Project Details	
Project Code	MRC21NMHBa Button
Title	Understanding the neural mechanisms of antidepressant withdrawal and links with depressive symptoms, anhedonia and relapse
Research Theme	Neuroscience & Mental Health
Summary	This project will investigate the effects of antidepressant withdrawal on neural markers of reward and emotion processing using event-related potentials in a longitudinal study of patients in primary care. We will also test whether changes in neural markers early in the withdrawal process can be used to predict later depressive relapse.
Description	One in ten adults in the UK take antidepressants and many do so on a long-term basis. While sustained use is needed to prevent relapse for some, it is estimated that half of patients could stop safely, but we currently lack the evidence to predict which half could do so. Neurocognitive theories suggest that SSRI antidepressants work by altering monoamine function which positively shifts emotion and reward processing, leading to more rewarding social experiences and subsequent changes in mood. This is supported by evidence that neurocognitive changes occur within hours of starting SSRIs, while changes in mood often take weeks. When discontinued, monoamine function is thought to revert back, leading to a return of dysfunctional processing, less social engagement, worse mood and eventually relapse. However, despite being putative markers of subsequent relapse, little is known about the effects of antidepressant withdrawal on emotion and reward processing. This project aims to address this in a series of studies using brain imaging, clinical assessment, and experience sampling to assess reward and emotion processing in those undergoing antidepressant withdrawal. Event Related Potentials (ERPs), assessed using EEG, are a reliable, cost-effective measure of brain activity with high temporal resolution. Recent research has identified robust alterations in ERP markers of reward (Reward Positivity) and emotion (LPP) processing in depression. This will be the first study to investigate how these neural markers change during withdrawal using cutting-edge computational methods to link neural, behavioural, and clinical levels of analysis, and predict depressive relapse up to 3 months later. All studies will be co-designed with patients and GPs. Study 1 Cross-sectional study of neural and neurocognitive markers of reward and emotion processing in patients being treated for depression with SSRIs compared to unmedicated depressed and non-depressed controls recruited from the community. Study 2 Longitudinal cohort study of patients recruited through primary care who are planning to stop taking antidepressants under GP supervision compared to patients who continue and non-depressed controls. ERP and neurocognitive markers of reward and emotion processing and clinical symptoms will be assessed at baseline (pre-withdrawal), 2 weeks and 3 months post-withdrawal with clinical interviews at 3 months to assess depressive relapse. Study 3 Ecological Momentary Assessment study tracking changes in mood reactivity to positive events or social interactions in the first 2 weeks following antidepressant withdrawal. An app downloaded to the patient's smartphone will prompt report of current symptoms and social interactions at various points across the day. The results will

	directly inform management of antidepressant withdrawal in primary care, shed light on how antidepressants work (and the brain changes occurring during withdrawal), and help identify early markers of relapse.
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