Project Details	
Project Code	MRC22NMHCa Riglin
Title	Investigating novel types of irritability using a developmental and genetic approach
Research Theme	Neuroscience & Mental Health
Summary	Severe childhood irritability is disruptive, impairing, a common reason for mental health service referral and a major treatment challenge. It is uncertain if irritability is a behavioural, neurodevelopmental or mood problem. This PhD will use longitudinal, population cohorts to examine irritability across development and test the hypothesis that there are different types of irritability, differentiated by developmental course, genetic and environmental aetiology.
Description	Childhood irritability – an increased propensity to anger, relative to peers – is disruptive, socially concerning and a common reason prompting referral to mental health services. It is strongly associated with future psychiatric morbidity, especially depression, suicidality and long-term negative health, education and employment outcomes (1,2). However, there is uncertainty regarding how irritability is best classified and limited knowledge about how to treat it. It thus presents a management challenge. Severe, chronic irritability is classified as a mood disorder (disruptive mood dysregulation disorder) by DSM-5 and as a behavioural problem (oppositional defiant disorder specifier) by ICD-11. A high prevalence in children with ADHD as well as genetic overlap have also led to the hypothesis that irritability may be a core feature of ADHD (3) which is a neurodevelopmental disorder. Whether irritability is conceptualised as an ADHD-like, behavioural or depression-like problem would suggest different treatment approaches. Preliminary treatment trials have attempted these interventions for irritability and heterogeneous outcomes suggest stratifying irritability may be key (2). This project will build on previous work (4) and use genetic and epidemiological approaches to test the hypothesis that irritability is not a homogenous construct, and that there are different types of irritability: ADHD-like, behavioural and depression-like. The goal of this project is to generate evidence to inform the conceptualisation of severe, childhood irritability needed for future diagnostic classification and intervention guidelines. The overarching aim is to test the hypotheses that there are different types of irritability: ADHD-like, behavioural and depression-like. These will be characterised by their developmental course, clinical features and genetic and environmental risk factors. This will differentiate ADHD-like (early-onset, ADHD genetic correlates, prenatal risk factors), behavioural (childhood-onset, parenting and social risk factors) and depression-like (adolescent/adult-onset, depression genetic correlates, stress-related risk factors) irritability. This hypothesis will be tested using a UK longitudinal, population-based cohort design (childhood to 25 years). The aims of this project are: 1) Characterise the different developmental patterns of irritability from childhood to adulthood, and associations with social and educational impairments. This will involve analysing repeated measures of irritability (growth mixture modelling) and examining potential bias arising from missing data. 2) Test whether associated clinical features of the different irritability trajectory groups are

	consistent with ADHD-like, behavioural or depression-like psychopathology. This will involve examining symptom clustering (latent class analysis) and modelling longitudinal relationships between irritability trajectories and other psychopathologies (multi-trajectory analysis). 3) Test whether associated genetic and environmental risk factors of the different irritability trajectory groups are consistent with ADHD-like, behavioural or depression-like psychopathology. This will involve generating polygenic risk scores based on large, published genome-wise association studies and examining associations for derived trajectories with time-invariant (e.g. early life factors) and time-varying (e.g. stressful life events) covariates. Data will primarily be analysed in the Avon Longitudinal Study of Parents and Children (ALSPAC), including approximately 8,000 individuals with irritability data at multiple time-points from age 7 to 25 years. Replication will be undertaken in the Millenium Cohort Study, a UK population cohort that is more diverse and includes irritability data at ages 7, 14 and 17 years. References: (1) PMID:28127909 (2) PMID:29083031 (3) PMID:28949337 (4) PMID:31256611
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