Project Details	
Project Code	MRC23NMHCa Riglin
Title	Investigating novel types of childhood irritability (emotional dysregulation) using a developmental and genetic approach
Research Theme	Neuroscience and Mental Health
Summary	Severe childhood irritability is a common symptom across many mental health disorders and a common reason for mental health service referral. 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 highly disruptive and a common reason for 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 about how to best classify irritability and limited knowledge about how to treat. It thus presents a management challenge. The goal of this project is to generate evidence to inform the conceptualisation of irritability needed for future diagnostic classification and intervention guidelines. Severe, chronic irritability is classified as a mood disorder (disruptive mood dysregulation disorder) by DSM-5 and a behavioural problem (oppositional defiant disorder specifier) by ICD-11. A high prevalence in children with ADHD plus genetic overlap have also led to the hypothesis that irritability may be a core feature of ADHD(3) (a neurodevelopmental disorder). Whether irritability is conceptualised as ADHD-like, behavioural or depression-like would suggest different treatment approaches. Preliminary irritability treatment trials have found heterogeneous outcomes, suggesting 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. Developmental course, clinical features and genetic/environmental risk factors, which 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. 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 due to 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 longitudinal relationships between irritability trajectories and other psychopathologies (multi-trajectory analysis): the student will be able to steer the project by selecting which

	psychopathologies to include (e.g. autism, anxiety). 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 scores based on genome-wise association studies and examining associations for derived trajectories with time-invariant and time-varying covariates. The student will be able to take steer the project by selecting which risk factors to examine (e.g. poverty, social relationships). Data will primarily be analysed in the Avon Longitudinal Study of Parents and Children, including approximately 10,000 individuals with irritability data across ages 7-25 years. Replication will be undertaken in the Millenium Cohort Study, a UK population cohort that is more diverse and includes irritability data from age 7-17 years. The student will be able to steer the project by focussing exclusively on population cohorts or including clinical replication samples based within the Cardiff child psychiatry team. References 1.Leibenluft (2017). PMID:28127909 2.Stringaris et al (2018). PMID:29083031 3.Riglin et al (2017). PMID:28949337 4.Riglin et al (2019). PMID:31256611
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