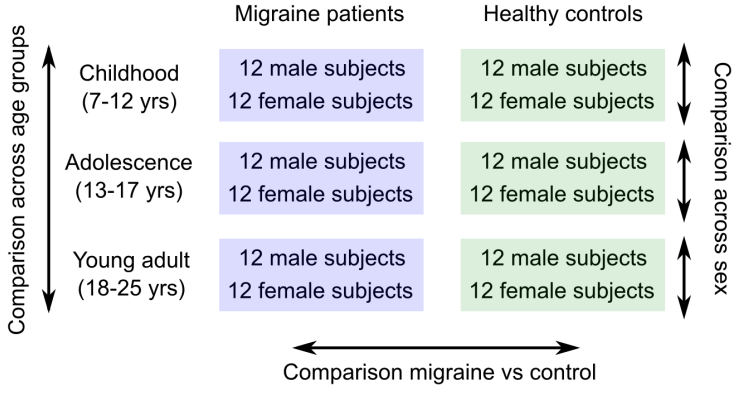
Sophie Wilcox – research summary

Research Summary

Migraine, along with other primary headache disorders, is among the most common medical conditions in childhood (Abu-Arafeh *et al.*, 2010). Despite this high prevalence in the pediatric population, there remains some ambiguity as to the unique aspects of migraine in childhood and adolescence and the progression to adulthood (Hershey, 2012). It is likely that the differential presentation of migraine in children and adolescents is related, among other factors, to the ongoing development of the nervous system during this critical point in development (Maleki *et al.*, 2016). Thus, while it is proposed that the underlying pathophysiological mechanisms of migraine are the same in both children and adults, their evolution during this developmental period represents a unique opportunity to explore how the central nervous system may mediate the expression of migraine (Pro *et al.*, 2014).

Several studies have examined age- and sex-related differences in the presentation of migraine and several notable differences have been observed between children and adults or younger and older children. These include a marked sexual dimorphism in migraine prevalence during adolescence, on average a shorter duration of headache attacks in younger children, a higher proportion of frontal location in the spatial distribution of their headache in younger children and a higher presentation of nausea and vomiting as associated symptoms in younger migraineurs (Gladstein *et al.*, 1993; Metsahonkala and Sillanpaa, 1994; Gallai *et al.*, 1995; Raieli *et al.*, 1995; Raieli *et al.*, 1996; deGrauw *et al.*, 1999; Hershey *et al.*, 2005; Chakravarty *et al.*, 2008).

At present, relatively little is known about the underlying neuromechanisms of migraine in the pediatric population and if (and how) they may evolve with age and disease progression. It is our proposal, given that the disease frequently begins at a young age, that new insights into the neurobiology of migraine at an early stage of the disease could provide valuable insight in terms of both 1) basic mechanistic understanding of migraine and 2) clinical implications, particularly in developing specific diagnostic criteria and therapeutic guidelines for pediatric migraine, based on clinically determinable biomarkers and/or surrogate markers (Katz, 2004).



The primary aim of my research is to evaluate both morphometric and volumetric changes in cortical and sub-cortical regions and measures of white matter tract integrity in episodic migraineurs and healthy controls within and across age groups and sex (See Figure 1 for study design and projected comparisons). These anatomical changes will be correlated with alterations in the presentation of migraine across age groups and sex.

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In initial findings, we have recently characterized age- and sex-related differences in the presentation of pediatric migraine. In this retrospective cohort study we observed that several migraine features differed significantly with age and/or sex. Of particular note be found that a higher proportion of adolescents, particularly female migraineurs, had a diagnosis of a comorbid anxiety (as shown in Figure 2).

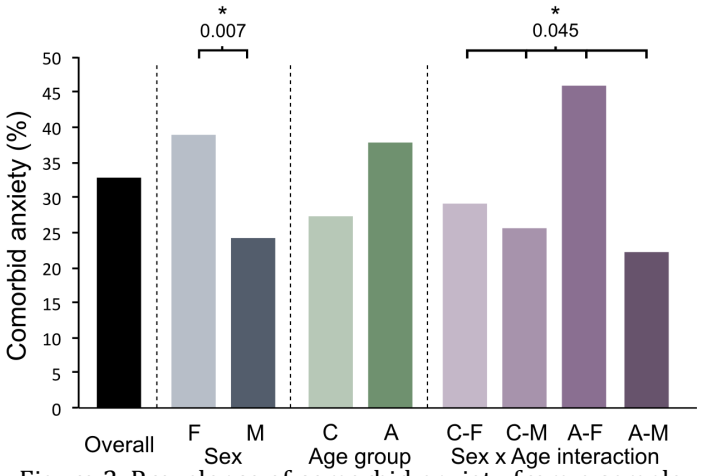

Figure 2. Prevalence of comorbid anxiety from a sample of 359 pediatric migraine patients 1) overall, 2) divided by age group (C – children, A – adolescents), 3) divided by sex (F – females, M – males) and 4) divided by both age and sex.

In light of these findings we have subsequently focused on the hippocampus, as this subcortical region has a unique vulnerability to maladaptive plasticity in response to repeated physiological and emotional stressors. During the developmental period of adolescence the physiological and emotional components of migraine may evolve, in conjunction with hippocampal (and brain-wide) structural remodeling. Migraine and age were found to have an interactional relationship with hippocampal volume, such that, while hippocampal volumes were lower in migraineurs (compared to age-matched controls) during childhood and adolescence, this contrast reversed during young adulthood. The transition of hippocampal volume during adolescent development in migraineurs suggests that hippocampal plasticity may dynamically reflect evolving components of migraine, including both its physiological expression and psychosocial impact.

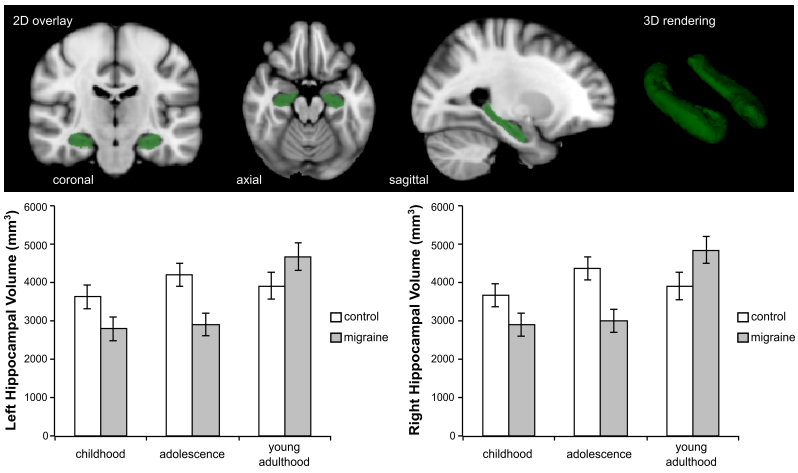

Figure 3. Upper panel – Hippocampal segmentation. Lower panel - Hippocampal volumes. Bar and line graphs (upper and lower panels, respectively) of mean hippocampal volume by group and development stage.

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