The effects of olanzapine treatment on brain regional glucose metabolism in neuroleptic-naive first-episode schizophrenic patients

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Running title: FDG-PET study of first-episode schizophrenia

CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

Abstract

Objective   The current study examined metabolic alterations associated with a positive response to olanzapine, and identified brain regions associated with treatment-related improvement of symptoms in neuroleptic-naive first-episode schizophrenic patients using [^{18}F]fluoro-deoxy-glucose positron emission tomography analysis.

Methods   Neuroleptic-naive first-episode schizophrenic patients who showed good or poor clinical responses to olanzapine were assessed using the Positive and Negative Syndrome Scale (PANSS). Data were analysed using statistical non-parametric mapping.

Results   Before treatment, responders showed significantly increased metabolism in the ~~right~~ superior temporal gyrus (STG) and cerebellum compared with healthy controls. Glucose metabolism in responders was significantly increased after treatment in the left precentral gyrus, left postcentral gyrus, and left paracentral lobule, and significantly decreased in the left hypothalamus. Analysis of the PANSS symptoms associated with olanzapine treatment revealed that 'suspiciousness/persecution' scores were positively correlated with metabolic changes in the right superior frontal gyrus.

Conclusions   These findings provide evidence of the neural mechanisms underlying the effects of olanzapine on metabolism in the early stages of schizophrenia.

INTRODUCTION

Recent studies have shown the importance of treating schizophrenia as early as possible at first episode. A number of studies have attempted to link schizophrenia symptoms to specific brain regions, including the widely reported relationship between negative symptoms and the frontal cortex (Lahti et al., 2001; Ziauddeen et al., 2011), and the association between the temporal lobes, auditory hallucinations (Barta et al., 1990; Kasai et al., 2003) and thought disorder (Horn et al., 2010). Interestingly, Liddle et al. (2000) described changes in hippocampal activity associated with clinical improvement in schizophrenia patients receiving risperidone treatment. Further, a decrease in the medial frontal cortex was reported after risperidone and was found to correlate with clinical improvement (Ngan et al. 2002). A longitudinal [18F]fluoro-deoxy-glucose positron emission tomography (FDG-PET) study by (Buchsbaum et al. 2007) reported that patients treated with olanzapine (OLZ) exhibited increased relative metabolic rates in the frontal lobe more than the occipital lobe in 30 psychotic adolescents who had not previously received medication. In contrast, a longitudinal FDG-PET study by Molina et al. (2005) reported no significant regional metabolic changes with OLZ in 17 patients previously treated with antipsychotics. The results indicated that the lack of significant regional metabolic changes was related to previous treatment with classical neuroleptics, an effect that was observed in all cases except two patients treated with risperidone.

The present study examined the effects of OLZ treatment, and localized the symptoms to specific brain regions in neuroleptic-naive first-episode schizophrenic (FES) patients. We evaluated patients with the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987), brain glucose metabolism during pre- and post-treatment with OLZ, and OLZ treatment-related changes. In addition, we examined differences between responders and non-responders in neuroleptic-naive FES patients using longitudinal resting-state FDG-PET,

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and assessed correlations between metabolic changes and PANSS scores in responders before and after OLZ treatment.

METHODS

Participants

A sample of 18 neuroleptic-naive FES patients were recruited for this study between April 2005 and March 2014. Three patients did not complete a second scan and were excluded from the study. Overall psychopathology was evaluated with the Clinical Global Impressions-Improvement (CGI-I) Scale (Guy 1976) and the PANSS. The CGI-I ratings used to designate OLZ treatment-responders were '1, very much improved' and '2, much improved'. The CGI-I ratings used to designate OLZ treatment-non-responders were '3, minimally improved', '4, no change', '5, minimally worse', '6, much worse', and '7, very much worse'. Handedness was determined using the Edinburgh Handedness Inventory (Oldfield, 1971). The 15 healthy right-handed volunteers included in the final analysis were screened for past clinical history, laboratory testing, past and current substance misuse, and either magnetic resonance imaging (MRI) or computed tomography (CT). Healthy volunteers matched with patients for age (Table 1), handedness, and drug non-use were recruited and scanned once. Patients underwent an initial scan with FDG-PET and were assessed with the PANSS in the neuroleptic-naive state. Within 24 hours after the scan, the patients received 5–20 mg/day of OLZ (Table 1). After OLZ treatment, the patients underwent a second FDG-PET scan and were assessed using the CGI-I and PANSS. The treatment durations at the time of the post-treatment scan corresponded to the established optimal response.

Patients were evaluated according to Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (American Psychiatric Association, 2000). All patients were later confirmed with a diagnosis of schizophrenia. All patients were screened for past clinical

history, laboratory testing, comorbidity, past and current substance misuse, and MRI or CT.

All patients or their caregivers and all healthy subjects gave written informed consent after

receiving verbal and written explanations of the nature of this study. This study was approved

by the scientific and ethics committee of Kagoshima University Graduate School of Medical

and Dental Sciences, Fujimoto Hospital, Fujimoto Medical System, and conducted in

accordance with the Helsinki Declaration of 1975 (revised in 1983).

Positive and negative syndrome scale (PANSS) analysis

Statistical analysis for PANSS scores was performed using SPSS version 17.0 software

(SPSS Inc., Chicago, IL, USA). We used Wilcoxon matched-pairs signed-rank tests

(nonparametric test algorithms) to evaluate the clinical outcome of each PANSS symptom

score, and compared the scores obtained before and after treatment. Multiple comparisons

were conducted, so $p < 0.05/8$ was required for statistical significance.

Scanning procedure

FDG-PET scanning was performed with a Siemens-Asahi ECAT ACCEL using lutetium

oxyorthosilicate (LSO) detectors. Before the examination, sugar intake was restricted for at

least 5 h. All patients and healthy subjects fasted for at least 5 h before the FDG injection.

Following injection of 185 MBq [18F]FDG, participants rested for 60 min in a quiet private

room and were scanned while resting with eyes closed while being monitored by video. The

image reconstruction was performed using filtered back projection, and a Gaussian filter was

employed.

Image analysis

Statistical non-Parametric Mapping (SnPM) 13 (Wellcome Department of Cognitive

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Neurology, Institute of Neurology, London, UK), implemented in MATLAB version 7.9 (MathWorks, Natick, MA, USA), was used for image preprocessing and statistical analysis. Raw PET images were converted to Analyze format using MRIcro software (http://www.mccauslandcenter.sc.edu/mricro/). Coordinates were converted from Montreal Neurological Institute coordinates to Talairach coordinates using non-linear transformation (http://www.talairach.org/). Linearly transformed FDG-PET images in individual patients were spatially normalized into a standard FDG-PET template, provided in SnPM13, using a 12-parameter affine and non-linear transformation. Spatially normalized images with a voxel size of $2 \times 2 \times 2$ mm were then smoothed by convolution using an isotopic Gaussian kernel, 12-mm full-width at half-maximum, to increase the signal to noise ratio. Spatial normalization accuracy was checked using a cross-registration function.

Data analysis

The PANSS data were analysed using Wilcoxon matched-pairs signed-rank tests. Information on the scanning procedure is provided in Table 1.

SnPM analysis of responders or non-responders vs. healthy controls at pre- and post-treatment with OLZ

Comparisons were performed using two-sample t-tests to examine differences in relative regional cerebral glucose uptake between patients and healthy controls. To control for type I errors, we used family wise error (FWE) corrected statistical significance of $p < 0.05$.

SnPM analysis of responders vs. non-responders

To identify differences in patterns of brain glucose metabolism between responders and non-responders using the two-sample t-test, we compared glucose metabolism between the

two groups pre- and post-treatment (i.e., responders [pre-treatment] *vs.* non-responders [pre-treatment], and responders [post-treatment] *vs.* non-responders [post-treatment). The height threshold was set to $p = 0.05$, FWE corrected.

To identify patterns of brain metabolic changes related to OLZ treatment responses using paired t-tests, we compared brain glucose metabolism between pre- and post-treatment in responders and non-responders. Paired t-tests were used to perform group comparisons on pre- and post-OLZ FDG-PET images in patients. In this analysis, to control for type I error, we accepted FWE corrected values with a significance threshold of $p < 0.05$.

Correlation between PANSS scores and FDG-PET imaging in responders

The pre-treatment data at baseline were subtracted from the post-treatment data using IMCALC. After spatial and global count normalization with proportional scaling, subtraction between pre- and post-treatment FDG-PET images was performed to create images showing changes in cerebral glucose metabolism in individual patients using IMCALC in SnPM13 (the pre-treatment image of each subject was set to i1 and the post-treatment image was set to i2, and the expression i1 - i2 was applied). The subtraction techniques for PET and MRI images are described in detail elsewhere (Woodward et al., 2011; Nudelman et al., 2014). The correlation between the changes in symptoms and the changes in metabolic activity from the pre- to the post-treatment conditions was also analysed with SnPM13 multiple regression. Age was added as a covariate 'mask'. To investigate brain regions correlated with symptoms that were improved by OLZ treatment in FES patients, we accepted FWE-corrected values with a significance threshold of $p < 0.05$ at the voxel level.

RESULTS

Clinical effects

Demographic and clinical characteristics of the three groups (i.e., responders, non-responders, and healthy controls) are presented in Table 1. There were no differences between responders and non-responders in terms of age, OLZ dosage, right handedness, duration of untreated illness, duration between the first PET scan and the second PET scan, and PANSS total score at baseline. There were also no differences between patients with schizophrenia and healthy controls in terms of age and handedness. Overall, patients in the responder group experienced significant improvements, as measured with the PANSS (Table 1).

SnPM analysis of responders or non-responders vs. healthy controls at pre- and post-treatment with OLZ

Pre-treatment: comparison with healthy controls

In responders, there were six significant clusters of hypermetabolism in bilateral superior temporal gyrus (STG) and bilateral cerebellar hemispheres, and three significant clusters of hypometabolism in the left inferior parietal lobule, right precuneus and right precentral gyrus ($p < 0.05$, FWE corrected; Table 2 and Figure 1A). In non-responders, there was a significant cluster of hypermetabolism in the right cerebellar hemisphere ($p < 0.05$, FWE corrected; Table 2 and Figure 1B).

Post-treatment: comparison with healthy controls

In responders, there were two significant clusters of hypermetabolism in the right putamen and left precuneus ($p < 0.05$, FWE corrected; Table 2 and Figure 1B). Non-responders exhibited a significant cluster of hypermetabolism in the left putamen.

SnPM analysis of responders vs. non-responders

There were no significant differences in metabolism between responders and non-responders before OLZ treatment. In addition, there were no significant differences in metabolism between responders and non-responders after OLZ treatment.

SnPM analysis of responders with pre- and post-treatment FDG-PET scan data

The SnPM13 analysis of pre- and post-treatment FDG-PET images in responders is shown in Table 3 and Figure 2. The results revealed three significant voxels exhibiting hypermetabolism in responders ($p < 0.05$, FWE corrected), in the left precentral gyrus, postcentral gyrus, and paracentral lobule. There was a significant voxel showing hypometabolism ($p < 0.05$, FWE corrected) in the left hypothalamus. In non-responders, no significant treatment-related metabolic differences were observed.

Correlation between differences in FDG-PET and differences in PANSS scores in responders during OLZ treatment

The score for 'suspiciousness/persecution' (P6) was positively correlated with metabolic changes in the right superior frontal gyrus ($p < 0.05$, FWE corrected; Table 4 and Figure 3). Some voxels in the right superior frontal gyrus that correlated with this PANSS score were consistent with brain regions metabolically normalized by OLZ treatment in responders.

DISCUSSION

Pre-treatment

We hypothesized that there would be some distinct differences between responders and non-responders before OLZ treatment, and that these changes may be associated with a positive response to OLZ. Although there was no difference in brain glucose metabolism

between responders and non-responders before treatment, responders showed significant increases in six clusters compared with healthy controls, in the bilateral STG and bilateral cerebellar hemispheres (Table 2). Non-responders showed significant increases in one cluster compared with healthy controls, in the right cerebellar hemisphere. Thus, the current results suggest that metabolic changes in the bilateral STG and bilateral cerebellar hemispheres in FES patients before OLZ treatment may be associated with a positive response to OLZ treatment.

Metabolic changes following OLZ treatment

In the present study, we evaluated differences in brain metabolic changes associated with OLZ treatment between responders and non-responders. Non-responders showed no significant metabolic changes with OLZ treatment. In contrast, responders exhibited significant increases in three voxels, and significant decreases in one voxel after OLZ treatment ($p < 0.05$, FWE corrected; Table 3). Responders showed significant metabolic changes in response to OLZ treatment in several different brain regions (Figure 2), which may help identify the brain regions affected by OLZ.

Previous studies have reported that the volume of the hypothalamus was enlarged (Tognin et al. 2012) or not changed (Klomp et al. 2012) in patients with schizophrenia compared with controls. In the present study, we found that glucose metabolism in the left hypothalamus was significantly decreased in FES patients ($p < 0.05$, FWE corrected; Table 3), and normalized by OLZ treatment in responders. Belvederi Murri et al. (2012) examined patients with first-episode psychosis and found that cortisol levels were associated with the severity of multiple schizophrenia symptoms. Issa et al. (2010) also reported a significant increase in cortisol levels in the prefrontal cortex and cerebrospinal fluid of subjects with schizophrenia compared with age-matched controls. In the present study, before OLZ treatment, 7 of 10

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patients exhibited relatively higher (but not significantly higher) glucose metabolic values at Talairach coordinates (−6, −6, −5) in the hypothalamus, compared with healthy controls. Following OLZ treatment, all patients exhibited decreased glucose metabolism (data not shown). These results suggest that OLZ may address abnormal hypothalamic function.

Correlation of FDG-PET and PANSS in responders

When determining correlations between FDG-PET and PANSS scores during OLZ treatment in responders, we found that glucose metabolism in the right superior frontal gyrus (BA9) and 'suspiciousness/persecution' (P6) symptoms were negatively correlated (voxel level, $p < 0.05$, corrected for FWE; Table 4 and Figure 3A).

To our knowledge, no previous longitudinal studies of symptoms and imaging in schizophrenia have reported a correlation between changes in brain activity and PANSS scores of 'suspiciousness/persecution'. In the present study, metabolic changes in the right superior frontal gyrus may represent the alleviation of excessive 'suspiciousness/persecution' (P6). 'Suspiciousness/persecution' is one of the warning signs of prodromal schizophrenia. Specifically, we found that the right superior frontal gyrus (BA9; dorsolateral prefrontal cortex; DLPFC) was positively correlated with the change in scores for 'suspiciousness/persecution' (P6). Overall, our results revealed that an OLZ treatment-related reduction in the hypermetabolism in the right superior frontal gyrus in the early stages of disease was associated with improved 'suspiciousness/persecution' scores.

There are a number of theories regarding the role of the cerebellum in schizophrenia. Lesions in the cerebellum and abnormalities of cerebellar non-motor functions have been reported to be associated with deficits in cognition, affective traits, verbal ability, learning, memory, and planning (Andreasen and Pierson, 2008). In the present study, prior to OLZ treatment, the cerebellum showed significantly higher glucose metabolic values in responders

compared with healthy controls. With OLZ treatment, glucose metabolism in the cerebellum was significantly decreased and normalized by OLZ treatment (Table 3 and Figure 2). These findings suggest that OLZ treatment improves cerebellar abnormalities in the early stages of the disease by decreasing metabolism.

The current study involved several limitations, including the small number of patients and the unequal numbers of males and females in our experimental sample. Because the sample size was small, type II errors and false negative results cannot be discounted. Moreover, the study period was limited in duration, and the long-term prognosis could not be assessed. Finally, the dose of OLZ (5–20 mg/day) was not standardized. No changes were observed in non-responders after OLZ treatment, which may indicate that the methodological approach was relatively insensitive to treatment-induced changes. As such, the absence of effects in some cases may have been secondary to the small sample size tested.

CONCLUSION

Using FDG-PET imaging, we examined glucose metabolism in neuroleptic-naive schizophrenic patients before and after treatment with OLZ. Metabolic differences in bilateral STG and bilateral cerebellar hemispheres in first-episode schizophrenic patients before OLZ treatment were observed in the OLZ treatment responder group. We identified several brain regions that were related to the improvement of symptoms in neuroleptic-naive first-episode patients with schizophrenia by evaluating brain metabolism in the neuroleptic-naive state, metabolic changes associated with OLZ treatment, and metabolism after treatment with OLZ using FDG-PET. These findings further our understanding of the neural mechanisms underlying the beneficial action of OLZ on metabolic abnormalities in the early stages of schizophrenia, and provide initial evidence for a correlation between the changes in PANSS

scores and metabolic changes before and after treatment with OLZ in neuroleptic-naive

first-episode schizophrenic patients with severe symptoms at baseline.

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Table 1. Demographic data for first-episode schizophrenic patients and healthy controls (mean ± S.D.) and PANSS scores for first-episode schizophrenic patients

	Healthy volunteers	First-episode schizophrenic patients	
		Responders (N = 10)	Non-responders (N = 5)
Male	8	7	2
Female	7	3	3
Right-handed	15	10	5
Age (years)	24.5 ± 3.01	23.1 ± 6.85	23.2 ± 7.16
Hospitalization	N/A	4	3
Outpatient	N/A	6	2
Auditory verbal hallucinations	N/A	8	5
Duration of untreated illness (weeks)	N/A	35.6 ± 66.7	39.17 ± 34.8
Duration between first PET and second PET (days)	N/A	48 ± 22.62	49 ± 24.14
Optimal therapeutic dosage of Olanzapine (mg)	N/A	13 ± 5.37	15 ± 5
PANSS total			
Pre-treatment	N/A	104.8 ± 17.04	113.4 ± 11.67
Post-treatment	N/A	46.4 ± 5.48*	102.8 ± 16.78
Positive scale total			
Pre-treatment	N/A	25.3 ± 3.37	32.2 ± 5.81
Post-treatment	N/A	10.5 ± 2.32*	27.8 ± 6.87
Negative scale total			
Pre-treatment	N/A	27.1 ± 6.74	29.6 ± 4.62
Post-treatment	N/A	12.6 ± 2.37*	26.8 ± 5.63
General psychopathology scale total			
Pre-treatment	N/A	52.4 ± 11.99	51.6 ± 6.80
Post-treatment	N/A	23.3 ± 3.53*	48.2 ± 9.12

PANSS = Positive and Negative Syndrome Scale. Patients in the responder group experienced significant improvements. Bonferroni's multiple adjustment was applied, with *$p < 0.00625$ (0.05/8).

Table 2. Brain regions showing significantly increased and decreased glucose metabolism in responders and non-responders compared with healthy controls

Region	BA or Subregion	Side	Cluster Ke	Talairach coordinates x {mm}	y {mm}	z {mm}	Peak T	Peak p (FWE-corr)
Responders (N = 10)								
Pre-treatment								
Increase								
Superior Temporal Gyrus	38	R	469	40	12	−21	7.94	0.0008
Cerebellum Anterior		L	125	−19	−53	−30	6.74	0.0068
Superior Temporal Gyrus	21	L	28	−47	−1	−16	6.60	0.0076
Cerebellum Posterior	Uvula	L	22	−25	18	−5	6.33	0.0136
Cerebellum Posterior	Semi-Lunar	R	59	16	−77	−35	6.11	0.0218
Cerebellum Posterior	Uvula	L	28	−17	−75	−34	5.94	0.0156
Decrease								
Inferior Parietal Lobule	40	L	54	−48	−43	44	6.22	0.0154
Precuneus	7	R	35	18	−72	54	6.15	0.0176
Precentral Gyrus	6	R	12	28	−18	68	5.91	0.0258
Post-treatment								
Increase								
Lentiform Nucleus	Putamen	R	58	30	−15	9	6.48	0.0094
Precuneus	7	L	5	−18	−27	55	5.77	0.0392
Decrease								
No significant differences								
Non-responders (N = 5)								
Pre-treatment								
Increase								
Cerebellum Posterior	Uvula	R	113	14	−77	−33	7.38	0.0112

<u>Decrease</u>

No significant differences

<u>Post-treatment</u>

<u>Increase</u>

Lentiform Nucleus	Putamen	L	3	−25	−3	0	6.45	0.0410

<u>Decrease</u>

No significant differences

BA = Brodmann's area; L = left; R = right; FWE-cor = family wise error-corrected; unc = uncorrected; Ke = the number of voxels in the cluster, threshold for voxel was set at FWE corrected $p = 0.05$, extent threshold {Ke} = 5

Table 3. Brain regions showing significantly increased or decreased metabolism after olanzapine treatment in first-episode schizophrenic patients (responders)

Region	BA or Subregion	Side	cluster Ke	Talairach coordinates x {mm}	y {mm}	z {mm}	peak T	peak p (FWE-cor)
Increase								
Precentral gyrus	4	L	19695	−17	−26	57	18.26	0.0020
Postcentral gyrus	2	L		−53	−20	34	13.30	0.0107
Paracentral lobule	5	L		−7	−38	51	12.14	0.0195
Decrease								
Hypothalamus	*	L	405	−6	−6	−5	12.66	0.0137

BA = Brodmann's area; L = left; R = right; FWE-cor = family wise error-corrected; unc = uncorrected; Ke = the number of voxels in the cluster, threshold for voxel was set at FWE corrected p < 0.05, extent threshold {Ke} = 300

Table 4. Significant correlation between changes in FDG-PET and changes in PANSS scores following olanzapine treatment in responders

PANSS	BA or Subregion	Side	Region	Cluster Ke	Talairach coordinates x {mm}	y {mm}	z {mm}	peak T	peak p (unc)
Positive correlation									
P6	9	R	Superior frontal gyrus	340	30	54	30	17.05	0.0002

P6 = suspiciousness/persecution; BA = Brodmann's area; R = right; Ke = the number of voxels in the cluster

Figure Legends

Figure 1. Responders: statistical non-parametric maps of two-sample t-test results

(A) Significant increases in glucose metabolism compared with healthy controls at

pre-treatment. (B) Responders: significant increases in glucose metabolism compared with

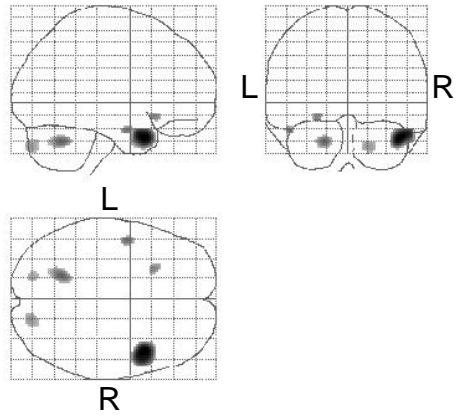healthy controls at post-treatment. Statistical significance was set at $p = 0.05$, FWE corrected.

Figure 2. Responders pre- *vs.* post-treatment: statistical non-parametric maps of paired t-test

results showing significant changes in glucose metabolism. Yellow and red regions represent

areas in which metabolism after OLZ treatment in responders was higher than before

treatment. Green and blue regions represent areas in which metabolism after OLZ treatment

in responders was lower than before treatment. Statistical significance was set at $p = 0.001$,

uncorrected.

Figure 3. Statistical non-parametric map of correlations between changes in PANSS score and

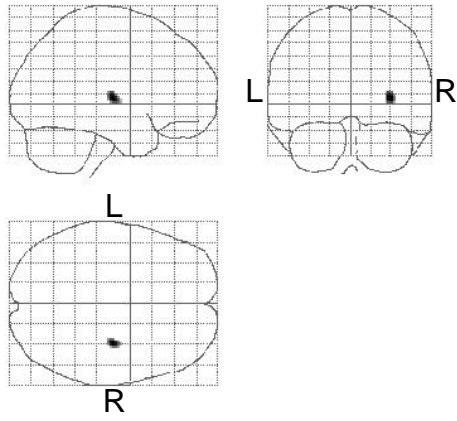metabolism in responders with acute first-episode schizophrenia during OLZ treatment.

Statistical significance was set at $p = 0.05$, FWE corrected; (Images pre-treatment – images

post-treatment) vs. (PANSS scores pre-treatment − PANSS scores post-treatment). (A)

Regions showing metabolic changes that were negatively correlated with changes following

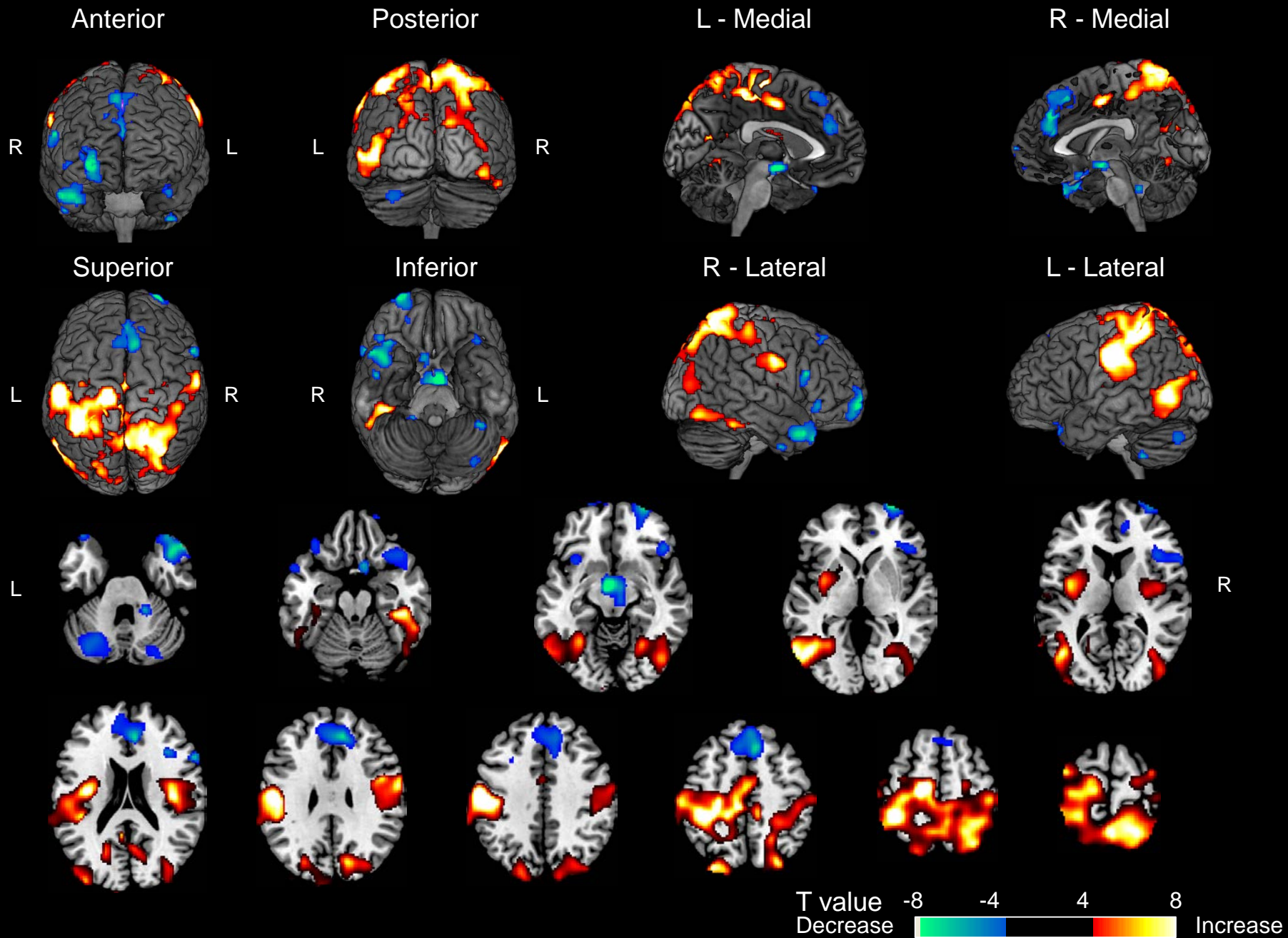OLZ treatment in 'suspiciousness/persecution' (P6) score.

A

B

L   R

L

R

L

R

L

R

Anterior   Posterior   L - Medial   R - Medial

Superior   Inferior   R - Lateral   L - Lateral

T value   -8   -4   4   8

Decrease   Increase

A P6-positive correlation