Background

Depression remains poorly understood despite being a leading contributor to the global burden of disease. A number of brain regions, particularly the hippocampus, have been implicated in the development of depression. However, the accuracy of grey-matter predictors of depression has remained limited.

Methods

In this study, we aimed to train brain-based predictors of major depressive disorder (MDD) using the voxel-wise grey-matter structure extracted from T1-weighted structural MRI imaging from the UK Biobank. We derived predictors using both machine-learning (Best Linear Unbiased Predictors [BLUP]) and deep-learning (ResNet3D) techniques, on a training sample comprising ~1,000 MDD cases and ~4,000 controls. The prediction accuracy of predictors was evaluated in an independent sub-cohort of ~500 MDD cases and ~2,000 controls from the UK Biobank, with replication in the DEP-ARREST CLIN clinical cohort (64 cases and 32 controls). To further understand the clinical relevance of the brain-based predictors, we also interrogated their overlap with a genetic predictor of major depression, using polygenic scores (PGS) derived from large-scale genome-wide association studies.

Results

In the UK Biobank cohort, the BLUP predictor showed moderate predictor accuracy (AUC=0.57), and a significant association with MDD status (OR=1.28 [1.15-1.43]; p-value=1.1×10^{-5}). By partitioning the BLUP predictor by brain regions of interest (ROI), we found nominal significance supporting the implication of ROIs previously linked to MDD (e.g. hippocampus and amygdala). The BLUP predictor overlapped partially with the depression PGS but also captured an additional signal supported by nominal significance (ΔAUC=0.01, p=0.024). Though no association passed multiple testing correction in the DEP-ARREST CLIN cohort, the overall direction of associations remained concordant with the UK Biobank. In contrast, the deep-learning predictor was not associated with MDD status after multiple testing corrections.

Conclusions

Our findings of brain-based predictors with modest AUC values underscore the difficulty of training brain-based MDD predictors for clinical applications. However, our findings suggest promising avenues for future research, such as the application of brain-based predictors, potentially on other brain modalities, in understanding the underlying predisposition to MDD and its comorbidities, as well as in informing differential diagnosis.