</td>
</tr>
<tr>
<td></td>
<td>- I have fun at school many times.</td>
</tr>
<tr>
<td>22</td>
<td>- I have plenty of friends.</td>
</tr>
<tr>
<td></td>
<td>- I have some friends but I wish I had more.</td>
</tr>
<tr>
<td></td>
<td>- I do not have any friends.</td>
</tr>
<tr>
<td>23</td>
<td>- My schoolwork is alright.</td>
</tr>
<tr>
<td></td>
<td>- My schoolwork is not as good as before.</td>
</tr>
<tr>
<td></td>
<td>- I do very badly in subjects I used to be good in.</td>
</tr>
<tr>
<td>24</td>
<td>- I can never be as good as other kids.</td>
</tr>
<tr>
<td></td>
<td>- I can be as good as other kids if I want to.</td>
</tr>
<tr>
<td></td>
<td>- I am just as good as other kids.</td>
</tr>
<tr>
<td>25</td>
<td>- Nobody really loves me.</td>
</tr>
<tr>
<td></td>
<td>- I am not sure if anybody loves me.</td>
</tr>
<tr>
<td></td>
<td>- I am sure that somebody loves me.</td>
</tr>
<tr>
<td>26</td>
<td>- I usually do what I am told.</td>
</tr>
<tr>
<td></td>
<td>- I do not do what I am told most times.</td>
</tr>
<tr>
<td></td>
<td>- I never do what I am told.</td>
</tr>
<tr>
<td>27</td>
<td>- I get along with people.</td>
</tr>
<tr>
<td></td>
<td>- I get into fights many times.</td>
</tr>
<tr>
<td></td>
<td>- I get into fights all the time.</td>
</tr>
</tbody>
</table>
# LIST OF JOURNAL ABBREVIATIONS

Arch. Dis. Child .......................................................... Archives of Disease in Childhood

Appl. Psychophysiol. Biofeedback ............... Applied Psychophysiology and Biofeedback

Biol. Psychol. ............................................................. Biological Psychology

Brain .............................................................................. Brain

Brain Res. Rev ............................................................... Brain Research Reviews

Cephalagia....................................................................... Cephalagia


Curr. Genomics ................................................................. Current Genomics

Curr. Pain Headache Rep ............................................. Current Pain and Headache Reports


Dtsch. Arztebl. Int............................................................. Deutsches Arzteblatt International


Front. Hum. Neurosci. .................................................... Frontiers in Human Neuroscience


Headache J. Head Face Pain ...................... Headache: The Journal of Head and Face Pain

Int. J. Psychiatry Med. ........................................... International Journal of Psychiatry in Medicine

JAMA ........................................................................... The Journal of the American Medical Association

J. Bone Joint Surg. .......................................................... The Bone and Joint Journal

J. Pediatr. Psychol. .......................................................... Journal of Pediatric Psychology
REFERENCES


CURRICULUM VITAE

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Education

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2014  

University of California, Davis  
B.S. Neurobiology, Physiology and Behavior  
2011

Professional Experience

Graduate Student Researcher  
PI: Dr. Alyssa LeBel  
Boston Children’s Hospital – Boston, MA and Waltham, MA  
Pediatric Headache Clinic (PHP)  
September 2013 – April 2014  
- Thesis project: Retrospective study on the prevalence of autonomic dysfunction in pediatric headache patients  
- Assisted in the establishment of an autonomic testing center in the clinic

English Teacher  
Rosie’s Place Women’s Education Center – Boston, MA  
September 2013 – April 2014  
- The Women’s Education Center is a place where poor and homeless immigrant women can come and work on their English skills or other everyday skills needed to help them secure a job or provide for their families
- Taught a Level 1 English course once a week – focused on everyday vocabulary words, basic grammar and appreciating cultural differences

Social Skills Co-leader
U.C. Davis MIND Institute – Sacramento, CA
September 2011 – June 2012
- Social Skills is an after school group for high-functioning children with Asperger’s Syndrome, PDD-NOS, and Autism Spectrum Disorder who have social problems
- Here we taught the kids how to deal with various social issues and to learn practical skills and techniques to help facilitate more successful peer interactions

Student Research Intern
Junior Specialist
PI: Dr. David Hessl
U.C. Davis MIND Institute – Sacramento, CA
Translational and Psychophysiological Assessments Laboratory (TPAL)
September 2008 – August 2012
- Started as a volunteer intern working on file processing and data entry, and quickly progressed to collecting and processing cortisol lab samples and running various protocols
- Hired full time as coordinator of the TPAL – scheduling and data collection
- Co-coordinator for the Limbic System Function in Fragile X Premutation Carriers Study
- Worked with patients aged 3-75 with Fragile X Syndrome, Autism Spectrum Disorder and other various developmental disorders
- Worked with a group to create and validate two different eye tracking protocols using TOBII eye tracking equipment
- Was responsible for administering various cognitive assessments
- Contributed to multiple research publications