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Three Latent Factors in Major Depressive Disorder Base on Functional Connectivity Show Different Treatment Preferences

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ABSTRACT

The heterogeneity of major depressive disorder (MDD) complicates the selection of effective treatments. While more studies have identified cluster-based MDD subtypes, they often overlook individual variability within subtypes. To address this, we applied latent dirichlet allocation to decompose resting-state functional connectivity (FC) into latent factors. It allows patients to express varying degrees of FC across multiple factors, retaining inter-individual variability. We enrolled 226 patients and 100 healthy controls to identify latent factors and examine their distinct patterns of hyper- and hypo-connectivity. We investigated the association between these connectivity patterns and treatment preferences. Additionally, we compared demographic characteristics, clinical symptoms, and longitudinal symptom improvements across the identified factors. We identified three factors. Factor 1, characterized by inter-network hyperconnectivity of the default mode network (DMN), was associated with treatment response to antidepressant monotherapy. Additionally, factor 1 was more frequently expressed by younger and highly educated patients, with significant improvements in cognitive symptoms. Conversely, factor 3, characterized by inter-networks and intra-networks hypoconnectivity of DMN, was associated with treatment response when combining antidepressants with stimulation therapy. Factor 2, characterized by global hypoconnectivity without DMN, was associated with higher baseline depression severity and anxiety symptoms. These three factors showed distinct treatment preferences and clinical characteristics. Importantly, our results suggested that patients with DMN hyperconnectivity benefited from monotherapy, while those with DMN hypoconnectivity benefited from combined treatments. Our approach allows for a unique composition of factors in each individual, potentially facilitating the development of more personalized treatment-related biomarkers.

Summary

- Using latent dirichlet allocation, we identify three latent factors.
- Patients with more DMN hyperconnectivity benefited more from monotherapy, while patients with more DMN hypoconnectivity benefited more from combined treatments.
- Younger and highly educated patients tended to be prescribed antidepressants.

1 | Introduction

Major depressive disorder (MDD) is a prevalent public health problem, and the treatment outcomes remain unsatisfactory. Almost only 50% of depressive patients respond to first-line antidepressant treatment (Rush et al. 2009; Thase et al. 2007). The heterogeneity of MDD makes it challenging to determine the most effective treatment at baseline. Antidepressant and stimulation therapy are common treatment approaches. Antidepressant is the first-line treatment approach. Stimulation therapy, such as electroconvulsive therapy (ECT) or repetitive transcranial magnetic stimulation (rTMS) is commonly administered to patients who have suicidal tendencies or treatment-resistant conditions. However, stimulation therapy increases the risk of adverse events. This trade-off between its efficiency and risk requires careful decision-making (Zou et al. 2023; Peterson et al. 2014; Nahas and Anderson 2011). Despite its potential benefits, it is important to determine how to determine the necessity of augmentation of antidepressants with stimulation therapy.

One of the challenges to precise treatment is a neurobiologically and clinically heterogeneous profile in MDD. The clustering-based subtyping approaches aim to address this heterogeneity by dividing individuals with similar symptom profiles and neuroimaging characteristics into subgroups. The underlying hypothesis suggests that patients within the same subtype, sharing comparable pathophysiological signatures, might benefit from the same intervention (Williams 2017; Beijers et al. 2019). This hypothesis is supported by some studies. The subgroups based on symptom-driven functional connectivity patterns can inform treatment selection between antidepressant and neuromodulation therapies (Wang et al. 2022).

Additionally, the subtype differences could be used to predict antidepressant treatment outcomes (Sun et al. 2023). However, growing evidence reveals limitations of this approach. While Drysdale et al. identified distinct functional connectivity subtypes predictive of rTMS response (Drysdale et al. 2017), subsequently, Dinga et al. tried to replicate the findings. They failed to confirm the stability of these biotypes, suggesting subtyping needs cautious utilization (Dinga et al. 2019). A systematic review observed that four out of five neuroimaging studies found evidence for groups with structural and connectivity differences, but results were inconsistent (Beijers et al. 2019). Additionally, a study of electroencephalography suggested that the subtype, whose functional connectivity differed most from those of healthy controls, was hard to predict antidepressant treatment response for MDD (Zhang et al. 2020). These studies suggest that subtyping approaches suffer from limited stability, reproducibility, and consistent predictive power across studies. The fundamental limitation might stem from the core assumption of clustering methods. Cluster-based subtyping approaches hypothesize that patients within the same subgroup share similar characteristics, often ignoring the individual variability within the subgroup. The individual inter-variability within the subgroup is ignored. The subtyping methods need to be further explored.

Recently, a paradigm called the dimensional neuroimaging approach has emerged. Compared to the cluster-based subtyping approach, which divides individuals into distinct groups, the dimensional method views endophenotypes as a continuous variable, where individuals are assessed along a spectrum (Tang et al. 2020). This approach allows individuals to express one or more factors to varying degrees of biomarkers. Thus, interindividual variation can be quantified. The dimensional approach with the Bayesian model can decompose biomarkers into distinct and independent factors. Latent dirichlet allocation (LDA) (Blei et al. 2003) is a typical model to decompose the neuroimaging biomarkers. The LDA has revealed a latent atrophy factor with dissociated cognitive trajectories in Alzheimer's disease (Zhang et al. 2016). LDA also revealed phenotypical variants of posterior cortical atrophy (Groot et al. 2020). It also found shared and unique endophenotypes of structural connectivity for different antidepressant-sensitive patients in MDD (Xue et al. 2022) and dysfunctional activation across bipolar and unipolar disorder (Shao et al. 2022). These studies suggested that the above factors represented dissociable patterns in brain function or structure, promoting shared and unique biomarker development.

Here, we employed LDA to model functional connectivity as expressed by multivariate factors. Our goal was to identify distinct latent factors capturing hyper- and hypo-connectivity within and between brain networks. Each individual's connectivity profile could be explained by a unique combination of these factors (Figure 1), reflecting how strongly each factor is expressed in that individual. In this way, these latent factors quantify the magnitude of each connectivity pattern within each patient. We then evaluated the associations between factors and treatment preferences, demographics, clinical symptoms, and longitudinal treatment response.

2 | Methods and Materials

2.1 | Sample

Patients with MDD and healthy controls were enrolled from the Affiliated Brain Hospital of Nanjing Medical University or local communities from July 2021 to June 2023. Patients were diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) (Association AP 2000) by the MINI-international Neuropsychiatric Interview (MINI Chinese version). Depressive symptoms and severity were evaluated using the 17-item Hamilton Rating Scale for Depression (HAMD) (Hamilton 1960). The inclusion criteria for patients' recruitment were as follows: (1) score of HAMD more than 17 at baseline; (2) aged 18–55 years; (3) no comorbidity with other

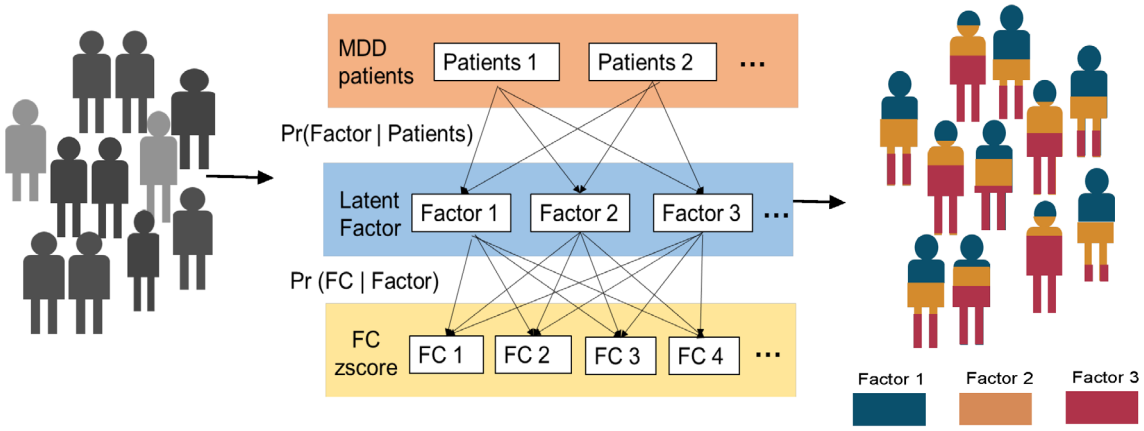

FIGURE 1 | The diagram of latent factor analysis.

psychiatric disorders; (4) no stimulation therapy during the past 6 months; (5) no use of psychotropic medication including antidepressants, antipsychotics, and benzodiazepines during the past 2 weeks. The exclusion criteria for patients contained: (1) a history of substance abuse or dependence; (2) serious medical conditions such as organic brain disorders and severe somatic disease as assessed by past medical history; (3) current pregnancy or breastfeeding; (4) any contraindication to undergo magnetic resonance imaging (MRI) scanning. Healthy controls (HC) were screened using the non-patient version of the MINI Chinese version. The criteria to include HC were: (1) aged 18–55 years; (2) no family history of psychiatric disorder in their first-degree relatives; (3) no history of using psychotropic medications. Exclusion criteria for HC were: (1) substance dependence or abuse; (2) neurological illness; (3) contraindication to MRI scans. A complete description of the study was informed to all subjects. Written informed consent was obtained from all participants as approved by the Research Ethics Review Board of the Affiliated Brain Hospital of Nanjing Medical University.

2.2 | Treatment Administrations

Two experienced clinicians determined each patient's treatment strategy by considering both the patient's prior treatment history and current clinical symptoms. we categorised four types of treatment modalities: (1) selective serotonin reuptake inhibitors monotherapy (SSRI); (2) selective serotonin-noradrenaline reuptake inhibitors monotherapy (SNRI); (3) ECT or rTMS combined with SSRI (SSRI+Stimulation); (4) ECT or rTMS combined with SNRI (SNRI+Stimulation).

We used HAMD to measure the depressive severity. The treatment outcomes were the reduction of HAMD scores after 2 weeks of treatment. The response was defined as a reduction of 50% or more of the HAMD score after 2 weeks of treatment. Patients who achieved response were defined as responders.

2.3 | Imaging Acquisition and Preprocess

All MRI data were collected from the Affiliated Brain Hospital of Nanjing Medical University using a 3T Siemens Verio scanner (Erlangen, Germany) with an 8-channel radiofrequency coil. Parameters for T1-weighted axial images were: repetition time/echo time (TR/TE) = 1900/2.48 ms, flip angle = 9°, matrix = 256 × 256, field of view (FOV) = 250 mm × 250 mm, and slice = 176. The resting-state MRI data were obtained using the parameters as follows: TR/TE = 3000 ms/40 ms, FOV = 240 mm × 240 mm, flip angle = 90°, 32 slices with slice thickness = 4 mm without gap, matrix size = 64 × 64, and 133 volumes, voxel size = 3.75 × 3.75 × 4 mm^3. For resting-state functional imaging data, frame-wise motion parameters were calculated using six rigid motion parameters. Subjects with translations greater than 2 mm or rotations greater than 2° were excluded.

We preprocessed resting-state MRI data through SPM8 (www.fil.ion.ucl.ac.uk/spm/software/spm8) and REST toolbox (www.restfmri.net). We removed the first six functional volumes to exclude the T1 saturation effect. Subsequently, we employed slice-timing correction and head-motion correction for all the remaining images. Images were then co-registered to the corresponding high-resolution T1 anatomical images, which were transformed into the Montreal Neurological Institute (MNI) space. Afterwards, functional images were resampled to 3 × 3 × 3 mm^3 voxels, smoothed with a 6-mm full-width, half-maximum Gaussian kernel. Linear detrending and temporal band-pass filtering (0.01–0.08 Hz) were performed. Motion parameters, white matter, and cerebral signal fluid were regressed out from the time series.

2.4 | Functional Networks and z-Normalized FC in LDA

We defined the functional networks based on seven neural circuits, including the default mode circuit, salience circuit, attention circuit, negative affective sad circuit, negative affective threat circuit, positive affective happy circuit, and cognitive control circuit. We defined the functional network regions by using an anatomical approach for subcortical regions and an automated meta-analysis (via neurosynth.org (Yarkoni et al. 2011)) for cortical regions. The details of 98 regions were listed in the Goldstein et al. publication (Goldstein-Piekarski et al. 2022). We calculated the *Pearson* correlation values between node pairs as functional connectivity (FC).

To control for confounding variables and isolate depression-specific effects, we trained a linear regression model using only HC, regressing out the effects of age, sex, and head motion. The estimated coefficients from this model were then applied to all participants, allowing us to remove these confounding effects and obtain residual FC values. Next, we standardized each patient's residual FC by comparing it to the residual distribution of the HC group. Details on the z-normalization procedure are provided in the Supporting Information. Because LDA requires that the FC be an integer, the z-scores were multiplied by 10 and rounded to the nearest integer. The discretized z-score of the FC larger (smaller) than zero notes hyperconnectivity (hypoconnectivity) in relation to HC.

2.5 | Latent Factor Identification

We only identify latent factors for all patients. The z-normalized, discretized FC was used to estimate latent factors using the LDA. It hypothesized that each patient with MDD expressed one or more latent factors associated with different hypoconnectivity and hyperconnectivity (Pr(Factor | Patient)). Each latent factor was associated with distinct but possibly overlapping patterns of hyper-or hypo-connectivity ((Pr (FC | Factor)). LDA estimated Pr(Factor | Patient) and Pr (FC | Factor) with the variational expectation–maximization algorithm (https://www.cs.princeton.edu/~blei/lda-c/). The LDA analysis was described in detail in our previous publications (Xue et al. 2022; Shao et al. 2022; Wei et al. 2024).

We estimated K, the number of factors, from 2 to 5. For each K, the estimation was repeated with 100 initializations, resulting in 100 estimates. For each estimate, we recorded the latent factors to maximize the correlation of Pr (FC | Factor) between corresponding pairs of latent factors. The correlations between the final estimation and solutions from 100 random initializations were calculated. Among those 100 estimations, we selected the final estimation with the highest average correlation for each K.

To estimate confidence intervals for the factor-specific FC pattern (Pr (FC | Factor)), we applied bootstrapping procedures to generate 100 new random datasets. They were randomly sampled from all patients. The bootstrapped z-scores were calculated by dividing factor-specific FC patterns by the bootstrap-estimated standard deviation. To reduce multiple comparisons, we averaged the factor-specific FC patterns across region pairs within and between seven functional circuits, resulting in a 7×7 matrix. The p values were converted from bootstrapped z-scores and corrected using the false discovery rate (FDR) ($q < 0.05$).

2.6 | Associations Between Latent Factors and Efficient Treatment

We used the response to evaluate the effective treatment. In responders, we plotted their distribution among the factors as a triangle plot. We compared the group differences among four treatment modalities in each factor loading (Pr (Factor | Patient)) using analysis of variance with FDR corrections.

2.7 | Associations Between Latent Factors and Patient's Demographic Characteristics

To investigate whether characteristics varied across factors, we applied separate general linear models (GLMs) or logistic regression to the factor loading and each characteristic (age, sex, and education). For each GLM and logistic regression, the patient's demographic characteristics and factor loadings were treated as the dependent and independent variables, respectively. The details of GLMs and logistic regression were presented in Supporting Information.

2.8 | Association Between Latent Factors and Longitudinal Treatment Response and Baseline Clinical Characteristics

For longitudinal data analysis, we focused on two measurements to estimate treatment response: total HAMD score reduction and cognitive symptom score reduction. The cognitive symptom scores were defined as the sum of six HAMD items: self-blame, suicidal thoughts, agitation, depersonalization, and derealization, paranoid symptoms, and obsessive symptoms. We calculated *Pearson* correlations between each factor loading and the two treatment response measurements.

For baseline data, we applied canonical correlation analysis (CCA) between each group of baseline clinical characteristics and each factor loading. The clinical characteristics have two groups: HAMD items and four clinical symptoms. The four clinical symptoms included depression, anxiety, somatic, and insomnia (Shafer 2006). Therefore, there were $K \times 2$ runs of CCA (K: the number of latent factors). Through the CCA, we aimed to find an optimal linear combination of HAMD items or four clinical symptoms that maximally correlated with the factor loading. We performed 1000 permutations to assess statistical significance for CCA. The multiple comparisons were corrected using FDR. To interpret the relative importance of all items of clinical characteristics, we defined importance (r) for each item of HAMD and each clinical symptom. For each item or symptom, the correlation between canonical variables and absolute item value across participants was the importance (r) (Tang et al. 2020). The high positive importance (r) would imply the higher item value was more strongly correlated with factor loading.

3 | Results

3.1 | Sample

We initially enrolled 345 participants, including 240 patients and 105 HC. In the MDD group, 10 patients were excluded due to excessive head motion and 4 due to antidepressant changes. In the HC group, 5 participants were excluded for excessive head motion. Finally, 226 MDD and 100 HC were finally enrolled. Of 226 patients, 95 received SSRI monotherapy (63 responders), 28 received SNRI monotherapy (22 responders), 61 received SSRI combined with stimulation therapy (47 responders), and 42 received SNRI combined with stimulation therapy (31 responders). Of 226 patients, 163 were responders. The demographic

TABLE 1 | Demographic and treatment modalities.

		MDD	HC	*p*
Sex		103/123	47/53	0.82[a]
Age		32.54 ± 10.98	31.56 ± 9.04	0.44[b]
Education		14.48 ± 2.88	15.13 ± 3.10	0.068[b]
HAMD score		22.59 ± 7.06	—	
HAMD reduction		61.92% ± 34.87%	—	
Treatment modalites (*N*)				
	SSRI	95	—	
	SNRI	28	—	
	SSRI + Stimuatlion	61	—	
	SNRI + Stimulation	42	—	
Responders (*N*)		163	—	
	SSRI	63	—	
	SNRI	22	—	
	SSRI + Stimuatlion	47	—	
	SNRI + Stimulation	31		

Abbreviations: HAMD: Hamilton Depression Rating Scale; SNRI: selective serotonin-noradrenaline reuptake inhibitors monotherapy; SSRI: selective serotonin reuptake inhibitors monotherapy.
[a]*p* value obtained from chi-square test.
[b]*p* value obtained from two-sample *t* test.

and clinical variables are presented in Table 1. The number of first-episode, treatment-free patients and baseline HAMD comparison were listed in Table S1. The baseline HAMD had no significant differences among four depression groups.

3.2 | Latent Factors

We found $K = 2$ and $K = 3$ were stable for correlations between the final estimation and solutions from 100 random initializations (Figure S1). As the stability decreased slightly with increased K, we did not consider the larger K. We aimed to find the distributional differences pattern across factors. For $K = 2$, the distributions of four treatment modalities across two factors were almost identical (Figure S2). It limits the variability of factors and results in simplified patterns. Therefore, we determined $K = 3$ as the optimal solution.

Each of three-factor hyper- and hypo-connectivity patterns (Pr (FC | Factor)) among 98 regions is shown in Figure 2A. Figure 2B illustrates these patterns averaged within and between seven brain networks. To clearly present statistically significant hyper- and hypo-connectivity, we binarized within-networks and between-networks blocks with significant bootstrapped z-scores (Figure 2C). Figure 2D demonstrated the circus-plots for significant hyper- (red) and hypo-connectivity (blue). Factor 1 was featured as hyperconnectivity, while factor 2 and factor 3 specialized in hypoconnectivity. Specifically, factor 1 was associated with hyper-connectivity between DMN and cognitive control, negative affective, and positive affective networks. Factor 2 was associated with global hypoconnectivity among seven networks, except for DMN. Factor 3 was associated with hypoconnectivity within and between DMN and other networks. We concluded that factor 1 and factor 3 mainly showed hyperconnectivity and hypoconnectivity stemming from DMN, respectively. Factor 2 presented a general hypoconnectivity.

3.3 | Latent Factors Associated With Efficient Treatment

We visualized the Pr (Factor | Patient) as a dot inside a "factor triangle" (Figure 3A,C). Each dot corresponded to each patient. The size and color of the dot indicated HAMD reduction and treatment modality, respectively. Each patient was expressed as the sum of the possibility of three factors. For example, the Pr (Factor | Patient) = [0.1, 0.3, 0.6] implied that patients express a pattern of FC caused by 10% factor 1, 30% factor 2, and 60% factor 3, respectively. From Figure 3A, most of the dots fell inside the triangle, rather than on the vertices. This suggests most patients were determined by multiple factors, and a few patients were determined by a single factor.

By comparing factor composition, we found significant group differences among four treatments modalities in Pr (Factor | Patient) for factor 1 and factor 3 (Figure 3B). To present results clearly, we categorized four treatment modalities into two groups: medication therapy and medication + stimulation therapy (Figure 3D). We found that patients with a higher possibility

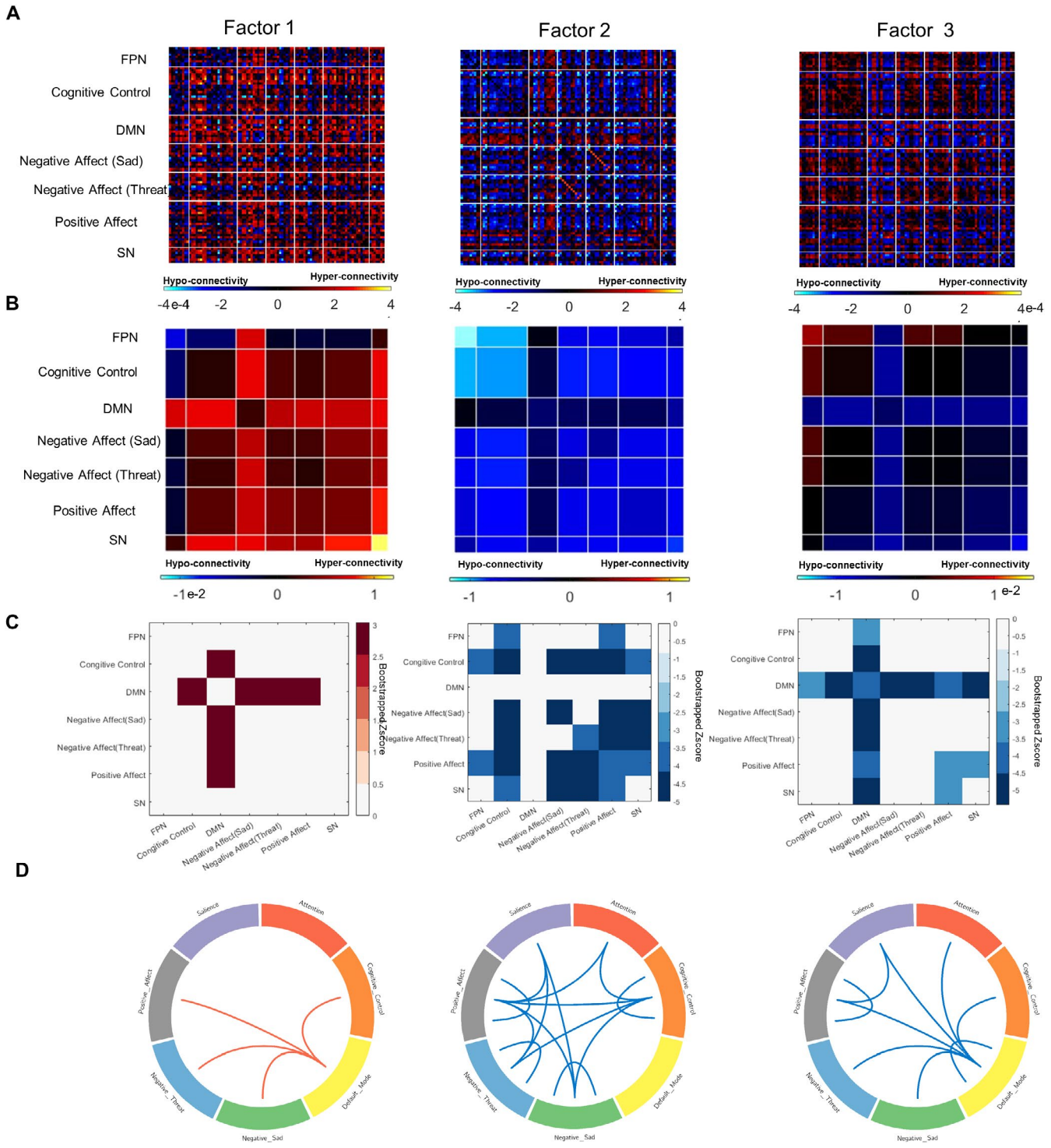

FIGURE 2 | The three factor-specific hyper- and hypo-connectivity pattern. (A) The patterns of hypo- and hyper-connectivity (unthresolded) associated with each factor. (B) Averaged patterns of hypo- and hyper-connectivity within and between networks. (C) Statistical significant and binarized hypo- and hyper-connectivity. (D) Circus plots for significant hyper (red) and hypo-connectivity (blue).

of factor 1 benefited from monotherapy. Conversely, patients with a higher possibility of factor 3 benefited from combination of medication and stimulation therapy, which will be referred to as "stimulation therapy" in the following contexts. We speculated that factor 1 was associated with the response of medication therapy, while factor 3 was more likely related to the response of stimulation therapy.

3.4 | Latent Factors Associated With Demographic Characteristics

Factor 1 was preferentially expressed by younger patients in relative factor 3 ($p = 0.026$) and factor 2 ($p = 0.057$) (Figure 4A). Factor 2 was preferentially expressed by less-educated patients in relation to factor 1 ($p = 0.0084$) (Figure 4B). There was no

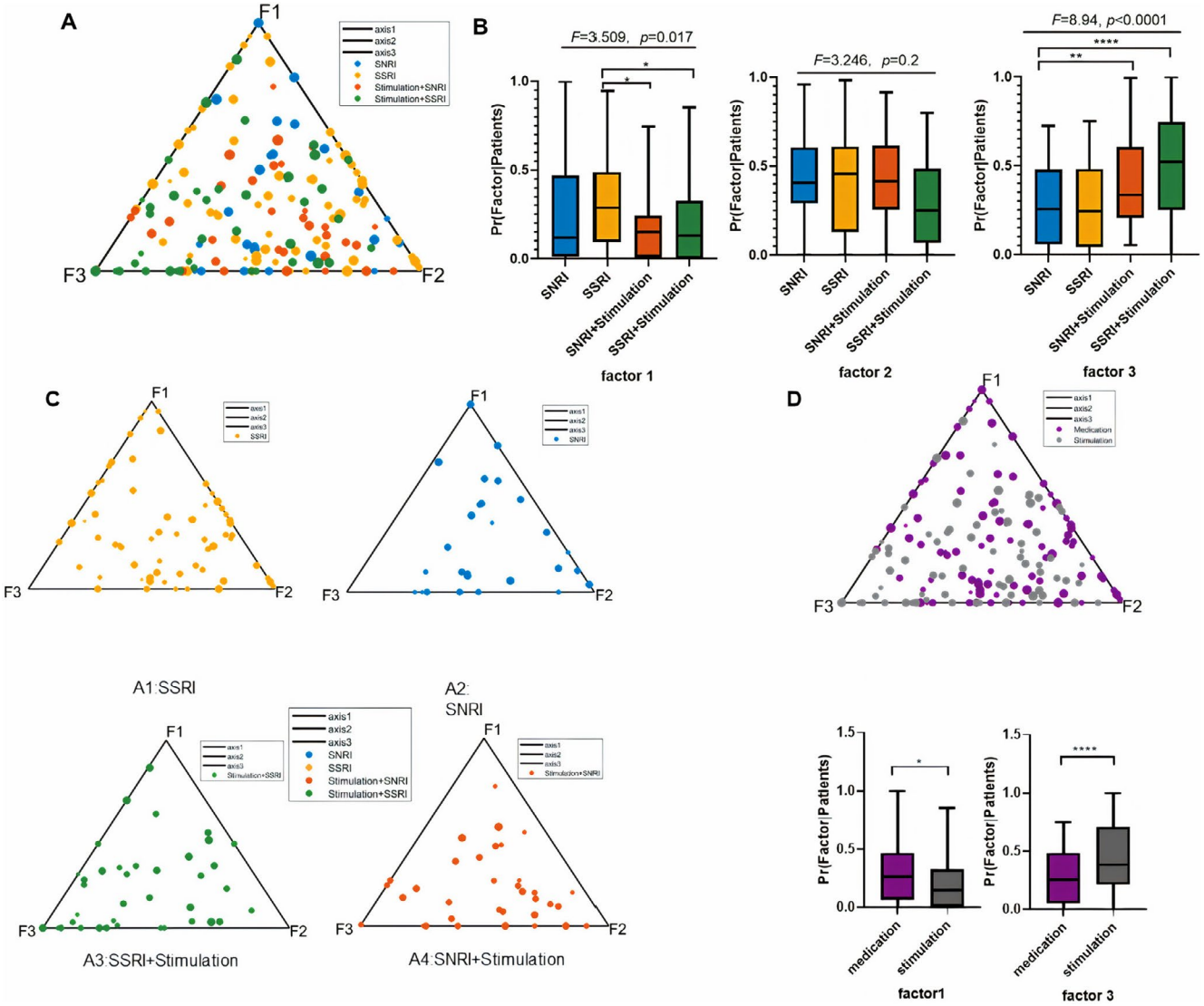

FIGURE 3 | (A, C) Factors compositions of responders from four treatments. Each patient corresponds to a dot. The size of the dots indicates the reduction of HAMD. The color of the dots corresponds to different treatments. F1, F2, F3 indicates Pr(Pr (Factor 1 | Patient)) =1, Pr (Factor 2 | Patient) =1, Pr (Factor 3 | Patient) = 1, respectively. The axis 1, axis 2, axis 3 indicated Pr (Factor 1| Patient) = 0, Pr (Factor 2| Patient) = 0, Pr (Factor 3| Patient) = 0. (B) The box plot shows the distribution of four treatment modalities for each factor. The group differences were evaluated by analysis of variance. (D) The factors compositions for two new treatment categories. Medication indicates antidepressant monotherapy, while stimulation indicates a combination of antidepressant and stimulation therapy. HAMD: Hamilton Depression Rating Scale.

difference in sex across factors (Figure 4C). From the results of the comparison trend (Age: F1 < F2 < F3), we concluded that factor 1 was associated with younger and highly educated patients.

3.5 | Latent Factors Associated With Longitudinal Treatment Response and Baseline Clinical Characteristics

For longitudinal treatment response, we found factor 1 loading significantly correlated with HAMD reduction and cognitive symptom reduction (Figure 5A). The treatment response, especially for cognitive symptom reduction, was only associated with factor 1.

While $K = 3$, there were six sets of CCA. After multiple comparison corrections, factor 2 was associated with HAMD and four clinical symptoms (Figure 5B,C, upper-right panel). Factor 1 and factor 3 were not associated with any clinical characteristics. The higher importance (r) value implied higher symptom severity. The asterisk indicates significant importance (r) in Figure 5C; thus, factor 2 was associated with worse depression symptom and anxiety symptom.

4 | Discussion

In this study, we identified three latent factors with dissociable hyper- and hypo-connectivity using Bayesian LDA modeling. Each factor was associated with different treatment responses, demographic, and clinical characteristics in MDD. This approach estimated the factor composition rather than assuming membership to a single FC subtype. It retained interindividual variability across MDD patients.

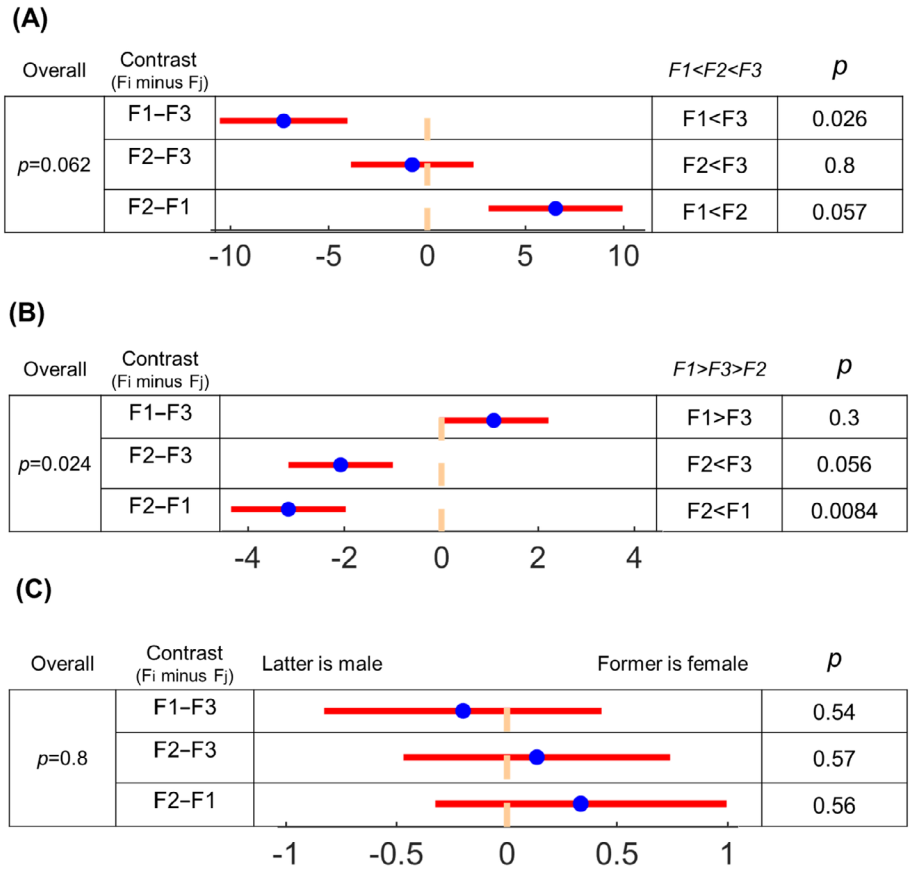

FIGURE 4 | Demographic characteristics differences across factors. (A) Age difference; (B) education difference; (C) sex differences. Blue dots are estimated differences between factors, and red bars correspond to standard errors. For example, the first row (F1—F3) in (A) implies that factor 1 was more strongly associated with younger patients than factor 3. F1: Factor1, F2: Factor 2, F3, factor 3.

In the study, three latent factors would imply whether stimulation therapy should be considered as part of treatment. These factors also demonstrate associations of treatment preferences with hyper- or hypoconnectivity patterns in depression. Factor 1 and factor 3 were expressed by different directions of intranetwork DMN connectivity. The difference suggested whether to apply the combined treatment. Specifically, factor 1, preferentially expressed by younger and highly educated patients, tended to prescribe antidepressants and recovery through cognitive symptom relief. Factor 2, with global hypoconnectivity, was associated with baseline depressive severity and anxiety symptoms. Overall, these results provide evidence of heterogeneity in patterns of resting-state FC and that these hyper- and hypo-connectivity patterns are associated with distinct treatment preferences.

We infer that factor 1 and factor 3 are dissociated and opposite factors. Factor 1 and factor 3 are characterized separately by hyperconnectivity (or hypoconnectivity) between the DMN and other networks. The two factors also show opposite preferences in treatment modalities. The DMN hyperconnectivity indicates a response to antidepressant therapy, while DMN hypoconnectivity suggests a response to stimulation therapy. The association between DMN hyper- and hypo-connectivity and treatment preferences has been reported in previous studies. Patients with MDD characterized by hyperconnectivity of the DMN at baseline were likely to benefit from short-term antidepressant treatment and achieve acute remission (Korgaonkar et al. 2019). Studies also found that after antidepressant treatment, the enhanced functional connectivity of the DMN was normalized (Li et al. 2013; Siegel et al. 2021; Li et al. 2021). For rTMS studies, consistent with our results, studies found a hypoconnectivity between DMN and subgenual anterior cingulate cortex (sgACC) in responders (Liston et al. 2014; Taylor et al. 2018). In a review study, the decrease in FC between dorsolateral prefrontal cortex and DMN areas was observed after rTMS treatment, suggesting these decreases may redirect cognitive focus from internal rumination to external stimuli (Schiena et al. 2021). For ECT studies, the modulatory effects of ECT on FC present distinct mechanistic patterns. ECT reduced hyperconnectivity between the ventral striatum and the ventral DMN and improved hypoconnectivity with the anterior DMN (Leaver et al. 2016). After ECT, three hippocampal subregions became less connected to the core nodes of the posterior DMN (Gbyl et al. 2024), while enhanced FC between DMN and central execution networks was observed (Pang et al. 2022). The relationship between hypoconnectivity and treatment response in ECT is complex, as hypoconnectivity FC patterns may lead to varied therapeutic outcomes. This needs further exploration. In conclusion, different treatment modalities for MDD exert distinct effects on DMN connectivity, highlighting their unique mechanisms of action.

Apart from brain connectivity, the relationship between factor 1 demographic preferences and symptom response was also an interesting finding. Factor 1 was preferentially expressed by younger and highly educated patients and was associated with

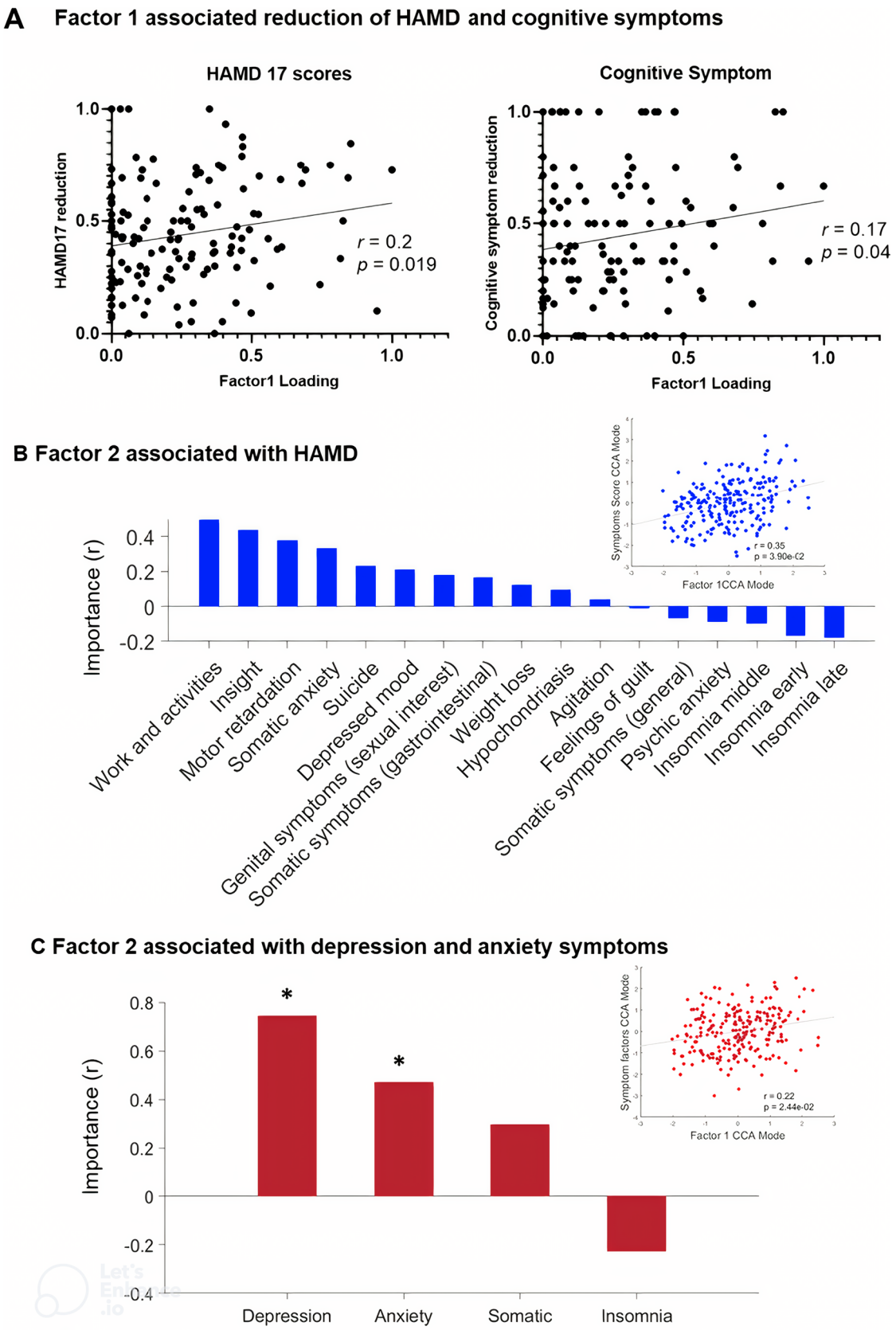

FIGURE 5 | Latent factors associated with longitudinal treatment response and baseline clinical characteristics. (A) Correlation between factor 1 loading and HAMD reduction, cognitive symptoms reduction. (B, C) CCA between factor loadings and clinical characteristics. (B) Associations between factor 2 and HAMD. (C) Associations between factor 2 and depression and anxiety symptoms. The upper-right panel is the result of CCA. The bar plots show the importance (r), which is defined as the Pearson correlation between symptom factors CCA mode (y-axis in scatter plot) and symptom score. The asterisk indicates a corrected significant correlation. The scatter plots show the correlation between the optimal linear combination of factor loading and symptom scores. Each dot represents a patient. CCA: canonical correlation analysis; HAMD: Hamilton Depression Rating Scale.

improvements in depressive symptoms especially for cognitive symptoms. Evidence shows that young and highly educated populations have higher cognitive abilities and neural plasticity. Previous studies reported a decline in neuronal activity and massive deterioration in the human entorhinal cortex and hippocampus with age (Scheibel et al. 1976; Scheibel 1979). Thus, younger patients tend to exhibit greater neural plasticity, which may enhance their ability to recover cognitively. Additionally, studies have shown that high education significantly enhances cognitive functioning. A study based on a large and diverse sample has found that high-level education predicts better performance in an online cognitive test (Guerra-Carrillo et al. 2017). Research also has found that higher educational attainment reduces the risk of depression later in life (Patria 2022; Ibrahim et al. 2013). Therefore, these high-level neural plasticity and cognition contribute to a higher recovery ability.

Our study has some limitations. First, the non-randomized allocation of treatment strategies based on clinical characteristics may introduce selection bias. Our study has a limited sample size. It limited our explanation and validity of findings. The results of comparing different treatment strategies are not stable enough, and further replications and validation from independent datasets are needed. Another limitation is lacking individual treatment prediction. The current study only conducted a dimensional analysis based on a single dataset and found treatment preferences. The findings quantified the possibility of individual treatment preferences but did not predict treatment outcomes and choices at the individual level. Importantly, an independent dataset is needed for individual prediction and factor validation.

Our study revealed three latent factors associated with treatment modality choices. The DMN hyper- and hypo-connectivity guided whether applied combined treatment. We found that younger age and higher education levels were linked to greater improvement in symptom severity, especially in cognitive symptoms. Our approach allows for a unique composition of factors in each individual, potentially facilitating the development of more personalized treatment-related biomarkers.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.