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Gray matter increases in fronto-parietal regions of depression patients with aripiprazole monotherapy

An exploratory study

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Abstract

We investigated the treatment effects of aripiprazole monotherapy in first-episode medication-naïve patients with major depressive disorder (MDD). The accompanying changes in the gray matter volume (GMV) were also explored.

Fifteen patients completed the trial and received structural scans by 3-Tesla magnetic resonance imaging at baseline and partially responding state (sixth week). To account for the test–retest bias, 27 healthy controls were scanned twice within 6 weeks. We utilized optimized voxel-based morphometry with different comparisons between groups.

The partially responding patients with MDD had greater GMV in left middle frontal gyrus and left superior parietal gyrus when compared with baseline. However, they had decreases in the GMV of right orbitofrontal gyrus and right inferior temporal gyrus after response. The partially responding patients with MDD still had residual GMV deficits in right superior frontal gyrus when compared with controls. However, the lack of second patient group without aripiprazole intervention would be a significant limitation to interpret the aripiprazole-specific effects on GMV.

The changes in the GMV of fronto-parieto-temporal regions and residual GMV deficits in the superior frontal gyrus might represent "state-dependent brain changes" and "residual-deficit brain regions," respectively, for aripiprzole monotherapy in MDD.

Abbreviations: GMV = gray matter volume, HARS = Hamilton Rating Scales for Anxiety, HDRS = Hamilton Rating Scales for Depression 17-item, IOFG = inferior orbitofrontal gyrus, ITG = inferior temporal gyrus, MDD = major depressive disorder, MFG = middle frontal gyrus, MR = magnetic resonance, QIDS-SR16 = Quick Inventory for Depressive Symptoms-Self Rating 16-item version, SFG = superior frontal gyrus, SPG = superior parietal gyrus, VBM = voxel-based morphometry.

Keywords: aripiprazole, gray matter volume, major depressive disorder, middle frontal gyrus, superior parietal gyrus

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1. Introduction

Major depressive disorder (MDD) was associated with social and occupational impairments in many dimensions. The untreated depression usually will enter a deteriorating course. The treatment of MDD is an important issue for clinical practices. The typical therapy for MDD mostly focuses on the antidepressants. For the monotherapy of atypical antipsychotics in MDD, it remained controversial and inconclusive even with proved efficacy in augmentation therapy.

The brain structure is an important issue for the pathophysiology in MDD. The voxel-based morphometry (VBM) studies[1–3] and meta-analysis[4] revealed fronto-limbic deficits in gray matter volume (GMV) of MDD patients. The meta-analysis also addressed the connection between prefrontal–limbic GMV deficits and medication-naïve depression.[4] GMV reductions in the frontal regions play a major role for neuropsychological impairments in MDD.[1,5–7] GMV of the superior frontal cortex is related to cognitive impairments of depressed patients[8] and inferior frontal cortex may reflect disorder-specific symptom clusters for MDD.[1] These results suggested that the patients with MDD probably have frontal-specific pattern of neuroanatomical deficits, either in status of partial response or untreated.

The medication therapy for MDD in the field of neuroanatomical plasticity and modulation has been an intriguing issue for research. Our previous reports showed the possible association of antidepressants with structural changes in the frontal–limbic network of MDD comorbid with panic disorder.[2,9] The recent report of MDD also found that the remitted patients had significant increases in GMV of right orbitofrontal cortex and temporal cortex after antidepressant treatment.[10] Similar increases in the GMV of dorsolateral prefrontal cortex were also replicated.[11] However, no evidence for GMV increases in depressed patients has also been reported in several studies after treatment or after remission.[12,13] In addition to the antidepressants, the augmentation role of atypical antipsychotics for MDD treatment has been emphasized in recent years, and more evidences support the augmentation efficacy of aripirazole in MDD.[14,15] The therapeutic mechanisms probably include aripiprazole's unique effects of partial agonism at dopamine D2, D3, and serotonin 5-HT1A receptors, and antagonism at serotonin 5-HT2A receptors.[16] However, aripiprazole monotherapy for MDD has not been addressed much in modulating effects on the brain. There are only several case reports with the findings of GMV and subcortical changes after aripiprazole monotherapy.[17–19] The therapeutic effects of aripiprazole monotherapy and related effects in the GMV for MDD remain unclear. In the current study, a 6-week monotherapy of aripiprazole in patients with MDD would be implemented. In addition, different comparisons of GMV between patients and controls at baseline and sixth week will be done, which might clarify the unresolved issue.

From the above literature review, we hypothesized that first-episode, medication-naïve patients with MDD would have partial response after aripiprazole monotherapy. The reason to choose aripiprazole in this study was purely scientific interest in depression pathology. In addition, MDD patients might have GMV deficits in the fronto-limbic regions, which would be improved after clinical responses (state-dependent brain changes). However, residual deficits in the GMV would persist even with partial response (residual-deficit brain regions). We would use optimized VBM method to estimate the differences in GMV between patients and controls at baseline and at sixth week to identify the "state-dependent brain changes" and "residual-deficit brain regions" for the aripiprazole monotherapy in MDD.

2. Methods

2.1. Participants

The selection criteria for the patients were as follows: first-episode, medication-naïve (psychotropic medication) outpatients with a pure MDD diagnosis made on the basis of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria using the Structured Clinical Interview for DSM-IV[20]; no comorbid mental disorders or significant medical illnesses for life time; severity of MDD was at least moderate: Clinician Global Impression of Severity[21] >4; the rationale to choose such criteria was based on the significant findings of frontal region in our previous report,[22] Quick Inventory for Depressive Symptoms-Self Rating 16-item version(QIDS-SR16)[23] score >19, Hamilton Rating Scales for Depression 17-item (HDRS) score[24] >20, Hamilton Rating Scales for Anxiety (HARS) score[25] <5; no previous cognitive behavioral therapy or other psychotherapies; and no past history of claustrophobia or discomforts while receiving magnetic resonance (MR) scanning. The healthy controls (mostly from hospital staff) had no mental disorders, significant medical illnesses, or family history of first-degree relatives for depression. This open-label protocol of aripiprazole monotherapy in MDD was approved by the Institute of Review Board, Buddhist Tzu-Chi Hospital, Taipei Branch. There was no placebo-controlled group in the approved protocol. All participants signed the inform consent to receive the open-label aripiprazole monotherapy and MR scanning at baseline and at sixth week. The format and content of informed consent were approved by the Institute of Review Board, Buddhist Tzu-Chi Hospital, Taipei Branch. At the time of the MR imaging, none of the participants received benzodiazepine to relieve MR scanning-related anxiety. Handedness was determined by using the Edinburgh Inventory of Handedness.[26] All patients in the study received initial dose of aripiprazole as 3.75 mg per day. Then the dose was titrated to 7.5 mg per day from second to sixth week. The arbitrary dosage selection was based on our previous explorative experiences. The approved additional medication was lorazepam 0.5 to 1 mg/d only in case of insomnia or presleeping anxiety. The partial response criterion was set as 25% reductions in the HDRS scores[27] after treatment of aripiprazole. None of the controls received aripiprazole in this study.

2.2. MR imaging procedure and data acquisition

The MR imaging scans of brain structures were obtained using the 3-Tesla Siemens version scanners (TRIO, Siemens Magneton, Germany) housed in the MR Center at the National Yang Ming University. Scans with 3-dimensional fast spoiled gradient-echo recovery (3D-FSPGR) T1W1 (TR 25.30ms; TE 3.03ms; slice thickness = 1mm [no gap]; 192 slices; matrix = 224×256; field of view: 256 mm; number of excitation = 1) were performed on the patients and controls at baseline and at sixth week.

2.3. VBM processing and statistical analysis

2.3.1. Preprocessing. After manually reorienting and centering the images on the anterior commissure, data were processed based on the optimized VBM approach. The SIENAX tool (Structural Image Evaluation, using Normalization, of Atrophy)[28] was used to calculate total GMV (from spatially normalized images to make images comparable in normalized space) for each participant. Structural MR images were also

processed with the FSLVBM (http://www.fmrib.ox.ac.uk/fsl/fslvbm/, version 1.1) function of FSL (FMRIB Software Library; version 4.1.1) to compare the differences in the GMV between patients and healthy controls. The theory of the FSLVBM method consists of 4 major steps. First, brain skull and other nonbrain tissues were removed by "Brain Extraction Tool" (version 2.1) to discard the nonbrain tissues in the subsequent analysis. Second, FSL Automated Segmentaion Tool (version 4) performed tissue-specific segmentation to produce partial volume images of gray matter,[29] which were then affine registered to Montreal Neurological Institute 152 template. The registered images were averaged and concatenated to establish a study-specific 4D template of gray matter. Third, the brain would be nonlinearly registered to the above template, and all the registered images were visually inspected by Dr Lai to check on the quality of registration. All the segmented gray matter images were concatenated into a 4D multisubject concatenated image, which was modulated by Jacobian of the warp field. The modulated 4D image was smoothed by Gaussian kernels (sigma 3 mm in FSLVBM protocol), which approximately equals to full width at half maximum 7.5 mm.[30] On the other hand, a FSLVBM gray matter mask was created by unsmoothed segmentations and unmodulated normalized segmentations. The smoothed 4D modulated image and gray matter mask were necessary for the following steps of permutations.

2.3.2. Estimated model and contrasts. A nonparametric inference (Randomize function of FSL, version 2.1) was used to calculate voxel-wise P values. Then we used the Threshold-Free Cluster Enhancement (TFCE)—a new method for finding clusters in data without defining an initial cluster-forming threshold or excessive smoothing.

We initially performed the F test to examine time × group interaction, and found significant interaction between time and group (corrected $P < 0.05$). Then a post hoc test was used under the impression of significant clusters found in the above F test. It was used to compare the differences in GMV using the following contrasts: "patients versus controls at baseline (meant week 0)" (for the GMV characteristics of MDD), "posttreatment versus pretreatment" (for the "state-dependent brain changes" related to the response in depression under aripiprazole monotherapy), "controls: week 6 versus week 0" (to investigate physiological and scanner-related changes in GMV), "patients versus controls at week 6" (for the "residual-deficit brain regions" that occurred in MDD even after partial response). Our model estimation used nonparametric computations, which were based on the randomized function of the FSL software. The randomized function also used a general linear model for permutations. For the pretreatment and posttreatment comparisons, we used the paired t test of randomized function to gain power. An independent-sample t test of randomized function was used to compare patients with controls. The method was comparable to multiple comparisons of random field theory.[31] We included age, sex, total GMV, duration of illness status, and educational years as nuisance variables in the general linear model. The reasons to choose the above covariates were based on the possible aging effects on the prefrontal and temporal lobes,[32] the sex effects on GMV,[33] total GMV to control for individual variations in GMV, the association of longer illness duration with lower GMV,[34] and the education-related intelligence would influence the gray matter of cerebral cortex.[35] A supplementary analysis of general linear model without any covariate was also performed.

2.3.3. Statistical criteria of significance. We used family-wise error (FWE)-corrected method to obtain results for continuous random processes to find P values. With regards to the significance threshold, we defined a TFCE-corrected image thresholded at FWE-corrected $P < 0.05$. The threshold number of voxels for all contrast models was 20, and the significant clusters were defined as the voxels greater than 20.

2.3.4. SPSS analysis of correlations and differences between groups. The changes in the scores of clinical rating scales (the HDRS and the QIDSR-16) between baseline and the sixth week were investigated by Wilcoxon signed-rank test, with the significance threshold set as $P < 0.05$. We also correlated the changes in total GMV to the changes in the HDRS scores using Spearman rank-correlation test. All tests were performed using SPSS version 17.

3. Results

3.1. Enrolled subjects

Nineteen patients were enrolled and all signed the inform consents. All patients were of Taiwanese (Han Chinese) origin. Among the 19 patients, 4 patients refused to continue aripiprazole monotherapy due to intolerable and persistent side effects (e.g., dizziness, fatigue, tiredness, sedation, akathisia, etc.). Therefore, 15 patients completed the trial to reach partially responding status in 6 weeks, and 27 healthy controls were enrolled (Table 1). The 15 patients and 27 controls received the acquisitions of MR imaging (without any benzodiazepine use) at baseline and at sixth week. No significant differences in ages, sex, and educational years were noted (Table 1). There were significant differences in HDRS and QIDS scores between patients and controls (Table 1).

Table 1

Demographic data of patients and controls.

	Patients (n = 15)	Controls (n = 27)	Sig. P (2-tailed)
Age, mean (SD), y	37.46 (5.93)	38.29 (11.80)	0.927
Sex (number)	F (9), M (6)	F (15), M (12)	0.355
Duration of illness, mean (SD), mos	4.20 (2.07)	0 (0)	N/A
Educational years, mean (SD)	15.61 (0.92)	15.92 (0.67)	0.072
Handedness	R (15)	R (27)	N/A
HDRS, mean (SD)	21.73 (2.37)	1.37 (0.88)	≤0.001
QIDS, mean (SD)	20.80 (2.36)	2.26 (1.13)	≤0.001

Sig. P (significance of P value) was from Mann–Whitney U test for nonparametric independent 2-sample t test.

F = female, HDRS = Hamilton Rating Scales for Depression 17-item, M = male, N = number, N/A = not applicable, QIDS = Quick Inventory of Depressive Symptoms—Self-rating 16-item version, SD = standard deviation.

3.2. Clinical data

All the 15 patients had improvements of MDD symptoms after a 6-week therapy of aripiprazole monotherapy. The depression symptoms improved significantly within 6 weeks (Wilcoxon signed-rank test, post hoc correction; scales: standard error: 95% confidence interval; CGI-S: 0.17: 1.57–2.28 [2-tailed $P=0.001$]; HDRS: 0.82: 5.92–9.27 (2-tailed $P=0.001$); QIDS: 0.67: 6.35–9.11 (2-tailed $P=0.001$]). The mean scores of HDRS (baseline: $21.73\pm2.37\geq$sixth week: 14.13 ± 2.09) and QIDS (baseline: $20.80\pm2.36\geq$sixth week: 13.06 ± 1.09) significantly decreased, respectively. It represented that these patients had partial response in the MDD symptoms and life qualities after the aripiprazole monotherapy as 7.5 mg/d in dose.

3.3. Brain GMV and FSLVBM data

The MDD patients had lower GMV in the right superior frontal gyrus (SFG) and left middle frontal gyrus (MFG) when compared with healthy controls at baseline (Fig. 1A, FEW-corrected $P<0.05$). The patients had subtle increases in the GMV of left MFG and left superior parietal gyrus (SPG) after partial response (Fig. 1C and Table 2: FEW-corrected $P<0.05$). In addition, patients had decreased GMV in the right inferior orbitofrontal gyrus (IOFG) and right inferior temporal gyrus (ITG) after partial response (Fig. 1D and Table 2: FEW-corrected $P<0.05$). There were residual-deficit brain regions (residual GMV deficits) in right SFG of partially responding patients with MDD after aripiprazole monotherapy (Fig. 1B and Table 3: FEW-corrected $P<0.05$). The partially responding patients with MDD did not have greater GMV than the controls. The supplementary analysis without covariate adjustment showed similar results of GMV deficits and "residual-deficit brain regions," except for "state-dependent brain changes" without reductions of the ITG after partial response (Supplementary Fig. 1, http://links.lww.com/MD/B222). The total GMV was negatively correlated with the scores of HDRS ($r=-0.596$; Spearman rho $P=0.014$). Moreover, a positive correlation between the changes in HDRS scores and the changes in total GMV was found ($r=0.583$; Spearman rho $P=0.023$). No significant correlation between QIDRS-16 and the changes in total GMV was observed.

3.4. The repeated testing in control group

There were no significant MR imaging interscan biases (anatomical landmark displacement between 2 scans at baseline

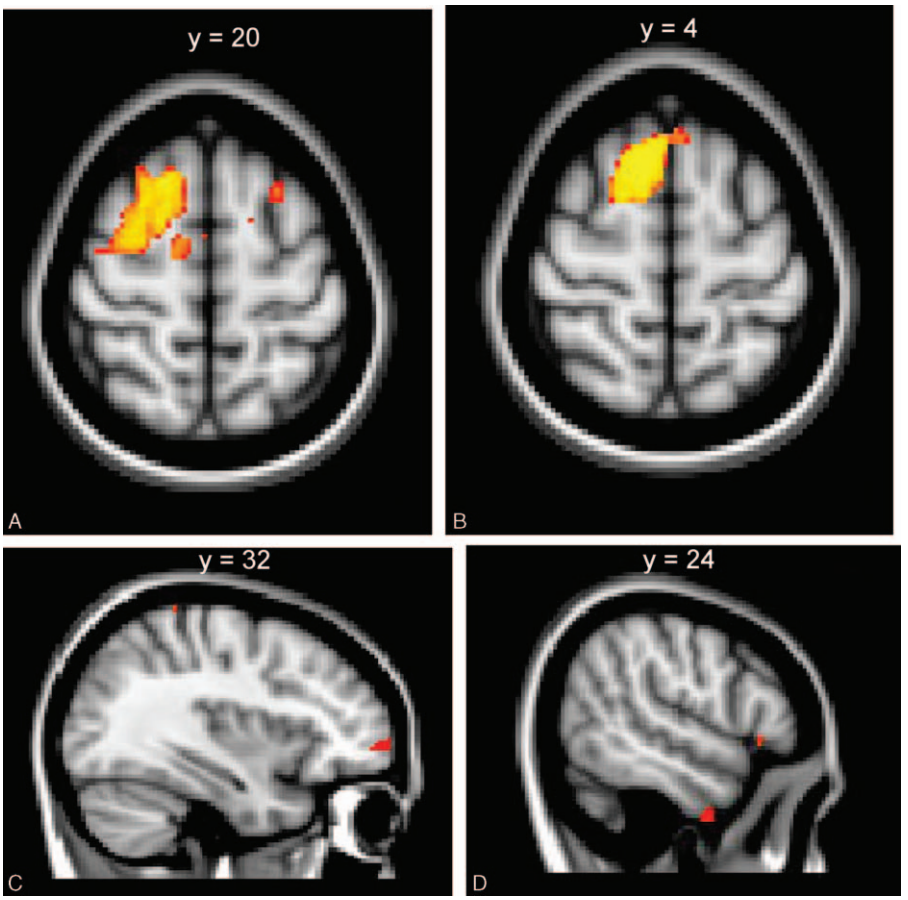

Figure 1. The patterns and characteristics of GMV deficits, state-dependent brain changes, and residual-deficit brain regions in MDD patients: Bright yellow color represented more significant differences in GMV than the red color, and corrected *P* threshold is 0.045. A, The MDD patients had significant reductions in the GMV of right SFG and left MFG (family-wise error corrected [FEW-corrected] $P<0.05$). B, Residual reductions in the GMV of right SFG were still found after aripiprazole monotherapy (residual-deficit brain regions) (family-wise error corrected [FEW-corrected] $P<0.05$). C, The partially responding patients with MDD had higher GMV in the left MFG and left SPG when compared with baseline (state-dependent brain changes) (FEW-corrected $P<0.05$, contrast C). D, In the contrast, lower GMV was observed in the right IOFG and right ITG after partial response (FEW-corrected $P<0.05$) (state-dependent brain changes). IOFG = inferior orbitofrontal gyrus, ITG = inferior temporal gyrus, MFG = middle frontal gyrus, SFG = superior frontal gyrus; SPG = superior parietal gyrus.

Table 2

GMV changes after a 6-week therapy of aripiprazole.

Posttreatment ≥ pretreatment (corrected $P<0.05$)	MNI coordinate (peak voxel)	Cluster voxels	*T* value (peak voxel)
Left SPG	(−14, −46, 78)	22	5.85
Left MFG	(−32, 32, 16)	39	6.13
Right IOFG	(54, 24, −6)	24	5.98
Right ITG	(56, −68, −2)	35	6.02

IOFG = inferior orbitofrontal gyrus, ITG = inferior temporal gyrus, MFG = middle frontal gyrus, MNI = Montreal Neurological Institute, SPG = superior parietal gyrus.

and at sixth week) and no significant changes in GMV within 6 weeks in the control group, for "baseline versus sixth week" and "sixth week versus baseline" (contrast E and F).

4. Discussion

In this study, we found that aripiprazole monotherapy might improve the symptoms of depression. In addition, partially responding patients with MDD had subtle increases in the GMV of left MFG and SPG, and decreases in the GMV of right IOFG and ITG. The correlation between the increases in GMV and the improvements in clinical symptoms probably supported the theory of "state-dependent brain changes" for aripiprazole monotherapy. However, the GMV deficits of right SFG still remained even after partial response, which might represent "residual-deficit brain regions."

The possible bias related to educational years (intelligence) should be noted. The intelligence has significant and widespread impacts on cerebral cortex.[35–37] The inclusion of education covariate can exclude the possible bias related to education and intelligence. Our results were also in line with recent findings of the GMV increases in frontal lobe after antidepressant treatment.[10,11,38,39] In addition to the frontal lobe, these recent reports showed significant increases in the GMV of temporal and parietal lobes.[10,38,39] The short-term study results supported that the neuroplasticity of MDD could occur in such a short time course. However, our report showed significant decreases in the GMV of right IOFG and ITG combined with significant increases in the left MFG and SPG. We hypothesized this pattern of modulations in the GMV might be specific to antipsychotic characteristics of aripiprazole. However, the current study design would suffer from the lack of second patient group which should show a similar decline in depressive symptoms but without aripiprazole intervention. The design pitfall would limit us to find the specific modulations of GMV related to aripiprazole due to lack of comparison between aripiprazole and other typical treatments for MDD, such as antidepressants. In addition, the design of exploratory study would limit the interpretation of changes in GMV after aripiprazole therapy and it might be related to the adverse effects of aripiprazole. Further study with well-controlled design and region-of-interest, based on previous literature, is needed to compare the different effects between antidepressants and antipsychotics in MDD to confirm such specific pattern.

The GMV deficits of frontal cortex have been reported in several articles of MDD. Abe et al[5] found that patients with MDD might have GMV deficits in fronto-temporo-limbic regions, which also included the MFG. Our study also replicated the findings of Leung et al,[40] who found that MDD patients had attention bias-related gray matter decreases in the right SFG. The SFG is also a part of "hate circuit," which involve the pathogenesis of depression symptoms, risk and action responses, attention, reward, and emotion.[41] The above studies supported our results of GMV deficits in the SFG and MFG for patients with MDD at baseline status.

The increases in GMV of the MFG after aripiprazole monotherapy suggested that MDD patients might reverse the GMV deficits of the MFG after treatment. The remitted MDD patients would have less decline of GMV in the prefrontal cortex than nonremitted patients.[42] The subtle increases of GMV in the MFG might suggest compensatory mechanisms of aripiprazole in the GMV deficits. The increases in GMV of the SPG were out of our expectations. However, the GMV of the parietal lobe might represent a predictor of treatment response for MDD and interact with clinical severity.[43] Reduced serotonin synthesis in the SPG is specific for depression pathophysiology.[44] The changes in GMV of the SPG might represent a kind of "state-dependent brain changes" for MDD under aripiprazole treatment. In addition, the aripiprazole alters the regional cerebral blood flow of the fronto-parieto-temporal regions,[45] and has high affinity for serotonin 5-HT1A receptors in the parietal cortex.[46] The modulating effects of aripiprazole for the cerebral blood flow and serotonin 5-HT1A high affinity probably play a role in the explanation of our results.

The decreases in the GMV of right IOFG and right ITG raised another issue for the aripirpazole monotherapy in MDD. The reduced GMV of orbitofrontal cortex has been found in patients with MDD.[47,48] The decreased GMV of right IOFG might be related to aripiprazole-related reductions in binding potential of serotonin 5-HT1A receptors in the orbitofrontal regions[49] and modulations of regional cerebral blood flows in the temporal regions.[45] The findings of right IOFG and ITG in our study were also different from those of antidepressant treatment, which showed no significant decreases in the GMV after remission.[2,9,10,39] An opposite effect in fronto-parietal regions (MFG and SPG) and fronto-temporal regions (IOFG and ITG) might suggest that low dose of aripiprazole seems more beneficial for the fronto-parietal regions (cognitive network)[50] than the fronto-temporal regions.[51]

Table 3

GMV differences between patients and controls at follow-up.

Controls > patients (corrected $P<0.05$)	MNI coordinate (peak voxel)	Cluster voxels	*T* value (peak voxel)	Patients >controls (corrected $P<0.05$)
Right SFG	(16, 4, 64)	421	6.87	No significant voxels

MNI = Montreal Neurological Institute, SFG = superior frontal gyrus.

The possible association between aripiprazole and changes in GMV were also an important finding in the current study. The chronic treatment of aripiprazole might induce differential expression of gene, chromatic remodelling, and transcription regulation in rat frontal cortex.[52] The aripiprazole treatment would also increase brain-derived neurotrophic factor, glycogen synthase kinase 3 beta, and B-cell lymphoma-2 phosphorylation, which can induce further neurogenesis.[53,54] Aripiprazole can also affect cognitive function and frontal metabolisms due to higher D2 receptor occupancy.[55] The changing effects of GMV might also be related to the following reasons, such as synaptic remodeling and neurogenesis[56] from the stimulation of neutrophic factors by antipsychotics,[57] prevention of oxidative stress or 6-OH-dopamine lesioning and with subsequent increased proliferation of glial cells in the frontal cortex,[58] and modulation of glutamate receptor function.[59] The serotonin system might be stabilized due to the aripiprazole-related 5-HT1A partial agonism and 5-HT2C antagonism effects.[18] Serotoninergic and dopaminergic actions of aripiprazole might help MDD symptoms improve, which might be related to GMV changes of patients with MDD.[14–16,60]

The residual GMV deficits of SFG might suggest that aripiprazole treatment could not reverse the GMV deficits in this region. The GMV deficits of SFG also have been reported in several VBM studies.[7,8,40,41,61] The findings of residual GMV deficits might suggest that SFG represents the "residual-deficit brain regions" for patients with MDD under aripiprazole treatment. It also replicated our previous study of residual GMV deficits after antidepressant treatment.[2] From the current results, we suggested pure MDD patients might have residual GMV deficits under aripiprazole treatment, and the SFG might be the specific region for the "residual-deficit brain regions" for partially responding patients with MDD under aripiprazole treatment. However, we still need further well-controlled and organized studies to confirm our findings in the SFG.

4.1. Limitations

Our study has several limitations: an open-label aripiprazole monotherapy study, a relatively inadequate sample size of patients, and a lack of placebo-controlled group limited the interpretation of the treatment effects in brain structures; aripiprazole may not directly be related to the GMV changes and the increase in the GMV may be totally unrelated to MDD; placebo intake by patients or aripiprazole intake by controls was not applied in the current study, which might limit the ideal explanation of our results. However, these control conditions may not be feasible due to ethical reasons.

5. Conclusions

To our knowledge, it is the first study to investigate aripiprazole monotherapy for MDD and related GMV changes. The changes in the GMV of fronto-parieto-temporal regions and residual GMV deficits in the SFG might represent "state-dependent brain changes" and "residual-deficit brain regions," respectively, for aripiprzole monotherapy in MDD.

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