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A neuroimaging-based precision medicine framework for depression

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ABSTRACT

Background: Symptom-based diagnostic criteria of depression leads to notorious heterogeneity and subjectivity. *Methods:* The study was conducted in two stages at two sites: development of a neuroimaging-based subtyping and precise repetitive transcranial magnetic stimulation (rTMS) strategy for depression at Center 1 and its clinical application at Center 2. Center 1 identified depression subtypes and subtype-specific rTMS targets based on amplitude of low frequency fluctuation (ALFF) in a cohort of 238 major depressive disorder patients and 66 healthy controls (HC). Subtypes were identified using a Gaussian Mixture Model, and subtype-specific rTMS targets were selected based on dominant brain regions prominently differentiating depression subtypes from HC. Subsequently, one classifier was employed and 72 hospitalized, depressed youths at Center 2 received two-week precise rTMS. MRI and clinical assessments were obtained at baseline, midpoint, and treatment completion for evaluation.
Results: Two neuroimaging subtypes of depression, archetypal and atypical depression, were identified based on distinct frontal-posterior functional imbalance patterns as measured by ALFF. The dorsomedial prefrontal cortex was identified as the rTMS target for archetypal depression, and the occipital cortex for atypical depression. Following precise rTMS, ALFF alterations were normalized in both archetypal and atypical depressed youths, corresponding with symptom response of 90.00% in archetypal depression and 70.73% in atypical depression.
Conclusions: A precision medicine framework for depression was developed based on objective neurobiomarkers and implemented with promising results, actualizing a subtyping-treatment-evaluation closed loop in depression. Future randomized controlled trials are warranted.

1. Background

Depression is one of the most common psychiatric disorders with a lifetime prevalence of 15%– 18%, and around 350 million people suffer from depression worldwide (Smith, 2014). Depression severely impairs many aspects of daily functioning, including education and employment, economy, and intimate relationships, leading to stunted individual and social development (Malhi and Mann, 2018). Unfortunately, the efficacy of conventional treatments for depression remains suboptimal; up to 40% of patients who receive antidepressant monotherapy achieve remission, even with a treatment duration of 3–6 months (Henssler et al., 2022). Moreover, in sharp contrast to many other medical conditions, the global burden of depression has not decreased in the past thirty years (Global Burden of Disease

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Collaborative Network, 2020). Altogether, these issues underscore the urgent need for novel and precise therapeutic strategies for depression.

Symptom-based diagnostic criteria result in notorious heterogeneity in depression, which impeded precision medicine (Nemeroff, 2020). One approach to eliminating the heterogeneity is to define depression into different subtypes (Insel and Cuthbert, 2015). Clinical specifiers are empirically applied by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) for subtype characterization, yet the descriptive symptom features fail to differentiate depression subtypes etiologically (Hasin et al., 2018). Neuroimaging studies have leveraged a tectonic shift in reconceptualizing depression beyond symptoms (Xia et al., 2019; Chang et al., 2018; Chang et al., 2019). Combined with machine learning techniques, depression could be delineated into distinct neuroimaging subtypes with subtype-specific neural deficits in a data-driven fashion. The resulting reproducible and objective neurobiomarkers for subtyping would have highly promising potential to guide precision medicine in depression. In our prior work, we identified two neurobiological subtypes in psychiatric disorders including major depressive disorder (MDD) based on the amplitude of low-frequency fluctuations (ALFF): archetypal and atypical subtypes (Chang et al., 2021). ALFF may reflect regional spontaneous neural activities at rest and has shown to be a reliable measure for psychiatric disorders (Chang et al., 2019). The identified archetypal and atypical subtypes had converse patterns of frontal-posterior functional imbalance associated with differentiation in white matter integrity, cortical thickness, polygenic risk scores, tissue profiles for risk gene expression, and medication effects, implicating frontal-posterior functional imbalance as a potential neuromodulation target for precise repetitive transcranial magnetic stimulation (rTMS) in depression (Chang et al., 2021).

As a non-invasive form of brain stimulation, rTMS has been approved by the U.S. Food and Drug Administration for adult treatment-resistant depression (TRD) in 2008 (O'Reardon et al., 2007). Studies adopting rTMS as first-line treatment in depressed youths have been rapidly increasing ever since, confirming good tolerability, safety, and efficacy in adolescent populations as well (Hett et al., 2021). Compared with pharmacologic methods or electroconvulsive therapy, rTMS can directly target dysfunctional brain regions, and stimulation parameters can be adjusted accordingly. Therefore, it is one of the most promising antidepressant therapies for achieving precision (Nestor and Blumberger, 2020). However, the majority of studies in rTMS precision have aimed at improving spatial targeting of the dorsolateral prefrontal cortex (dlPFC), which is an empirically selected target and may not induce a response in all depressed individuals (Cash et al., 2021). Prior study has shown that rTMS response varies significantly among neurophysiological depression subtypes (Drysdale et al., 2017). Therefore, identification of subtype-specific rTMS targets based on neuroimaging subtypes of depression hold a great expectation in optimizing the precision of current rTMS therapy.

Concerningly, depression during adolescence and early adulthood often results in significant developmental disruptions and has long-term implications for future psychiatric illness and functioning in adulthood (Davey and McGorry, 2019). Nevertheless, 30–50% of depressed adolescents do not respond to their first treatment intervention, and 10% of depressed adolescents do not improve despite multiple treatment trials (Cullen et al., 2019). Young populations with depression would benefit significantly from more effective and precise treatment. As such, we elucidated the study objective into two parts: developing a neuroimaging-based subtyping and precise rTMS strategy for depression, and its clinical implication in depressed youths. We hypothesized that frontal-posterior functional imbalance could be indicated as an objective neurobiomarker for the identification of depression neuroimaging subtypes and subtype-specific rTMS targets. We also hypothesized that neuroimaging alterations in each subtype of depressed youths would normalize post precise rTMS, corresponding with symptomatic improvements.

2. Methods

The study was conducted in two stages at two sites; see Fig. 1 for flow diagram. Firstly, we recruited a cohort of MDD individuals and healthy controls (HC) to identify depression subtypes and subtype-specific rTMS targets based on ALFF patterns at Renmin Hospital of Wuhan University (Center 1). We then employed the subtyping and precise rTMS strategy to a group of hospitalized, depressed youths with diagnoses of mood disorder for two-week precise rTMS and neuroimaging and symptomatic evaluations at Affiliated Nanjing Brain Hospital of Nanjing Medical University (Center 2).

2.1. Participants

Center 1 participants consisted of 238 outpatients with DSM-IV diagnosis of MDD and 66 HC aged 13–55. HC did not have personal or family history of psychiatric disorders. Center 2 participants consisted of 72 hospitalized youths aged 13–24 with DSM-IV diagnosis of mood disorder (38 MDD and 34 bipolar II disorder) and were in a current major depressive episode and had a baseline score of at least 17 on the 17-item Hamilton Rating Scale for Depression (HAMD-17) or at least 16 on the 14-items Hamilton Rating Scale for Anxiety (HAMA). Participants were excluded from study at both centers if any major medical condition, neurological disorder, MRI contraindications, or excessive head motion during MRI scan. Two-sample t-tests and chi-square tests for demographic and clinical information were performed using SPSS, version 25 with significance level of $p < 0.05$.

All participants provided written informed consents; for those < 18 years, written informed consents were obtained from their legal guardians and assent from the minor participant. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration. All procedures involving human subjects/patients were approved by the Ethics Committee of Renmin Hospital of Wuhan University and the Medical Ethics Committee of Nanjing Brain Hospital (2020-KY029–01). The clinical trial has been registered in the Chinese Clinical Trial Registry (ChiCTR2100045391). See Supplemental Data and Supplemental Table S1 for additional participant characteristics. See Supplemental Fig. S1 for CONSORT diagram.

2.2. MRI data acquisition and processing

Participants in Center 1 received a resting-state functional MRI (fMRI) scanning on an GE Discovery MR750W 3.0 T scanner using gradient echo planar imaging (GRE-EPI) sequence. For each patient in Center 2, MRI scanning were performed at three time points: baseline T0 (one day before precise rTMS), midpoint T1 (after one-week precise rTMS) and terminal point T2 (after two-week precise rTMS). The imaging data were obtained from a Siemens MAGNETOM Prisma 3.0 T scanner, which used GRE-EPI sequence for resting-state fMRI scanning and magnetization-prepared rapid acquisition gradient echo sequence for T1-weighted MRI scanning. Preprocessing of resting-state functional MRI for ALFF analyses was the same across both centers. See Supplemental Data for center-specific protocols and data processing.

2.3. Identifying neuroimaging subtypes of depression

For each MDD patient, the high-dimensional ALFF data were reduced to two dimensions by using the t-distributed Stochastic Neighbor Embedding algorithm (Van der Maaten and Hinton, 2008). The MDD patients were then divided into two subtypes based on the Gaussian Mixture Model algorithm (Tråveń, 1991). The stability of clustering results was tested using the Consensus Clustering method (Monti et al., 2003). The subtype diagnostic performances were further evaluated by using Support Vector Machine (SVM) classifiers to distinguish each

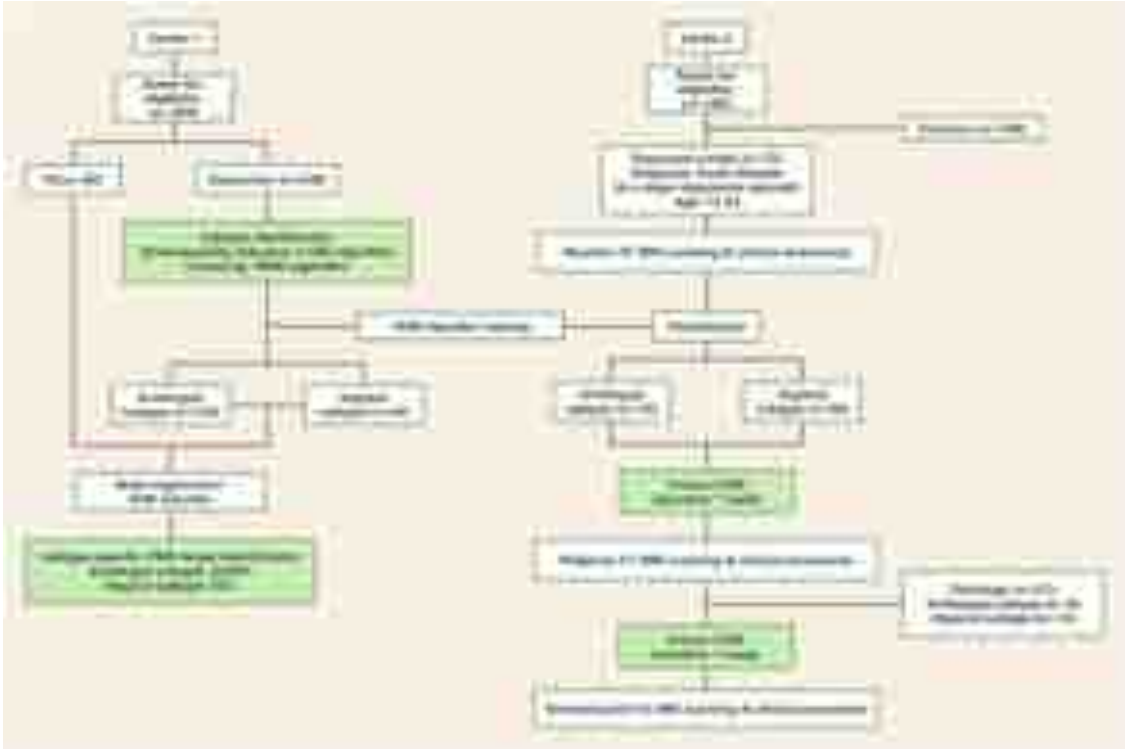

Fig. 1. Schema of developing a neuroimaging-based subtyping and precise repetitive transcranial magnetic stimulation (rTMS) strategy for depression and implementing it in hospitalized, depressed youths.

subtype and total MDD sample from HC (Cortes and Vapnik, 1995). Five-fold cross-validation was used to evaluate the performance of each SVM classifier; the F1 score and area under the curve (AUC) were calculated as measures. Permutation testing was employed to further assess the reliability of subtypes with a significance level of $p < 0.002$ (Golland and Fischl, 2003). For detailed methods, see online Supplemental Data.

2.4. Identifying subtype-specific rTMS targets

We separately extracted 90 brain regions' ALFF values based on automated anatomical labeling-90 atlas; for every brain region, an SVM classifier was trained to distinguish depression subtype from HC (Tzourio-Mazoyer et al., 2002). Five-fold cross-validation was used to evaluate the classifier performance measured by F1 scores. For each subtype, we ranked the 90 brain regions based on their F1 scores and selected top-10 brain regions as candidate regions. Subsequently, the anatomical distribution of the top-10 brain regions was examined, and the dominant regions of alteration were identified. The current neurobiological understanding was then used to finalize an rTMS target for each subtype. See Supplemental Data for further details.

2.5. Precise rTMS for depressed youths

Hospitalized, depressed youths at Center 2 received precise rTMS with a total of 20 sessions over two weeks. An SVM classifier was trained based on neuroimaging data of Center 1 for depression subtype separation. The classification model was then used to divide depressed youths into subtypes at Center 2. For the subtype labeled as 'archetypal', the stimulation was high frequency (10 Hz), with 1200 pulses per session; for the subtype labeled as 'atypical', the stimulation was low frequency (1 Hz), with 1000 pulses per session (see results section for label characteristics). Stimulation of both subtypes was applied at 100% resting motor threshold. The international 10–10 system and individualized three-dimensional MRI were jointly used for the precise localization of rTMS targets in each participant; see Supplemental Fig. S2 for its schematic diagram. See Supplemental Data for detailed rTMS protocols and procedures of neuroimaging-guided precise localization.

2.6. Neuroimaging data assessments

Neuroimaging analyses were processed using the Statistical Parametric Mapping 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm) and Data Processing Assistant for Resting-State fMRI (DPARSF; http://www.restfmri.net/forum/DPARSF) toolkits. At Center 1, whole-brain voxel-wise two-sample t-test of ALFF values was performed between each subtype and HC to examine subtype ALFF alterations. At Center 2, whole-brain voxel-wise paired t-test was performed to examine ALFF alterations post- and pre-rTMS for each subtype. Voxel-level statistical significance was set to $p < 0.05$, with Gaussian random field multiple-comparison correction (cluster-level $p < 0.05$, cluster size > 250).

2.7. Clinical assessments

Clinical assessments were performed by three blinded, certified psychiatrists at baseline T0, midpoint T1, and terminal point T2, on the same days as participant MRI scans. The primary outcome was symptom severity as measured by both the HAMD-17 and HAMA. A secondary outcome was suicidality as measured by Item 3 on HAMD-17. The response was defined as $\geq$ 50% symptom reduction on scales and suicidality item; specifically, the primary outcome was considered overall response when HAMD-17 or HAMA reached response. Remission for primary and secondary outcomes was determined by HAMD-17 or HAMA scores ≤ 7, and a score of 0 for Item-3 of HAMD-17, respectively. Response rates and remission rates of both primary outcome and secondary outcome at midpoint T1 as well as terminal point T2 were calculated in both subtypes.

3. Results

3.1. Identified depression neuroimaging subtypes reveal a distinct frontal-posterior functional imbalance

Using machine-learning techniques, we identified two neuroimaging subtypes in the Center 1 MDD cohort (n = 238). The two depression subtypes (n_1 =143 and n_2 =95, respectively) showed distinct frontal-posterior functional imbalance patterns, specifically across the prefrontal and occipital cortices (Fig. 2A). The ALFF patterns of the two subtypes were consistent with our previous finding, so we denoted the two subtypes identified herein as *archetypal depression* and *atypical depression* (Chang et al., 2021). Compared to HC, archetypal depression had significantly increased ALFF in frontal regions (prefrontal cortex, limbic, para-limbic, and striatum) and significantly decreased ALFF in posterior regions (primary visual, sensory, motor cortices and unimodal association cortices); whereas atypical depression exhibited significantly decreased ALFF in similar frontal regions and significantly increased ALFF in similar posterior regions. A clustering stability test showed that both subtypes had robust stability (m_1 =0.93, m_2 =0.73, Fig. 2B). No significant difference was detected between two subtypes in terms of age (t = −0.68, p = 0.50) or sex (χ^2 =0.11, p = 0.74).

Remarkably, both subtypes had superior diagnostic capability compared to that of the total MDD sample (Fig. 2C). We trained three SVM classifiers based on ALFF to separately distinguish the total MDD group and the archetypal and atypical subtypes from HC. Classifiers for the archetypal and atypical depression collectively achieved higher performance (archetypal: F1 =0.70, AUC=0.77; atypical: F1 =0.71, AUC=0.77) than that of MDD diagnosis (F1 =0.44, AUC=0.60), supporting the validity of the two identified depression subtypes. The statistical significance of permutation testing confirmed the reliability of the two subtypes (p < 0.002) (Fig. 2D).

3.2. Dominantly altered brain regions were indicative of subtype-specific rTMS targets

To identify subtype-specific rTMS targets, we assumed that the effective targets would be brain regions with prominent differentiation between depression subtypes and HC. We designed a novel method to identify rTMS targets based on brain-region level classifiers (Fig. 3A). For each subtype, the top-10 brain regions whose ALFF values were most significantly discriminative from the HC were identified as candidate target regions; based on the dominant regions amongst, subtype-specific rTMS targets were identified.

For archetypal depression, candidate regions included the superior, middle, and inferior frontal gyri, precuneus, calcarine cortex, and lingual gyrus, which all exhibited significantly higher discriminative power. Since these regions were located predominantly in the bilateral frontal region (6 of the 10), dorsomedial prefrontal cortex (dmPFC) was selected as the rTMS target for archetypal depression instead of the conventional left dlPFC (Fig. 3B).

For atypical depression, candidate regions included the middle and inferior occipital gyri, calcarine cortex, cuneus, lingual gyrus, middle frontal gyrus, middle temporal gyrus, fusiform gyrus, and posterior cingulate gyrus. A bulk of these (6 of the 10) resided in the occipital region, so the occipital cortex (OCC) was selected as the rTMS target (Fig. 3C).

3.3. Precise rTMS normalized the frontal-posterior functional imbalance

Based on Center 1 findings, we deployed the neuroimaging-based subtyping and precise rTMS strategy to hospitalized, depressed youths at Center 2. The sample size was estimated as n = 38 with a power of 0.8 (see Supplemental Data). One classifier was trained to first divide the depressed youths (n = 72) into the archetypal subtype (n = 16) and the atypical subtype (n = 56). No significant differences in demographic or clinical characteristics were found between the two subtypes (Table 1). For archetypal depression, all 16 completed the treatment for the first week, and 10 completed the entire course. For atypical depression, all 56 completed the first-week treatment, and 41 completed the full course. Drop-outs were due to discharge. No serious adverse events occurred in either subtype.

For both subtypes, significant changes in frontal-posterior functional imbalance were observed after one week of treatment and were maintained throughout the treatment period (Fig. 4A, Supplemental Table S2). In archetypal depression, significant ALFF decreases in frontal regions and significant ALFF increases in posterior regions were observed from T0 to T1 with sustained changes at T2, reversing the imbalance that was observed at the baseline. In atypical depression, converse changes in ALFF were detected with significantly increased ALFF in frontal regions and significantly decreased ALFF in posterior regions from T0 to T1. These changes were also sustained at T2. For both subtypes, ALFF

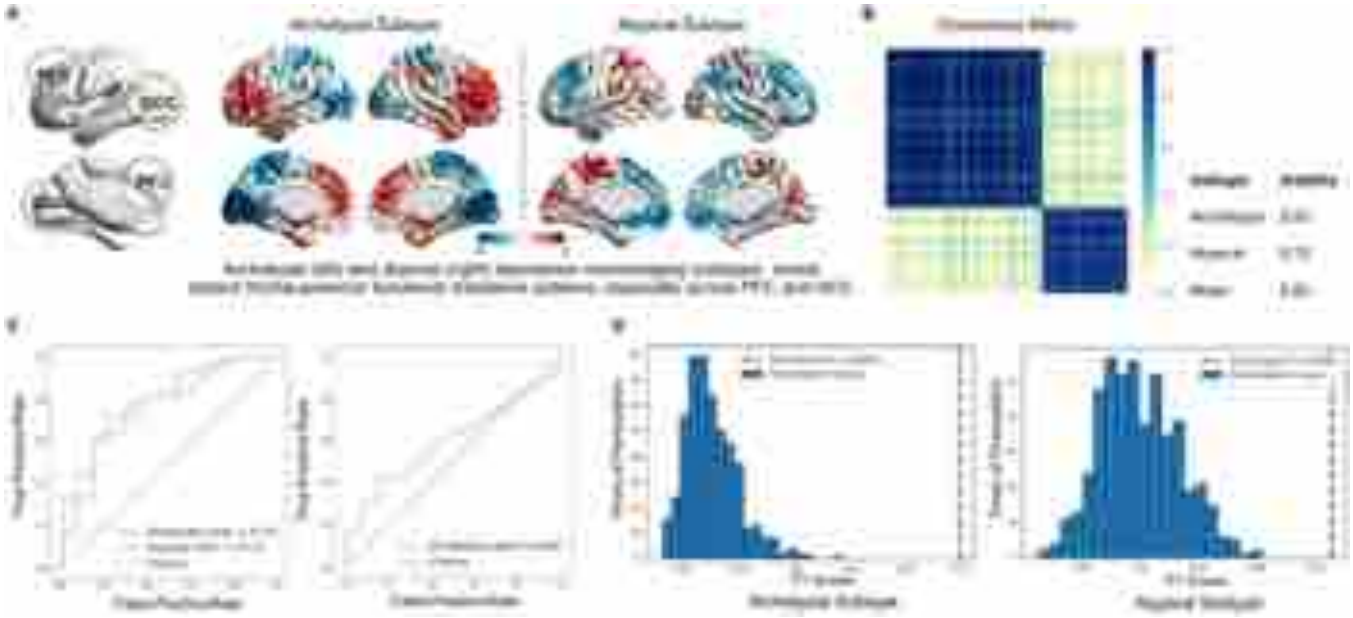

Fig. 2. Identified depression neuroimaging subtypes reveal a distinct frontal-posterior functional imbalance.

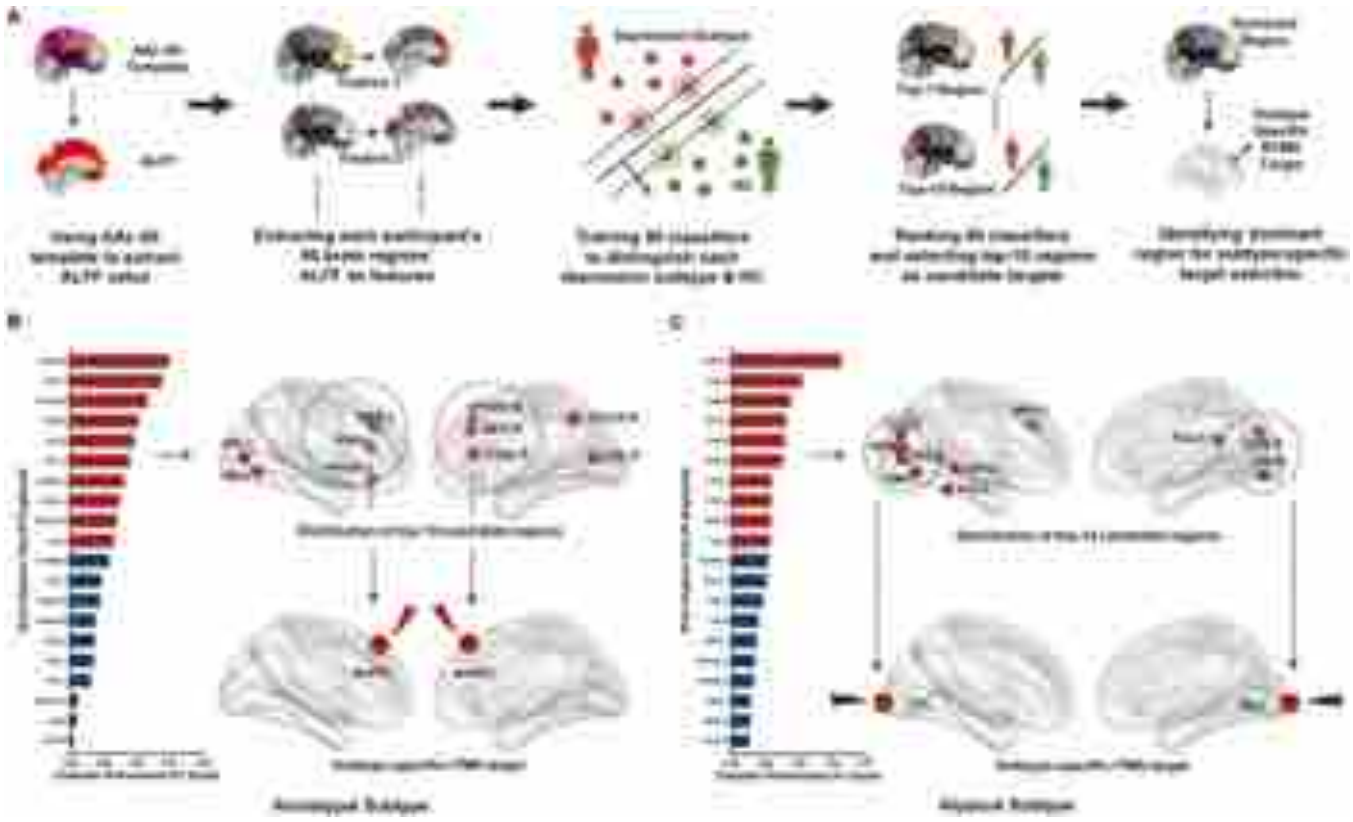

Fig. 3. Dominantly altered brain regions were indicative of subtype-specific repetitive transcranial magnetic stimulation (rTMS) targets.

Table 1
Demographic and clinical information of hospitalized, depressed youths at Center 2.

Variable	Archetypal Subtype (N = 16)		Atypical Subtype (N = 56)			
	mean	**SD**	**mean**	**SD**	**T**	**P**
Age at hospitalization (years)	16.38	2.25	16.05	2.39	0.48	0.63
Age at onset (years)	14.38	2.06	13.75	2.48	0.92	0.361
Body mass index	24.95	8.59	23.43	7.55	0.59	0.56
Baseline outcomes						
HAMD-17	25.25	5.85	24.73	4.34	0.39	0.70
HAMA	23.25	5.50	21.86	5.15	0.94	0.35
	N	**%**	**N**	**%**	χ^2	**P**
Female	10	62.50	42	75.00	0.45	0.50
First episode	4	25.00	29	51.79	3.60	0.06
Suicidality	12	75.00	44	78.57	0.00	1.00
Non-suicidal self-injury	9	56.25	43	76.79	1.69	0.19
Previous medications	13	81.25	40	71.43	0.22	0.64
Antidepressant	10	62.50	35	62.50	0.00	1.00
Antipsychotic	8	50.00	24	42.86	0.26	0.61
Mood stabilizer	3	18.75	17	30.36	0.36	0.55
Sedative hypnotic	3	18.75	9	16.07	0.00	1.00

SD=standard deviation; HAMD-17 = 17-items Hamilton Rating Scale for Depression; HAMA= 14-items Hamilton Rating Scale for Anxiety

changes from T1 to T2 were less significant, indicating the majority of changes occurred during the first week of rTMS (Supplemental Table S2).

3.4. Precise rTMS showed great clinical efficacy

We observed significant symptomatic improvements in both subtypes of depressed youths after precise rTMS. The primary outcome was symptom severity measured by both the HAMD-17 and HAMA since depressive and anxiety symptoms are highly co-occurring in depressed youths (Kalin, 2021). Changes in HAMD-17 and HAMA scores corresponded with ALFF changes from baseline T0 to T2 (Fig. 4B). For the primary outcome, 31.25% of the archetypal subtype and 28.57% of the atypical subtype had an overall response at T1; 90.00% of the archetypal subtype and 70.73% of the atypical subtype exhibited an overall response at T2. Remission was achieved in 6.25% of the archetypal subtype and 5.36% of the atypical subtype at T1, which increased to 30.00% and 46.34%, respectively, at T2 (Supplemental Table S3).

For the secondary outcome of suicidality, 12 patients in the archetypal subtype and 44 in the atypical subtype had a baseline score > 0 on HAMD-17 Item-3. At T1, 83.33% of the archetypal subtype and 65.91% of the atypical subtype had a response, which increased to 100.00% and 81.25% at T2. Remission was achieved in 58.33% of the archetypal subtype and 38.64% of the atypical subtype at T1; and 100.00% and 56.25%, respectively, at T2 (Supplemental Table S3).

4. Discussion

In this study, we identified an objective neurobiomarker to guide subtyping and precise treatment in depression, bridging critical translational gaps in actualizing precision medicine in Psychiatry. We developed a neuroimaging-based subtyping and precise rTMS strategy for depression at Center 1 and implemented it in hospitalized, depressed youths with pre- and post-treatment neuroimaging and symptom assessments at Center 2. Using machine learning techniques, we identified two depression subtypes based on ALFF patterns at Center 1, namely archetypal and atypical depression. The subtypes found herein replicated our prior findings, further implicating frontal-posterior functional imbalance as a reproducible neurobiomarker for depression (Chang et al., 2021). Moreover, we identified dmPFC and OCC as subtype-specific rTMS targets for the archetypal and atypical depressions, respectively. We next subtyped the hospitalized, depressed

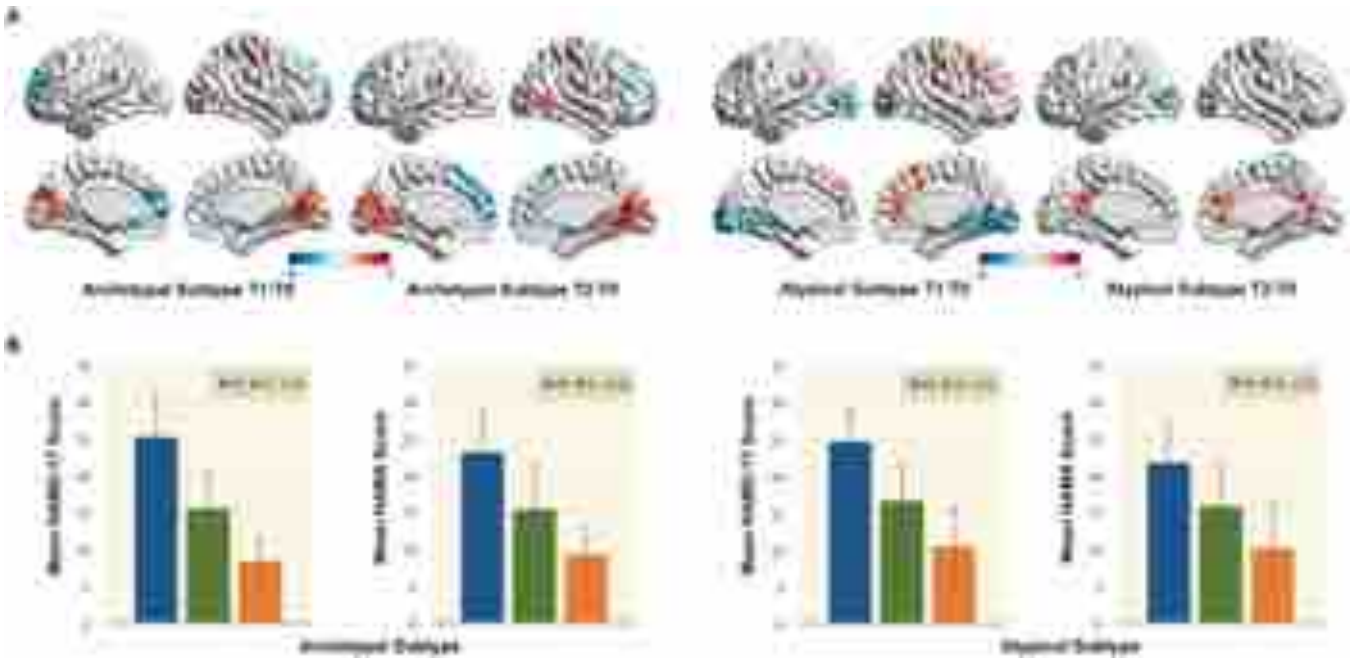

Fig. 4. Neuroimaging and symptomatic improvements after precise repetitive transcranial magnetic stimulation (rTMS) in hospitalized, depressed youths.

youths at Center 2 through a classifier we trained in Center 1 and delivered precise rTMS. Excitingly, the observed patterns of ALFF alterations in both archetypal and atypical depression subtypes appeared to normalize in response to rTMS of subtype-specific targets with corresponding improvement in depressive and anxiety symptoms, and suicidality.

Depression is highly heterogeneous with varying etiologies due to its diagnostic criteria relying primarily on descriptive symptoms (Nemeroff, 2020). Several attempts have been made to delineate its heterogeneity based on neuroimaging features, which have the potential of unveiling neural mechanisms of psychiatric disorders. However, the reliability of identified neuroimaging subtypes has been limited by the lack of cluster reproducibility, proper validation, or clinical ramification (Drysdale et al., 2017; Winter and Hahn, 2022; Cheng et al., 2014). Despite that no answer exists for universally applicable clustering due to the nature of clustering and the lack of class labels, to meet the urgent need in depression, we suggest an appropriate subtyping for depression would be identified by objective neurobiomarkers capable of guiding precision medicine (Zhang et al., 2022). Intriguingly, we identified two depression neuroimaging subtypes with high stability and reproducibility: archetypal depression, which had significantly increased ALFF in frontal regions and significantly decreased ALFF in posterior regions compared to HC, and atypical depression, which showed a converse pattern of ALFF alterations. Consistent with our previous finding in a nonoverlapping sample, the archetypal and atypical depression subtypes showed converse patterns of frontal-posterior functional imbalance, suggesting the functional hierarchy between higher-order, heteromodal areas and primary, unimodal cortices as a latent mechanism of depression (Chang et al., 2021; Xia et al., 2022). Moreover, neurostimulation of frontal and posterior cortices could be transmitted through their functional connectome and accordingly modulate regional neuroimaging deficits (Castrillon et al., 2020). Normalization of the frontal-posterior functional imbalance following rTMS in the depressed youths herein supports strong promise for our neuroimaging-based subtyping in clinical practice. Further studies are warranted to confirm the translational implications of the depression subtypes identified by objective neurobiomarkers.

The dmPFC was selected as the rTMS target for archetypal depression. It has significant connections to sensorimotor areas and the anterior cingulate cortex, serving as a conduit between cognitive control and emotional processing regions (Helion et al., 2019). Historically, the dlPFC was selected as the conventional rTMS target due to its potential pathophysiological modulation of depression (Cash et al., 2021). However, convergent studies in lesion, stimulation and neuroimaging suggested that the dmPFC was not only the most promising target alternative to the dlPFC but also played a more central role in the underlying neurophysiology of depression, as was proposed by Downar et al. (2013) Our findings further supported the dmPFC as an effective rTMS target, which was identified based on objective neuroimaging measures rather than based on purely empirical findings. Conversely, the OCC was identified as the rTMS target for atypical depression. The OCC is a primary sensory region responsible for visual processing. Decreased gamma-aminobutyric acid (GABA) in the OCC has been previously observed in depressed patients (Sanacora et al., 1999). Further, it was found to be associated with the altered visual perception that correlated with symptom severity in acute MDD (Song et al., 2021). Decreased GABA may underlie neural mechanisms for increased ALFF in posterior regions in atypical depression (Kiemes et al., 2021). Of note, both human and animal neuroimaging studies have observed excitatory effects of high-frequency rTMS and inhibitory effects of low-frequency rTMS on OCC (Castrillon et al., 2020; Sun et al., 2021; Guo et al., 2021). Hence, in attempt to dampen the increases in posterior ALFF, we delivered low-frequency rTMS to the OCC in atypical depression. Altogether, the dmPFC and OCC appear to be subtype-specific rTMS targets with strong translational implications, bolstered by prior neurophysiological findings.

Our novel strategy for precise rTMS in hospitalized, depressed youths achieved reasonably high efficacy based on both neuroimaging and symptom outcomes. The normalization of ALFF patterns in both subtypes strongly supported the importance of frontal-posterior functional imbalance as an objective biomarker to guide precision medicine in depression. Given the high concurrence of depression and anxiety during adolescence and early adulthood, we used depressive and anxiety symptoms in determining the primary outcome (Zhang et al., 2019). Due to limited studies in depressed youths, there is no consensus on the efficacy of conventional rTMS targeting the dlPFC. However, conventional rTMS generally have response rates of 29–46% and remission rates of 18–31% in depression (Cash et al., 2021). In this study, we achieved

higher response rates of 90.00% and 70.73% in archetypal and atypical depression, respectively, as well as respective remission rates of 30.00% and 46.34%. Furthermore, consistent with conventional rTMS studies, our precise rTMS also reduced suicidality in depressed youths (Croarkin et al., 2018). While not strictly meeting the criteria of TRD, our hospitalized, depressed youths had complicated clinical features that could be defined as having difficult-to-treat depression (Cosgrove et al., 2021). In short, our precise rTMS strategy outperformed conventional rTMS in depressed youths.

The current study may be improved in several ways. Sham-controls were not applied due to the exploratory nature of our rTMS trial. Further, participants were not blinded to their rTMS targets, and placebo effects may confound the findings. In addition, the sample size of our rTMS trial was relatively small. Notably, we are conducting larger, double-blinded, and randomized controlled trials to confirm the clinical implications of our neuroimaging-based framework (ClinicalTrials.gov ID: NCT05465928). Besides, longer treatment courses may also be warranted to improve clinical efficacy and increase remission rates. The high response but comparatively low remission rates may indicate the need for extended treatment beyond two weeks.

5. Conclusions

In summary, we developed a novel precision medicine framework for depression that went beyond symptomatic measures and incorporated neuroimaging-based subtyping to guide precise rTMS with promising results. Further studies are warranted in larger depressed samples and for longer durations, as well as using a double-blinded, randomized controlled design.

Declaration of Competing Interest

The authors report no competing interests.

Acknowledgement

None.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ajp.2023.103803.

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