Title: Grey matter morphology as a predictor of individual response to cognitive behavioural therapy in depression - findings from a preliminary machine learning study.

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Abstract

Major depression is a disabling illness, with many treatment options, but no reliable predictors of treatment response. In the present study, we utilised a longitudinal design to test if pre-treatment grey-matter morphology could predict individual response to computerized guided-self-help cognitive-behavioural therapy for major depression. Using an advanced machine learning technique, in a sample of 43 un-medicated patients, we found that grey matter morphology predicted response to cognitive-behavioural therapy with 73.92% ($p=0.001$) accuracy and a proportionate reduction in uncertainty of 82%. We provide preliminary evidence that pre-treatment grey matter morphology is a biomarker of response to cognitive-behavioural therapy.

Keywords: Grey matter morphology; cognitive behavioural therapy; depression.

Depression (MDD) is a severe and disabling psychiatric disorder that affects around 5 - 10% of the general population ¹. Cognitive-behavioural therapy (CBT) has emerged as an effective evidence-based intervention for people with mild to moderate depression. Modern evidence based guidelines recommend a stepped care approach, where those with mild to moderate depression are offered low-intensity psychological interventions ². Guided-self-help computerized cognitive-behavioural therapy (cCBT) is an effective low-intensity intervention for mild to moderate depression (MDD) ³. Yet, only 50% of patients respond to cCBT, and routine clinical practice involves trial and error, often associated with greater disease burden ³. While neuroimaging studies have provided insight into cortical and subcortical structural abnormalities in MDD, attempts to translate these findings into meaningful biomarkers, that predict treatment response have met with modest success ^{4,5}. In addition, most studies that have explored the utility of neuroimaging in predicting treatment response to psychotherapy, base their findings on group-level differences ⁶. However, individual-level inferences based on group-level differences, can lead to high misclassification rates. To be clinically useful, predictors of response should be validated at an individual level. Modern machine learning approaches offer a novel way of testing if subtle brain grey-matter differences can help predict individual level response to treatment ⁶. In this preliminary study, we apply an advanced machine learning framework to explore if grey-matter morphology predict treatment response to cCBT at an individual level ⁶.

Methods

The study received ethics approval from the West of Scotland Research Ethics Committee. We included 43 consenting un-medicated patients with a primary

diagnosis of acute depressive episode (ICD-10), confirmed using the Clinical Interview Schedule - Revised (CIS-R), and scored ≥ 14 on the Beck's Depression Inventory II (BDI-II). We excluded those who received other CBT-based interventions (past 3 years), with comorbid mental disorders or brain injury. We used a longitudinal study design, pre-treatment assessment and MRI scan, was followed by a 10-week guided self-help programme "Living Life to The Full interactive" (<http://lltff.com>). Treatment response was defined as a 50% reduction in pre-treatment BDI score 2 months after completion of the cCBT. We used an intention to treat analysis with last observation carried forward approach. Six subjects were lost to follow-up and were considered as non-responders.

An axial 3D T1-weighted IR-FSPGR (TR=6.8ms; TE = 1.5ms, Flip angle=12°; FOV = 26cm; matrix: 320 x 320; 160 slices; slab thickness = 1mm) was acquired using GE, 3T Sigma Excite HD system with an eight channel phased array head coil. The data was pre-processed with FSL-VBM pipeline (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM>), an optimized VBM protocol carried out using FSL tools ⁷. Briefly, structural images were brain-extracted and grey-matter segmented before being registered to the MNI-152 standard space using non-linear registration. The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific grey matter template. All native grey matter images were non-linearly registered to this study-specific template. The un-modulated grey matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 5 mm ⁸. These images were subjected to a supervised machine learning approach using a linear binary Gaussian Process Classifier (GPC) implemented in PRoNTo software (<http://www.mlnl.cs.ucl.ac.uk/pronto>) ⁸. A GPC uses probabilistic modelling to

estimate the likelihood that a test subject belongs to a given group. GPCs are kernel classifiers and have shown high levels of performance for neuroimaging data where classes are likely to be heterogeneous. Unmodulated grey matter images were used as features, and an expectation propagation approximation used to estimate posterior predictive distribution. Classifier performance and generalizability was evaluated using a leave-one-out cross-validation (LOOCV) scheme. In LOOCV, data are divided into N folds (here, each fold is a subject). The classifier is trained on N-1 subjects and tested on the left out subject. This procedure was repeated N times by leaving out a different subject each time. Finally, the classification accuracy is the average accuracy across all the left-out folds. In addition to classification accuracy, we estimated classification accuracy (CA), the area under the receiver operator curve (AUC), and class predictive values. Class (responder/non-responder) predictive values (CPV) represent the proportion of actual responders/non-responders that were correctly classified. We present 95% confidence intervals of the above measures⁹.

$$\text{Classification Accuracy} = \frac{\text{True Responder} + \text{True Nonresponder}}{\text{Total number}}$$

$$\text{Class Predictive Value (responder)} = \frac{\text{True responder}}{\text{True responder} + \text{False Responder}}$$

$$\text{Class Predictive Value (nonresponder)} = \frac{\text{True nonresponder}}{\text{True nonresponder} + \text{False nonresponder}}$$

Results

Our final sample included 21 responders and 22 non-responders. There was no statistically significant difference in age (mean difference = -4.23; 95% CI= 11.48, -3.016), sex ($X^2 = 0.22$; $p = 0.64$), or baseline BDI scores (mean difference=4.94; 95%CI= -0.46,10.35) between responders and non-responders. The GPC, produced a balanced CA of 73.92% ($p = 0.001$; 95%CI= 58.83 - 86.48%) and AUC was 65% ($p = 0.04$; 95%CI= 50.18 - 77.58%). CPV for responders was 91.67% (95%CI=60.83 - 98.73%) and non-responders, 67.74 % (95%CI=57.06% - 76.85%). Using a gaussian process regression model, grey matter differences did not predict baseline BDI score with significant accuracy ($R^2 = 0.32$; $p = 0.68$). The weights of regions that contributed to the classification and the ROC are shown in the figure 1.

Discussion

Using a robust machine learning approach, we have demonstrated for the first time that pre-treatment grey matter morphology predicted response to cCBT at an individual level with reasonable accuracy. Regions that best predicted treatment response included bilateral hippocampi, amygdala and dorsal precuneus. Regions that best predicted treatment non-response included bilateral paracentral lobule, left medial prefrontal and anterior cingulate cortices, right insula, ventral precuneus and cerebellar vermis. These regions have been previously implicated in the pathophysiology underlying MDD ^{4,5}. Some of these regions (e.g. paracentral lobule) have also been shown to be predictive of treatment response/non-response to antidepressants ⁶. Our findings suggest that subtle grey matter morphological differences that underlie this pathophysiology may also be potential markers of response to treatment. The 91% CPV in responders suggests that grey-matter

morphology of subcortical structures like hippocampi and amygdala can help predict response to cCBT at an individual level with high certainty. We estimate that for a clinician facing uncertainty regarding the choice of treatment, this information will reduce the uncertainty by around 82% (proportionate reduction in uncertainty) ¹⁰. This has potential clinical utility in faster allocation to effective treatments, thereby reducing disease burden. Limitations of our study included a small sample size and the absence of an independent validation dataset. However, our findings are preliminary and the cross-validation scheme has ensured some degree of generalizability using methods validated previously ⁶. Non-responders had higher BDI scores at baseline (average of 5 points, but not statistically significant). However, using a gaussian process regression, grey matter morphology did not predict BDI scores with reasonable accuracy, suggesting that the accuracy of classifying responders vs. non-responders was independent of BDI scores. Robust identification of predictors will also consider other clinical factors (e.g. duration of episode of depression severity) and biological parameters (e.g. genetic and inflammatory markers). In summary, we found that pre-treatment grey matter morphology predicted response to CBT, with reasonable accuracy. The findings of our preliminary study has potential translational implications and requires replication.

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Declaration of Interest:

Rajeev Krishnadas, Filippo Queirazza, John McLean and Jonathan Cavanagh have not conflict of interest to declare. Chris Williams is an author of a variety of written and cCBT resources. These are licensed through Five Areas Ltd, a company that delivers free and licensed online life skills resources based on a CBT model in a variety of settings including the NHS and voluntary and private sectors. This includes resources used within the Living Life Course. He receives royalty and is shareholder and director of Five Areas Ltd. The present study was funded and sponsored by NHS Greater Glasgow and Clyde R and D department and had no role in data collection or analysis.

Figure Legends:

Figure 1: a) Grey matter regions contributing to the classification. Hot regions (>0 on colour bar) show the regions that best contributed to classification of responders (hippocampi, amygdala, dorsal precuneus) and cold regions (<0 on colourbar) show the regions that contributed to classification of non-responders (cerebellar vermis, anterior cingulate/medial prefrontal lobe, ventral precuneus, right insula, paracentral lobule) b) ROC curve and the area under the curve.