Project Details	
Project Code	MRC22NMHBa Button
Title	Understanding the neural mechanisms of antidepressant withdrawal and links with depressive symptoms, reward processing 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 (ERPs) in a longitudinal study of patients in primary care. We will also test whether changes in neural markers early in the withdrawal process predict depressive relapse and investigate links between neural markers and mood changes, focusing particularly on experiences of reward in everyday life.
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 up to half of all patients could stop safely, but we currently lack the evidence to predict outcomes on an individual basis. Neurocognitive theories suggest that SSRI antidepressants work by altering monoamine function which causes a positive shift in 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 to develop. When discontinued, monoamine function is thought to revert back, leading to a return of negative processing biases, reduced social engagement, deterioration of 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 gap using brain imaging, neurocognitive testing, clinical assessment, and experience sampling to assess reward and emotion processing in a longitudinal study of patients recruited through primary care who are planning to stop taking antidepressants under GP supervision compared to patients who continue on antidepressants and non-depressed controls. The study will be co-designed with patients and GPs to ensure that it generates clinically useful findings. Workpackage 1: Event-Related Potentials (ERPs) 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. Clinical interviews will be done at baseline and 6 months post-withdrawal to assess depressive relapse / re-emergence of symptoms. ERPs, assessed using EEG, are a cost-effective measure of brain activity with high temporal resolution and good test-retest reliability. 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, and assess whether they predict depressive relapse up to 6 months later. Neurocognitive tasks tapping reward and emotion processes will also be administered to investigate withdrawal-related changes in performance. Workpackage 2: Ecological Momentary Assessment (EMA) methods will be used during the first 2-weeks of withdrawal to track changes in positive and negative affect, anhedonia and mood reactivity to social interactions. An app downloaded to the

	patient's phone will prompt report of current mood states and social interactions at various points across the day. This will provide information about sensitivity to social rewards and reward processing in everyday life. Workpackage 3: Data from WP1 and WP2 will be triangulated using advanced computational methods (e.g., network analysis, machine learning) to link neural, neurocognitive, EMA, and clinical data from the same individuals to: 1) identify which features are most predictive of depressive relapse and 2) investigate how well the different outcomes map onto each other and the broader construct of reward processing. 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. The student will be encouraged to present the results at conferences, to the groups involved in co-production of the research, at various meetings and seminars at Bristol and Bath, via public engagement opportunities (e.g. Pint of Science), through social media (e.g., Twitter), as well as high impact peer-reviewed papers. Knowledge exchange between the two Universities will be facilitated through monthly team meetings.
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