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Duloxetine's modest short-term influences in subcortical structures of first episode drug-naïve patients with major depressive disorder and panic disorder

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ABSTRACT

We developed this study to follow up the hanges in subcortical structures after 6 weeks' treatment with therapy of duloxetine in first episode drug-naïve patients with major depressive disorder and panic disorder. Fifteen patients received duloxetine 60 mg/d therapy for 6 weeks and achieved remission. They all underwent structural magnetic resonance imaging (MRI) of the brain at baseline and week 6. Fifteen healthy controls were also scanned twice at baseline and week 6 to exclude possible biases. Structural MRI data were preprocessed with FMRIB's Integrated Registration and Segmentation Tool function (FIRST version 1.2) of FSL (FMRIB Software Library; version 4.1.1) to perform subcortical segmentations of the brain using a shape and appearance model. Nonparametric corrections of these structural volumes in an *F*-test between pre- and post-treatment were used to identify the changes after duloxetine therapy. A false discovery correction of the *F*-test by FIRST was also performed. A paired t-test using SPSS was applied to confirm the changes in these structures. The patients had consistent changes of volumes in bilateral nucleus accumbens, left putamen, left hippocampus and brainstem after 6 weeks of treatment with duloxetine. There were no consistent changes in other subcortical structures. There were modest increases of the volumes of the above areas, which were not significant after false discovery correction by FIRST *F*-test comparisons. The volumetric increases were correlated with responses of clinical symptoms. The results suggested that duloxetine possibly contributed to modest increases in several subcortical areas of these patients with remission.

1. Introduction

Major depressive disorder (MDD) co-morbid with panic disorder (PD) is prone to be associated with more severe and early-appearing form of illness (Grunhaus et al., 1994). It has been reported that MDD has important moderating effects "important moderating effects on patterns of comorbidity for PD" (Biederman et al., 2005).

MDD is usually associated with structural and functional deficits in limbic structures. Higher activity in the nucleus accumbens (NAc) in response to fearful faces and lower activity in response to happy faces have been reported in subjects at risk for MDD (Monk et al., 2008). The decrease of mesolimbic dopaminergic innervations in the NAc has been related to anhedonia, affective flattening and psychomotor retardation in MDD (Bragulat et al., 2007). The putamen has been associated with symptoms of anhedonia in MDD, and dysfunction of the basal ganglia probably influences the consummatory phase of reward processing (Pizzagalli et al., 2009). In a meta-analysis of magnetic resonance imaging (MRI) findings, MDD patients had moderate volumetric decreases in subcortical structures such as the putamen and hippocampus (Koolschijn et al., 2009). Geuze et al. suggested that MDD patients had hippocampal volume loss in their review of data-driven studies (Geuze et al., 2005). Hippocampal volumes in currently depressed patients have been reported to be lower than those of remitted MDD patients and to be inversely correlated with the length of illness (Caetano et al., 2004). Neumeister et al. found smaller total and posterior hippocampal volume in drug-naïve MDD and this type of atrophy appears to be a trait characteristic for MDD (Neumeister et al., 2005). The changes of hippocampal structure are associated with chronic stress, memory problems, poor clinical outcomes, treatment resistance and cortisol toxicity in MDD (MacQueen and Frodl, 2011). Cannon et al. also found that serotonin transporter binding was higher in several brainstem regions of MDD patients, including periaqueductal gray matter and pontine raphe nuclei. This result supports the role of brainstem serotonin in the pathophysiology of MDD (Cannon et al., 2007).

Parent et al. indicated that the NAc or the putamen might regulate the inhibitory neurotransmitter GABA (Parent et al., 2002) and, accordingly, our model of MDD+PD invokes a possible dysregulation of inhibition in the NAc or the putamen. In a voxel-based morphometry study, a putaminal gray matter volume decrease was found in PD patients and was also associated with the severity of

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illness and duration of illness (Yoo et al., 2005). The decrease of inhibitory neurotransmitter in the hippocampus and possible changes of basal/compensatory regulation also may contributes to PD pathophysiology (Hasler et al., 2008). Increased gray matter volume in the midbrain and rostral pons were found in a small-sample study, which suggested structural abnormalities in the brainstem of PD patients (Protopopescu et al., 2006).

Duloxetine, a kind of serotonin and norepinephrine reuptake inhibitor, probably can cause subtle changes of gray matter volumes in patients with remitted MDD combined with PD (Lai and Hsu, 2011). It suggested that duloxetine treatment might be associated with gray matter volume increase in left inferior frontal cortex, right occipital fusiform gyrus and right cerebellum (Lai et al., 2010). Frodl et al. also reported that continuous antidepressant treatment might contribute to subtle increases of hippocampal volumes (Frodl et al., 2008). From the above review of studies, we hypothesized that duloxetine might induce volumetric changes of subcortical structures, such as the putamen, NAc, brainstem and hippocampus in remitted patients with MDD combined with PD. In this investigation, we also used a new analytic tool for subcortical structures, FMRIB's Integrated Registration and Segmentation Tool function (FIRST version 1.2) of FSL (FMRIB Software Library; version 4.1.1), to confirm MRI changes after 6 weeks of therapy with duloxetine in these patients. We focused on subcortical structures due to the application of the FIRST program and the fact that these regions are considered important in MDD and PD.

2. Methods

2.1. Participants

This study was approved by the Institutional Review Board, Buddhist Tzu-Chi Hospital Taipei Branch. The criteria of selection for patients were as follows: (1) First episode of concurrent MDD and PD, with psychiatric diagnoses being made on the basis of DSM-IV criteria and the Structured Clinical Interview for DSM-IV. (2) No other psychiatric illnesses except MDD or PD and no concurrent serious medical illnesses. (3) The severity of MDD and PD was at least moderate: Clinician Global Impression of Severity>4, Quick Inventory for Depressive Symptoms-Self Rating 16-item version (QIDS-SR16)>19, Hamilton Depression Rating Scale (HDRS) score>24, Panic Disorder Symptom Severity Scale (PDSS)>15, and occurrence of full blown symptoms of panic attacks>4 times within previous 4 weeks before the baseline visit. (4) No cognitive behavioral therapy or other forms of psychotherapies. (5) Drug-naïve for psychotropic medicine (no previous treatments). (6) No alcohol and substance abuse or dependence. (7) No past history of claustrophobia or discomfort when undergoing MRI. Rating scale assessments were performed at baseline and at weeks 3 and 6. We also used the Panic and Agoraphobia Scale to measure and identify co-morbid agoraphobia. All the patients received duloxetine therapy as 60 mg/d for 6 weeks. If the patients' HDRS scores were lower than 9 and if their PDSS scores were lower than 5, they were classified as “remitted patients”. No concurrent psychotherapies, including cognitive behavioral therapy or other forms of psychotherapeutic input (including occupational therapy), were performed on these patients. The healthy controls had no psychiatric illnesses or medical illnesses. The controls were all interviewed by a psychiatrist, received ratings on all the above scales, and had scores that were lower than the symptomatic threshold for MDD or PD. The information about physical illness was based on the past history of medical records. At the time of baseline MR imaging, all these participating subjects (patients and controls) were free of psychotropic medications. Handedness was determined by using the Edinburgh Inventory of handedness (Oldfield, 1971). The second MR scans were performed at week 6, and and all the patients received duloxetine treatment at that time. The patient population was a part of our previous report (Lai et al., 2010).

2.2. Behavioral data statistical analysis

All the rating scale data were processed using SPSS 16 (SPSS Inc, Chicago, Illinois). The ANOVA (analysis of variance) test was performed to compare the rating scale scores at baseline and at weeks 3 and 6. Post-hoc correction (Scheffé's test) was performed in multiple comparisons between the scores at these time-points and to reduce type I errors.

2.3. MR imaging procedure

2.3.1. Data acquisition

Structural MRI scans for patients and controls were obtained with a 3 T GE scanner housed at the Buddhist Tzu-Chi Hospital Taipei Branch. Scans with three-dimensional fast spoiled gradient-echo recovery (3D-FSPGR) T1W1 (TR = 11.2 ms, TE = 5.2 ms, matrix = 256×256, field of view = 260 mm, number of excitation = 1, slice thickness = 1 mm, 180 slices, no gap) were performed in all participating subjects at baseline and week 6.

2.3.2. FIRST analysis of subcortical structures and vertex-wise analysis

We used the FIRST function of FSL to compare the subcortical structures of these participating subjects at baseline and week 6 with remission. FIRST is a part of FMRIB Software Library (FSL; version 4.1.1) and performs both registration and segmentation of the mentioned subcortical regions. The reliability of subcortical segmentation is comparable to the well-established tool FreeSurfer and showed highly reliable results for segmentations in subcortical structures (Morey et al., 2010). FIRST is based on shape/appearance models, which are constructed from a large set of manually labeled (317 brains) and segmented images from the Center for Morphometric Analysis (MGH, Boston), and use a Bayesian probabilistic approach. The shape and appearance model is based on multivariate Gaussian assumptions and constructed from a library of manually segmented images. The deformable surfaces will be parameterized as surface meshes containing volumetric labels and then modeled as point distribution. Using the learned model, FIRST searched through shape deformations that were linear combinations of the models of variations (principal components) to find the most probable shape given the observed intensities from the input image. The principal components of variations and most probable shape instance in the model will be used to construct the shape. FIRST used T1 images with NIFTI headers and segmentation was performed with two-stage affine transformation to the standard space of Montreal Neurological Institute (MNI) atlas 152 at 1-mm resolution. The processing steps were as follows: First, the subcortical structures of each participating subject were registered with a standard 12 degrees of freedom to the template. Then the registered images were registered again using an MNI 152 subcortical mask to exclude voxels outside the subcortical regions.(de Jong et al., 2008; Morey et al., 2009). Second, the segmented images were used to produce mesh and volumetric outputs with boundary correction. Boundary voxels were thresholded at $z = 3$, along with the recommended number of iterations. The boundary voxel threshold is an important parameter that represents the z-score of the amount of noise in the boundary voxels. FIRST includes these boundary voxels as part of the segmented region. Voxels were classified as “boundary” due to the ambiguity of their structural characteristics, which were usually located at the borders between adjacent structures (Seror et al., 2010). The vertex information or models were automatically transformed back to native space by FIRST using the inverse transformation matrix where the boundaries were corrected and labels were generated. Third, the summary images of the segmentation outputs were checked for