Psychiatry Research 329 (2023) 115542

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Towards a neuroimaging biomarker for predicting cognitive behavioural therapy outcomes in treatment-naive depression: Preliminary findings

Yange Wei [a,b,c], Ran Zhang [a,c], Yang Wang [a,c], Fay Y Womer [d], Shuai Dong [e], Junjie Zheng [a,1], Xizhe Zhang [e,1], Fei Wang [a,c,1,*]

[a] Early Intervention Unit, Department of Psychiatry, The Affiliated Brain Hospital of Nanjing Medical University, Nanjing, China
[b] Department of Psychiatry, The Second Affiliated Hospital of Xinxiang Medical University, Henan Mental Hospital, Xinxiang, China
[c] Department of Psychiatry, The First Affiliated Hospital of China Medical University, Shenyang, China
[d] Department of Psychiatry and Behavioural Sciences, Vanderbilt University Medical Center, Nashville, TN, USA
[e] School of Biomedical Engineering and Informatics, Nanjing Medical University, Nanjing, China

ARTICLE INFO

Keywords:
Depression
Cognitive behavioural therapy
Neuroimaging biomarker

ABSTRACT

Clear prognostic indicators of cognitive behavioural therapy (CBT) are lacking for depression. This study aims to identify a biomarker that predicts CBT outcomes in depression. We developed a machine learning algorithm to predict post-CBT Hamilton Depression Rating Scale (HAMD) using pre-CBT regional homogeneity (ReHo). We examined transcriptomic signatures of regions with CBT-related ReHo changes. Twenty-five patients completed CBT and had increased ReHo in the dorsolateral prefrontal cortex (DLPFC) following CBT. Pre-CBT ReHo in left DLPFC was shown to be a predictor of post-HAMD scores. We identified left DLPFC ReHo as a neuroimaging biomarker for therapeutic effects of CBT in depression.

1. Introduction

Despite cognitive behavioural therapy (CBT) is effective for depression (Beck et al., 2005), it is time-intensive, with its efficacy to be determined after at least 6–12 weeks of treatment (Rubin-Falcone et al., 2020). Currently, the selection of CBT is based on patient preference and their ability to participate in CBT and complete related assignments. With initial treatment, less than half of individuals achieve clinical remission (Dunlop et al., 2017). Thus, biomarkers related to CBT effects would facilitate objective and personalised approaches to treatment selection in depression.

Functional magnetic resonance imaging (fMRI) is well positioned to identify biomarkers for treatment response given that it may capture phenotypic variations in molecular and cellular disease targets (Crowther et al., 2015; Drysdale et al., 2017; Siegle et al., 2006; Xia et al., 2022). Recent fMRI studies have demonstrated CBT affects distinct brain regions, suggesting pretreatment brain function may predict CBT outcomes (DeRubeis et al., 2008; Dunlop et al., 2017; Greicius et al., 2007; Rubin-Falcone et al., 2020). While raw neuroimaging data is highly dimensional hindering the identification of key biomarkers. Machine learning algorithms could quantify biomarkers in a low-dimensional latent space and provide us with a feasible approach to develop possible biomarkers of CBT outcomes (Dwyer et al., 2018).

Neuroimaging cannot by itself elucidate the underlying mechanisms of treatments in depression. Imaging transcriptomic approache could enhance understanding of therapeutic effects by delineating regional associations with specific biological processes (Fornito et al., 2019; Martins et al., 2021). For instance, the Allen Human Brain Atlas (AHBA) microarray atlas measures the transcriptional profiling of almost the entire genome quantified in thousands of brain tissue samples (Hawrylycz et al., 2012). Shen et al. demonstrated the role of microglia dysregulation in brain disorders using regional homogeneity (ReHo), a measure reflecting local synchronicity of brain activity and the regional gene expression (Shen et al., 2021). Recent study demonstrated an association between depression-related changes in connectome gradients and gene expression enriched in synaptic plasticity related signaling (Xia et al., 2022). These findings suggest that synaptic signaling may play a critical role in depressive symptomology and pathology. Here, we hypothesised that neuroplasticity-related signaling may be associated with CBT-induced functional reorganization.

* Corresponding author at: Early intervention Unit, Department of Psychiatry, The Affiliated Brain Hospital of Nanjing Medical University, 264 Guangzhou Street, Nanjing, Jiangsu 210029, China.
E-mail address: fei.wang@yale.edu (F. Wang).
[1] These authors contributed to the work as the corresponding author.

https://doi.org/10.1016/j.psychres.2023.115542
Received 2 June 2023; Received in revised form 8 October 2023; Accepted 9 October 2023
Available online 17 October 2023

To test our hypothesis, this study includes three major steps: (1) determine CBT-related changes in ReHo and symptom severity and their relationships, (2) identify predictors of CBT outcomes using machine learning, and (3) examine brain-wide transcriptomic signatures of regions with CBT-related ReHo changes.

2. Methods

2.1. Participants

Subjects included 34 treatment-naive patients and 50 matched healthy controls (HCs, Supplementary Table 1). Patients received 16 CBT sessions (Supplementary Table 2) over 8 weeks at the Department of Psychiatry, First Affiliated Hospital of China Medical University, Shenyang, China.The primary outcome measure was Hamilton Depression Rating Scale (HAMD) score. Details regarding the stepwise design to identify a neuroimaging biomarker for CBT are shown in Supplementary Figures 1–2.

2.2. Imaging preprocessing

MRI scans were conducted before and after CBT using a 3.0T GE Sigma system. The images were processed and analyzed as described in Supplemental Materials. Individual ReHo maps were generated by calculating kendalls coefficient of concordance of the time series for the given voxel with its neighboring 26 voxels.

2.3. Prediction of CBT outcomes

We developed a support vector regression (SVR) model for predicting CBT outcomes from pretreatment ReHo with significant CBT-related changes. A leave-one-out cross-validation was used to evaluate model predictions.The Mean Absolute Error (MAE), mean square error (MSE), and the correlations between the predicted value and true value (r) were also calculated.

2.4. Gene expression profiles for regions with CBT-related changes in ReHo

To estimate gene expression profiles for regions with significant CBT-related changes in ReHo, we utilized the AHBA transcriptomic dataset (Supplementary Table 3) (Hawrylycz et al., 2012). A list of 10,027 genes was used to select gene expression maps (Li et al., 2021). Partial least squares (PLS) regression was used to estimate the spatial relationship between ReHo alterations and transcriptional signatures for 10,027 genes from 1304 regions of interests (ROIs) in the left hemisphere. Either positive (PLS1+) or negative (PLS1−) were identified as top-ranking genes (Li et al., 2021b). To explore biological pathways, we pooled the list of PLS1+ and PLS1− genes into the Metascape website. Significantly enriched pathways were selected using a 5 % FDR cut-off. We identified the top-ranking genes for seven cell types by examining the genes that overlapped between those of each cell type and top-ranking genes. Significant p value was determined using permutation tests with FDR < 0.05.

3. Statistical analyses

Paired *t*-test was used to compare changes in symptom scores and ReHo following CBT. Pearson correlation analyses were conducted to examine the relationships with symptom improvement and ReHo changes after CBT. We used linear regression analysis to examine the association between pretreatment ReHo values and HAMD score change after controlling for pretreatment HAMD score. Significance was set at $p < 0.05$. In addition, the similar analysis was performed in treatment-naive patients with depression to further validate CBT-related findings for ReHo and transcriptomic profile.

4. Results

4.1. CBT-related changes in ReHo and clinical symptoms

Twenty-five patients completed CBT and had significantly increased ReHo in bilateral DLPFC, compared to pretreatment group (GRF corrected, voxel $p < 0.05$, cluster $p < 0.05$; Fig. 1A, and Supplementary Tables 4). Significant decreases in HAMD scores following CBT (Fig. 1B, and Supplementary Table 5). While patient group showed significantly lower ReHo in bilateral DLPFC, plus significantly higher ReHo in left hippocampus and bilateral primary sensorimotor cortices (GRF corrected, voxel $p < 0.05$, cluster $p < 0.05$, and cluster size > 180 voxels) compared to HCs (Supplementary Figures 3–4, Supplementary Table 6).

4.2. Pretreatment ReHo in left DLPFC predicts CBT outcomes

CBT-related changes in ReHo in the left DLPFC correlated with HAMD score changes from pre- to post-CBT (Fig. 1C). Significant linear relationship between pretreatment ReHo in the left DLPFC and decreased HAMD scores was also observed ($r = 0.766$, $p < 0.01$). Lower ReHo in left DLPFC at pretreatment significantly predicted lower posttreatment HAMD scores post-CBT (MAE = 4.44, MSE = 33.88). Changes in true HAMD score were positively correlated with changes in predictive HAMD score (Fig. 1D and Supplementary Figure 5).

4.3. Gene expression profiles for left DLPFC

PLS1 gene expression weights spatially correlated with pairwise t-map (Fig. 1E). A total of 1901 genes constituted ReHo changes (Fig. 1F). Top-ranking gene expression of left DLPFC was enriched with pathways involved in neuroplasticity and cellular resilience, which was abundant in neuronal (excitatory and inhibitory neurons) and neuroglial cells (oligodendrocytes and astrocytes) in patients who completed CBT (Fig. 1G-J, Supplementary Figure 6, and Supplementary Tables 7–8).

In addition, a similar gene expression profile was observed for treatment-naive patients with depression. Further details are presented in the Supplementary Material, Supplementary Figures 7–10, and Supplementary Tables 9–10.

5. Discussion

This is the first study to incorporate machine learning and imaging transcriptomic approaches in identifying a neuroimaging biomarker of CBT outcomes and examine the neural mechanisms underlying CBT in treatment-naive depression. Our study yielded three main findings. First, CBT completion was associated with increased ReHo in bilateral DLPFC in patients with depression.The left DLPFC was the only brain region in which a significant correlation was observed between pre- and post-CBT ReHo changes and symptomatic improvement. Second, pretreatment ReHo in the left DLPFC significantly predicted posttreatment HAMD scores. Third, top-ranking gene expression of the left DLPFC was enriched with pathways involved in neuroplasticity and cellular resilience and abundant in neuronal and neuroglial cells. Altogether, ReHo in the left DLPFC appears to be a promising biomarker for depression and CBT effectiveness.

We found increased ReHo in the left DLPFC was associated with CBT-related symptom improvement. The DLPFC plays a crucial role in top-down regulation of emotion processing and rumination in depression (Hamilton et al., 2012; Ma, 2015). Increased DLPFC function may be associated with improved emotional regulation with CBT and consequently improved depressive symptoms following CBT. Further, lower ReHo in the left DLPFC prior to treatment significantly predicted lower posttreatment HAMD scores. This suggested that objective measures are necessary to understand why depressive symptoms change in some patients and not others. Although we identified pretreatment ReHo in the left DLPFC as a potential predictor of CBT, neuroimaging alone cannot

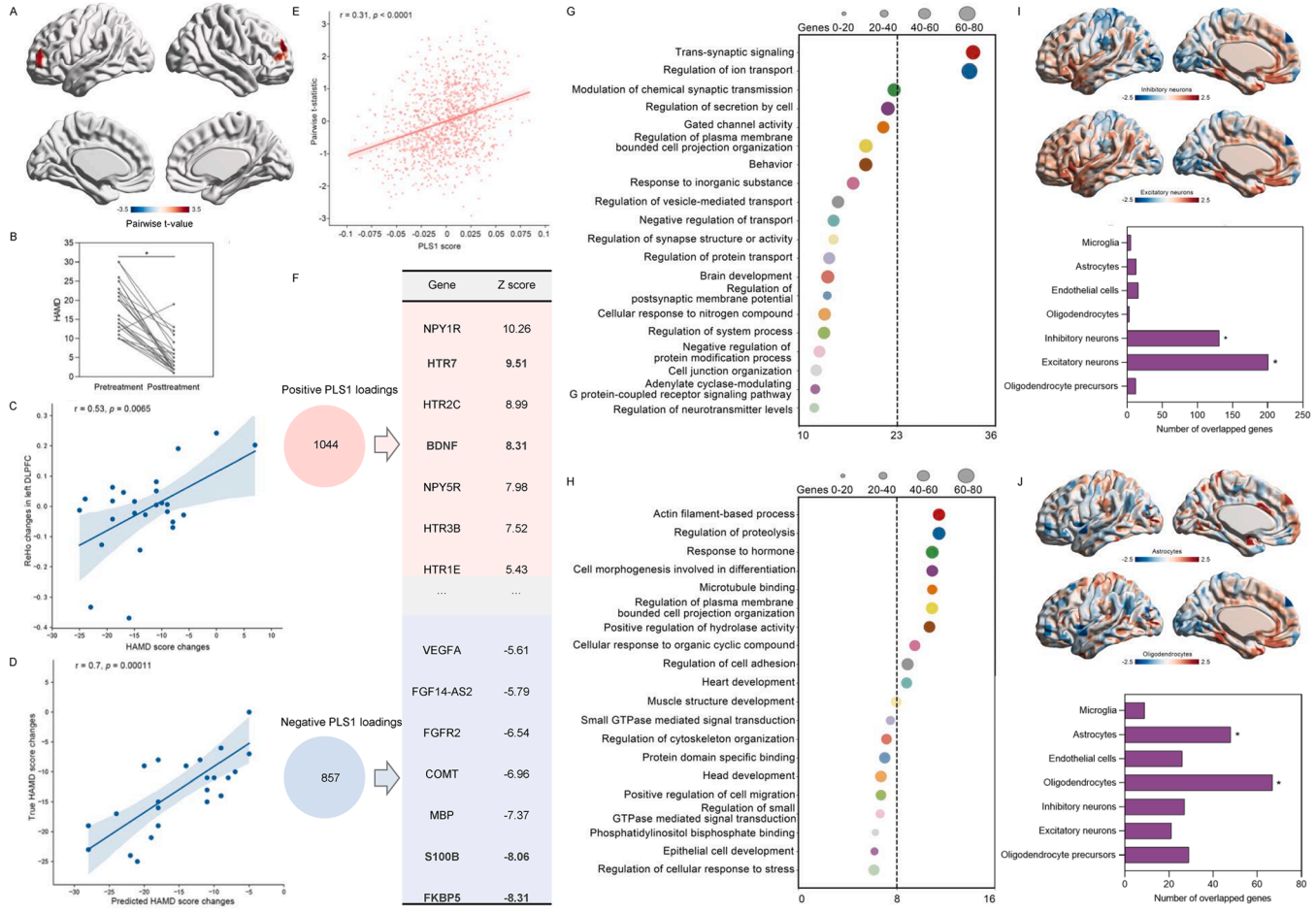

Fig. 1. Summary of the main findings in this study. **(A)** Brain regions showing significant differences in ReHo between the pretreatment and posttreatment group (GRF corrected, voxel $p < 0.05$, cluster $p < 0.05$). Red color indicates increased ReHo values after CBT. The color bar indicates the pairwise t-value. **(B)** Symptom changes in patients with depression who completed CBT ($n = 25$). *Significance level was set at $p < 0.05$. **(C)** Changes in ReHo from pre- to post-treatment in the left DLPFC were significantly correlated with HAMD score changes ($r = 0.53$, $p = 0.0065$). **(D)** Changes in true HAMD scores were positively correlated with changes in predictive HAMD scores. **(E)** A scatterplot of PLS1 gene expression weights and CBT-related ReHo alterations. **(F)** The PLS1 weighted gene expression was spatially correlated with CBT-related alternations in ReHo. **(G)** Top-ranking PLS1+ genes were significantly enriched for neuroplasticity-related pathways in depressed patients who completed CBT. **(H)** Top-ranking PLS1− genes were significantly enriched for cellular resilience-related pathways in depressed patients who completed CBT. $P_{FDR} < 0.05$ was treated as statistically significant. **(I)** Top-ranking PLS1+ genes were significantly abundant in excitatory neurons ($n = 201$, adjusted $p_{perm} < 0.001$, FDR-corrected), and inhibitory neurons ($n = 131$, adjusted $p_{perm} < 0.001$, FDR-corrected). **(J)** Top-ranking PLS1− genes were expressed in oligodendrocytes ($n = 67$, adjusted $p_{perm} < 0.001$, FDR corrected), and astrocytes ($n = 48$, adjusted $p_{perm} = 0.012$, FDR-corrected). Asterisks denote FDR-corrected $p < 0.05$. Abbreviations: BDNF, brain-derived neurotrophic factor; CBT, cognitive behavioural therapy; DLPFC, dorsolateral prefrontal cortex; FDR, false discovery rate; FKBP5, FK506-binding protein 5; GRF, Gaussian Random Field; HAMD, Hamilton Depression Scale; HTR7, 5-Hydroxytryptamine receptor 7; PLS, partial least squares; ReHo, regional homogeneity; S100B, S100 calcium-binding protein B. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

fully elucidate the biological mechanisms of these alterations (Arnatkeviciute et al., 2023). Our imaging transcriptomic analysis found that gene expression of the left DLPFC (e.g. BDNF, HTR7, FKBP5 and S100B) was enriched for neuroplasticity and cellular resilience-related pathways, and abundant in neuronal and neuroglial cells. Thus, enhancing left DLPFC activity through neuroplasticity and cellular resilience may be an antidepressant mechanism that contributes to CBT response.

This study has several limitations. First, the relatively small sample size, lack of blinding randomization, and placebo control group may confound the generalizability of our findings. Future larger-scale randomized controlled studies are necessary to confirm our preliminary findings. Second, we examined the effects related to CBT and not other depression treatments. Therefore, we are unable to determine the specificity of these findings to CBT. Third, we only found an association between regional gene expression patterns and CBT effectiveness, and not a causal relationship. There may be complexity in mechanisms of CBT outcomes in depression. Future randomized clinical trials are needed to confirm our findings and to identify the causal variants and its mechanism of action.

6. Conclusion

The left DLPFC may be a significant region involved in CBT response, and its gene expression is associated with neuroplasticity and cellular resilience, which may underlie the therapeutic effects of CBT. Furthermore, pretreatment ReHo in the left DLPFC appears to predict CBT outcomes and could be used as an objective biomarker to guide therapeutic decision-making for CBT.

Funding

This work was supported by research grants from the National Science Foundation for Distinguished Young Scholars (F.W., grant number 81725005) the National Natural Science Foundation of China (F.W.,

grant number 81571331; Z.Z., grant number 62176129, and Y.W., grant number 82301689), China Postdoctoral Science Foundation (Y.W., grant number 2021M691643), General Project of the Science and Technology Development Foundation of Nanjing Medical University (Y.W., grant number NMUB20210221), General Project of Henan Province Education Science (Y.W., grant number 2023YB0135), Project of Xinxiang Federation of Social Sciences (Y.W., grant number SKL-2023-118), and the Open Project of Psychiatry and Neuroscience Discipline of Second Affiliated Hospital of Xinxiang Medical University (Y.W., XYEFYJSSJ-2023-02).

CRediT authorship contribution statement

Yange Wei: Formal analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Ran Zhang:** Data curation, Investigation, Supervision. **Yang Wang:** Data curation, Investigation, Supervision. **Fay Y Womer:** Data curation, Investigation, Supervision, Writing – review & editing. **Shuai Dong:** Data curation, Formal analysis, Methodology, Software, Validation, Visualization. **Junjie Zheng:** Data curation, Formal analysis, Methodology, Validation, Visualization, Writing – review & editing. **Xizhe Zhang:** Data curation, Formal analysis, Methodology, Validation, Visualization, Writing – review & editing. **Fei Wang:** Conceptualization, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors have no biomedical financial interests or potential conflicts of interest to declare.

Acknowledgements

The authors would like to thank and acknowledge all participants for taking part in this study and their psychotherapists involved in treatments, as well as data managers and clinical coordinators. We appreciate the support provided by Prof. Wei Liao.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2023.115542.

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