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Brain metabolism changes in women with BPD undergoing olanzapine treatment

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1. Introduction

Borderline personality disorder (BPD) is characterized by symptoms (e.g. impulsivity) that are difficult to treat (Soloff and Fabio, 2008). Research is needed to better understand both the underlying neural mechanisms of BPD and the mechanisms of existing treatments. Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) studies have identified hypometabolism in frontally mediated networks associated with impaired emotion processing and impulsivity in BPD (Mauchnik and Schmahl, 2010; Schulze et al., 2016; Soloff et al., 2000). Our FDG-PET cross-sectional data reported an association between frontal hypometabolism with hostility in BPD (Schulz et al., 2013).

Olanzapine reduces BPD symptoms (Schulz et al., 2008) and has induced metabolism changes in other psychiatric disorders (Guo et al., 2017). It is crucial to understand how olanzapine impacts identified frontal hypometabolism in BPD to better inform treatment development.

The current study used FDG-PET to measure brain changes associated with response to an eight-week olanzapine intervention. Because FDG-PET depicts glutamatergic synaptic activity coupled with glucose consumption, it allowed us to examine correlations between symptomatology change and (i) brain metabolism change and (ii) baseline metabolism.

The identification of neural changes underlying successful olanzapine treatment can inform future treatment strategies to better target these brain changes and optimize treatment outcomes in BPD.

2. Methods

2.1. Participants

We recruited 17 BPD female subjects aged 18–45 years old with a BPD diagnosis (DSM-IV). (Inclusion/exclusion criteria in Supplementary Material).

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Conflicts of interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychresns.2018.06.015.

2.2. Clinical assessments

Patients underwent a diagnostic assessment (Structured Clinical Interview, DSM-IV-TR), Structured Interview for DSM-IV Personality, a physical exam, blood tests and urinalysis. The Brief Psychiatric Rating Scale (BPRS), Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD), Barratt Impulsivity Scale (BIS), the Hamilton Depression Scale (HAM-D), and Buss-Durkee Hostility Index (BDHI), and Symptom Checklist 90 (SCL-90) were administered at baseline and every week during the eight-week administration of olanzapine.

2.3. Imaging procedures

Pre- and post-treatment FDG-PET scans were collected with a Siemens Biograph 16 (details in Supplementary Material).

2.4. Medication treatment procedures

After baseline FDG-PET scan, subjects were given olanzapine 2.5 mg daily. Dose was titrated up to 7.5 mg daily by week-4 and then held constant until the end of week-eight. Patients underwent a second FDG-PET scan after completing 8-weeks of olanzapine treatment.

2.5. Imaging analysis

Preprocessing for pre- and post-treatment FDG-PET data was conducted using FSL. The first emission scan was affine registered to standard space (Montreal Neurological Institute). The second emission scan was affine registered to the registered first emission scan and filtered (full width half maximum: 12 mm). After non-brain masking, each volume was scaled ($M = 1000$) and z -transformed. For analysis of metabolism change, the z -transformed first emission scan was subtracted from the z -transformed second emission scan.

2.6. Statistical analyses

To identify regions with significant pre-post treatment change, voxel-wise within-group paired t -tests were conducted (AFNI-3dttest). Linear regression analyses (AFNI-3dRegAna) evaluated the relationship between (a) change in metabolism pre- versus post-treatment with change in clinical measures, and (b) baseline metabolism with change on clinical measures. Thresholding, clustering and multiple comparison correction details in Supplementary material.

3. Results

Fourteen (of 17 recruited) subjects completed olanzapine treatment.

3.1. Clinical improvement

BPD patients showed significant clinical improvement (see Supplementary Material).

3.2. Change in brain metabolism

Pre-post olanzapine treatment comparison showed increased metabolism in left superior frontal gyrus, left medial frontal gyrus, left insula, left precuneus, right inferior temporal gyrus, bilateral inferior parietal lobule, and bilateral superior parietal lobule (see Supplementary Material Table).

3.3. Correlation between metabolism change and clinical improvement (Fig. 1A)

F-statistic maps showing the strength of the linear regression between change in ZAN-BPD scores and change in metabolism revealed significant correlations in the following clusters: (i) left middle/superior frontal gyrus ($r = -0.692$, $p = 0.009$), (ii) middle occipital gyrus/cuneus/posterior cingulate ($r = 0.767$, $p = 0.002$), (iii) paracentral lobule/cingulate gyrus ($r = 0.750$, $p = 0.003$), and (iv) right fusiform/parahippocampal gyri ($r = 0.726$, $p = 0.005$). *F*-statistic maps showed a significant negative correlation between SCL-90 scores change and metabolism change in superior frontal gyrus ($r = -0.631$, $p = 0.021$). *F*-statistic maps showed significant negative correlation between BIS scores change and metabolism change in right thalamus ($r = -0.740$, $p = 0.004$).

3.4. Correlation between baseline metabolism and clinical change: Metabolic predictors of olanzapine response (Fig. 1B)

ZAN-BPD.—Higher metabolism in left middle frontal gyrus predicted larger clinical improvement (larger ZAN-BPD score decrease) ($F_{1,13} = 12.18$, $p = 0.004$; $\beta = -0.710$, $p = 0.004$).

SCL-90.—Higher metabolism in a cluster comprised of right posterior cingulate gyrus and parahippocampal gyrus predicted larger clinical improvement (larger SCL-90 score decrease) ($F_{1,13} = 12.03$, $p = 0.005$; $\beta = -0.707$, $p = 0.005$).

4. Discussion

This study examined the effect of olanzapine on brain metabolism in BPD patients. Olanzapine treatment led to reduced BPD symptomatology and metabolism changes in distributed brain regions previously associated with severity and hostility in BPD (Schulz et al., 2013).

Significant correlations between brain metabolism changes and changes in specific BPD symptomatology domains showed discriminant validity. Frontal metabolism increase has been associated with better emotion regulation in individuals with BPD (Silvers et al., 2016). Importantly, frontal metabolism at baseline was predictive of clinical improvement (ZAN-BPD score decrease) (Ruocco et al., 2016). Clinical improvement associated with metabolism decrease in regions known to mediate sensory attention and emotion processing is consistent with higher attention to emotions characteristic of BPD (Winter, 2016). Finally, the association between decreased impulsivity and decreased thalamic metabolism highlight the proposed role of thalamus in decisional impulsivity (Wang et al., 2017).

4.1. Limitations

The number of subjects is relatively small, limiting statistical power. Second, due to the lack of a placebo arm, our correlational analyses do not allow us to confirm that the neural correlates of clinical improvement reported here are necessarily drug-related or if they might have also been observed in responders to placebo. Third, under the pilot nature of the study we did not correct for number of clinical assessments used. Larger-scale studies addressing these limitations need to be conducted.

This first report demonstrating regional metabolic changes after olanzapine treatment for BPD provides a starting point for understanding the underlying mechanism of this treatment regarding specific domains of illness. Identified neural correlates represent candidates for markers that predict treatment response to inform future interventions. Research comparing the neural effects of different medication classes, psychosocial interventions and combined treatments will help inform the development of more comprehensive treatment toward the goal of improved outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

A. Left. Significant correlations (warm colors show positive correlations; cold colors show negative correlations) between ZAN-BPD scores change and metabolism change in (i) left middle/superior frontal gyrus, (ii) middle occipital gyrus/cuneus/posterior cingulate, (iii) paracentral lobule/cingulate gyrus, and (iv) right fusiform/parahippocampal gyri. Middle. Significant negative correlation between metabolism change in superior frontal gyrus and SCL-90 scores change. Right. Significant negative correlation between metabolism change in right thalamus and BIS scores change. Fig. 1B. Left. Higher baseline metabolism at baseline in left middle frontal gyrus predicts clinical improvement (ZAN-BPD score decrease). Right. Higher baseline metabolism at baseline in right posterior cingulate gyrus predicts clinical improvement (SCL-90 score decrease). Maps overlaid on average MNI-152. Change=post-treatment – baseline.