Journal of Affective Disorders 208 (2017) 68–75

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Alterations in the brainstem volume of patients with major depressive disorder and their relationship with antidepressant treatment

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ARTICLE INFO

Keywords:
Brainstem
Midbrain
Pons
Major depressive disorder
Antidepressant

ABSTRACT

Background: Morphologic changes of the brainstem in major depressive disorder (MDD) have rarely been reported in neuroimaging studies, even though, monoaminergic neurotransmitters are synthesized in several brainstem regions. We aimed to investigate volume changes in each region of the brainstem and their association with antidepressant use or the remission status of MDD.

Methods: A total of 126 patients with MDD and 101 healthy controls underwent T1-weighted structural magnetic resonance imaging. We analyzed volumes of each brainstem region, including the medulla oblongata, pons, midbrain, and superior cerebellar peduncle, and the volume of the whole brainstem using the FreeSurfer.

Results: The patients with MDD had significantly greater midbrain volumes (P=0.013) compared to healthy controls. In particular, drug-naïve patients with MDD had significantly greater brainstem volumes compared to healthy controls (P=0.007), while no significant findings were observed between the antidepressant treatment group and healthy controls. The remitted patient group had reduced pons (P=0.002) and midbrain (P=0.005) volumes compared to healthy controls, while the non-remitted MDD patient group had significantly greater midbrain volumes compared to the healthy controls (P=0.017).

Limitations: We could not distinguish gray versus white matter volumes changes in our analysis.

Conclusions: We observed that the midbrain is enlarged in patients with a current depressive episode, who are not undergoing antidepressant treatment. This volume then returns to normal after antidepressant treatment, and is even reduced, when the patient is in remission. Further studies are needed to confirm our observations.

1. Introduction

Major depressive disorder (MDD) is currently one of the most common psychiatric disorders worldwide and may affect the quality of life of patients (Papakostas et al., 2004). Numerous studies have focused on the underlying neurobiological mechanism of MDD and have suggested the presence of structural and functional alterations in brain regions affected by the interplay of genetic and environmental factors in patients with MDD (Kupfer et al., 2012). Recent neuroimaging studies have indicated that patients with MDD have volumetric reductions in the anterior cingulate, the orbitofrontal and prefrontal cortices, and the hippocampus, and these studies have also reported changes in the emotional and reward processing functions of the amygdala, the insula, and the ventral striatum in patients with MDD (Bora et al., 2012a; Koolschijn et al., 2009; Rive et al., 2013). However, unlike other brain regions, the role of the brainstem in psychiatric disorders such as MDD is less well known.

Several nuclei in the brainstem are interconnected to cortical regions involving emotional, cognitive, and behavioral functions (Lee et al., 2015). In addition, the brainstem may be one of the most important neural substrates in the neurobiology of MDD. The dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is considered to be one of the most consistent findings in the pathophysiology of MDD (Aihara et al., 2007). Furthermore, the HPA axis is regulated by several neural systems, including those of the brainstem (Smith and Vale, 2006; Watson and Mackin, 2006). The neurobiology of MDD is

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http://dx.doi.org/10.1016/j.jad.2016.08.066
Received 15 June 2016; Received in revised form 12 August 2016; Accepted 27 August 2016
Available online 11 October 2016
0165-0327/

also deeply implicated in deficits of monoaminergic neurotransmitters such as serotonin (5-HT), norepinephrine (NE), and dopamine (DA). In fact, the synthesis of these neurotransmitters mainly occurs in several nuclei of the midbrain and pons, such as the dorsal raphe nucleus, locus coeruleus, and the ventral tegmental area (VTA) (D'Ardenne et al., 2008; Gervais and Rouillard, 2000). Neurochemical disturbances in these monoaminergic systems lead to the impairment of emotional processing and mood regulation (Kupfer et al., 2012). Lesions within brainstem nuclei, such as raphe nuclei, locus coeruleus, and the periaqueductal gray, may induce symptoms that mimic depression in animals (Hillegaart, 1990; Rizvi et al., 1992; Simson and Weiss, 1988).

Currently, there are few studies on the functional and structural alterations of the brainstem and their correlations to the pathophysiology of MDD. Previous transcranial sonography (TCS) studies, conducted by Becker et al., provided evidence of structural brainstem alterations in patients with MDD (Becker et al., 1995, 1994). They suggested that patients with MDD have decreased echogenicity of the brainstem raphe. There are conflicting research results regarding the structural changes of the brainstem in patients with MDD. Soriano-Mas et al. (2011) reported increases in white matter volume within the upper brainstem tegmentum of patients with melancholic depression. Furthermore, another recent neuroimaging study also reported that the depressive patients with anxiety symptoms showed increased midbrain volume compared to healthy controls (Qi et al., 2014), while our previous study (Lee et al., 2011) using voxel-based morphometry (VBM) in 47 patients with MDD reported a reduction in gray matter concentration in the region of the midbrain encompassing the dorsal raphe nucleus. In regards to microstructural changes of white matter tracts, recent studies using diffusion tensor imaging (DTI) have reported lower fractional anisotropy in the midbrain (Bessette et al., 2014) and an increased mean diffusivity in the pons (Abe et al., 2010) in patients with MDD compared to healthy control participants. However, results of the above-mentioned studies relied on a relatively small sample sizes (Soriano-Mas et al., 2011, 70 patients; Lee et al., 2011, 47 patients; Qi et al., 2014, 38 patients; Abe et al., 2010, 21 patients; Bessette et al., 2014, 31 patients) and did not investigate the effect of antidepressant treatment or remission status on structural changes of the brainstem.

Previous imaging studies suggested that antidepressant treatment was associated with gray matter volume change of dorsolateral prefrontal cortex (Smith et al., 2013) and subcortical structures (Talati et al., 2015). Meta-analysis of 41 volumetric MRI studies by Bora et al. found that antidepressant use was associated with volume change in orbitofrontal and anterior cingulate cortex (Bora et al., 2012b). Other studies reported that remission status in patients with MDD was related with changes in cortical gray matter volume (Phillips et al., 2012; Salvadore et al., 2011), thickness (Phillips et al., 2015), shape and curvedness (Liao et al., 2013), and hippocampal volume (Phillips et al., 2015). Even though, there have been no studies investigating association of brainstem volume change with antidepressant treatment or remission status, considering the results of neuroimaging studies regarding other brain regions and that midbrain and pons play a pivotal role in monoamine neurotransmission (Hale and Lowry, 2011; Heshmati and Russo, 2015), there is a possibility that antidepressant treatment or remission status might influence the brainstem volume. Previous positron emission tomography (PET) study reported that remitted MDD patients after 3 months of antidepressant treatment showed decreased midbrain activity compared to non-remitted patients, which also supports this theory (Milak et al., 2009).

Therefore, in the present study, we aimed to investigate changes in the volumes of different brainstem regions in patients with MDD with a larger sample size. In addition, considering the absence of studies focused on the effects of psychotropic medication or remission status on morphologic changes in brainstem regions, we also aimed to elucidate the association between antidepressant use or remission status of the patient and volume changes in brainstem regions. Our *a priori* hypotheses were as follows: 1) There might be a significant difference in the volume of the midbrain and the pons between patients with MDD and healthy controls; 2) There might be a significant difference in the volume of the midbrain and the pons among the subgroups determined by antidepressant treatment and healthy controls; 3) There might be a significant difference in the volume of the midbrain and the pons among the subgroups determined by remission status and healthy controls.

2. Methods

2.1. Participants

A total of 126 patients diagnosed with MDD were recruited from the outpatient psychiatric clinic of Korea University Anam Hospital, located in Seoul, Republic of Korea. We included adults diagnosed with MDD, aged 18–65 years. The diagnosis of MDD was made by a board-certified psychiatrist based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria, and confirmed by an independent psychiatrist using the Structured Clinical Interview for DSM-IV-TR Axis I disorders (SCID-I). The concordance of the diagnoses for MDD was 0.95. The exclusion criteria were as follows: (1) presumptive primary comorbid diagnosis of any other major psychiatric illness (based on DSM-IV-TR criteria) on Axis I or Axis II within the last 6 months; (2) MDD with psychotic features; (3) serious or unstable medical illness; (4) primary neurological illness, such as cerebrovascular disease, Parkinson's disease, or epilepsy, and (5) any contraindication for MRI. We assessed the duration of the illness an interview using the life-chart methodology. One hundred and one healthy participants aged 18–65 years without a history of psychiatric illness were recruited from the community to serve as the control group. Two board-certified psychiatrists independently evaluated the healthy control participants with full psychiatric assessment to detect present or past history of any Axis I or Axis II diagnosis. The same exclusion criteria as those used for patients with MDD were applied to the healthy control group. All participants in both groups were right-handed, as assessed by the Edinburgh Handedness Test (Oldfield, 1971). The severity of the depressive symptoms in participants in both groups was evaluated on the same day as the MRI scans, using the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). Upon study enrollment, 71 patients with MDD were taking antidepressants and 55 patients were medication-naïve. Among the 126 patients with MDD, 30 patients were in remission. Remission was defined as a score of 7 or lower in the HDRS upon study enrollment. The details of the patients are described in Table 1. The study protocol was approved by the Institutional Review Board of the Korea University Anam Hospital, and all methods in this study were carried out in accordance with the approved guidelines and the Declaration of Helsinki. All subjects gave written informed consent to participate in the study after a full explanation and understanding of the study in accordance with the Declaration of Helsinki.

2.2. MRI data acquisition

MRI scans were acquired parallel to the anterior commissure–posterior commissure line using a 3.0 T Siemens Trio whole-body imaging system (Siemens Medical Systems, Iselin, NJ, USA), using T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) with the following parameters: 1900 ms repetition time, 2.6 ms echo time, 220 mm field of view, 256×256 matrix size, 1 mm slice thickness, 176 coronal slices without gap, 0.86×0.86×1 mm^3 voxels, 16° flip angle, number of excitations =1.