Project Details	
Project Code	MRCNMH24Ca Davies
Title	Using a new translational in vivo model to understand the neurobiology underlying ADHD subtypes
Research Theme	Neuroscience & Mental Health
Summary	In mice and humans loss-of-function of the steroid sulfatase (STS) enzyme results in inattention but enhanced motor response inhibition; we aim to understand the neurobiology underlying this dissociation using a new mouse model. The project will develop behavioural neuroscience research skills, will have direct clinical relevance to X-linked ichthyosis (STS deficiency), and will signpost mechanisms associated with Attention Deficit Hyperactivity Disorder subtypes.
Description	The project will investigate cognitive control and its underlying neural substrates in a new Sts (steroid sulfatase) deletion 'knockout' mouse model generated via the MRC Harwell Genome Editing Mice for Medicine (GEMM) programme; its findings will be of direct relevance to the 7.5million individuals worldwide affected by STS deficiency, and will inform our understanding of Attention Deficit Hyperactivity Disorder (ADHD) subtypes and sex differences in ADHD ADHD is a common neurodevelopmental condition characterised by age-inappropriate inattention, impulsivity and hyperactivity. In DSM-5, three ADHD presentations are recognised: 'predominantly inattentive', 'predominantly hyperactive-impulsive', and 'combined', but the neurobiology distinguishing these is unclear [1] In man, deletion of the STS gene (associated with the dermatological condition X-linked ichthyosis, XLI) is associated with a substantially-increased risk of ADHD, particularly of the inattentive subtype [2-4]; however, deletion carriers exhibit reduced motor impulsivity [5,6]. Consistent with this, genetic variation within STS is associated with attentive, but not impulsive, traits in boys with ADHD [7] and healthy men [8] STS is expressed in the developing human basal ganglia [7], and adult deletion carriers exhibit lower volumes of the globus pallidus, nucleus accumbens and putamen [9]. STS knockdown in human cells has implicated aberrant astrocyte development [10]. Chromosomal-mutant male 39,XY*O mice lacking Sts, and wildtype mice in which the STS enzyme is acutely inhibited, also exhibit attention deficits [11] but enhanced motor response inhibition [12]; the former group exhibit altered basal ganglia tissue monoamine levels [13] Unlike the 39,XY*O model, the Sts-deletion mouse only has the Sts gene disrupted and can be easily bred; Sts-deficient mice show no overt skin pathology, but are significantly more hyperactive than their wildtype littermates In Cardiff: • Sts-deletion and wildtype control mice will be subject to a battery of touchscreen-based cognitive tasks taxing attention and/or impulsivity to specify any between-group cognitive differences • a new task taxing behavioural flexibility (reversal learning) will also be developed, specified, and used to characterise Sts-deletion mice • the sensitivity of any significant effects to pharmacological modulation (e.g. of the monoamine systems) will be investigated • the effects of administering the STS inhibitor STX-64, or substrate dehydroepiandrosterone sulfate (DHEAS), acutely to wildtype mice will also be examined to dissociate between adult effects arising developmentally and/or due to ongoing STS activity [9,11] In Bristol:

	• the neuroanatomy and electrophysiology of the basal ganglia of mice with genetic/pharmacological manipulations of the STS axis will be investigated [14], with a focus on astrocyte biology, the monoamine systems and subthalamic nucleus-globus pallidus connectivity implicated in hyperactivity, distractibility, over-rigidity and motor response inhibition [15,16]. The project will identify neuroanatomical/neurochemical correlates of hyperactivity, inattention and reduced motor impulsivity which may be: a) manipulated in future animal work to demonstrate causality, and b) focussed upon in future human e.g. neuroimaging work. The work will be: conducted in parallel with ongoing work within Dr Davies' group on the neuropsychological profile of XLI, feed into world-leading clinical research on ADHD being conducted across GW4, and disseminated via our established links to relevant skin and ADHD charities (e.g. Ichthyosis Support Group) [1]PMID:27183902 [2]PMID:18413370 [3]PMID:29901853 [4]PMID:29672931 [5]PMID:27711218 [6]PMID:30768640 [7]PMID:21255266 [8]PMID:28293481 [9]PMID:32139392 [10] doi:10.3389/fmolb.2023.1176802 [11]PMID:19251250 [12]PMID:24842408 [13]PMID:22189290 [14]PMID:25843402 [15]PMID:32887694 [16]PMID:31031006
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