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ORIGINAL ARTICLE

The impact of external stress factors on hippocampus volume during antidepressant treatment

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Abstract
Background and objectives: Magnetic resonance imaging (MRI) studies suggest that depression is associated with volumetric hippocampal changes. Investigations of these structures during antidepressant therapy is therefore important, however, volumetric studies are rare in this case. We aimed to study the effect of AD treatment on volumetric changes in hippocampus depending on stress factors in depressive patients.
Methods: Thirty patients with major depressive disorder (MDD) underwent MRI of the brain on the day of admission and at the time of stabilization of acute depressive symptomatology by venlafaxine. The presence of long-lasting stress factors in these patients was investigated by the social readjustment rating scale questionnaire.

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Results: No significant differences were found in hippocampi volumes before and after venlafaxine treatment. However, regression analysis revealed significant positive relation between stress factors and volumetric hippocampus change during AD treatment.
Conclusion: It seems that antidepressant treatment by venlafaxine could be more suitable in the MDD patients with presence of stress-factors.

Introduction

The hippocampus represents a major brain region within limbic system which is critical in diverse cognitive and emotional processes.[1,2] Moreover, the studies have linked depression to structural and cellular alterations, such as neuronal loss and synaptic dysfunction, in cortico-limbic brain regions controlling mood and emotions.[3] The objective neuroimaging studies revealed a significantly lower volume of hippocampus in patients suffering from major depressive disorder.[4,5,6] However, the volumetric changes of the hippocampus are affected not only by depression alone, but also by other factors associated with depressive disorder. Meta-analysis revealed that the reduction of hippocampal volume was particularly marked among patients with major depressive disorder (MDD) whose duration of illness was longer than 2 years or who had more than 1 disease episode, whereas was independent on age at onset of disease, severity of depression and sex.[7] With respect to antidepressant (AD) treatment, the possible regrowth of hippocampus after treatment was supported by one study.[8]

Recent studies pointed to importance of stress and stress-related pathways in depressive disorder.[9] In particular, the hippocampus is highly sensitive to long-lasting stress as important pathomechanism leading to neurobiological changes in hippocampus volumes.[1] Specifically, one of the severest factors is child maltreatment, which is associated with remarkable functional and structural later changes resulting in reduced hippocampal volume in adulthood.[10,11] Furthermore, the childhood maltreatment is associated with reduced volume in dentate gyrus and cornu ammonis, which are the most stress or glucocorticoid sensitive subfields of the hippocampus.[12] Additionally, types of maltreatment in a specific age in males (neglect at age 7) and females (abuse at ages 10, 11, 15 and 16) are the most significant predictors of hippocampal volumes in adult age.[13] Thus, stressful life events play a crucial role in decreasing gray matter volume including hippocampus within a time period lasting at least 3 months already in healthy adults.[14]

However, the studies related to the impact of external stress factors on volumetric hippocampus changes dependent on antidepressant treatment in adult patients with major depressive disorder are rare. Therefore, we addressed the hypothesis that hippocampal volume may be altered by AD treatment with respect to stress factors. We aimed to study hippocampal volume in patients with the major depressive disorder with respect to long-lasting stress factors using magnetic resonance imaging.

Methods

Subjects

The study consisted of patients with moderate and severe depressive episodes hospitalized at the Psychiatric Clinic of the University Hospital Martin for the year 07/2016 to 07/2018. The MDD diagnosis, single or recurrent episode, moderate or severe severity without mixed and atypical features was assessed according to the DSM-5 criteria[15] by the consensus of two independent specialist- psychiatrists. The exclusion criteria were as follows: a history of serious neurological diseases, head trauma, unstable hypertension, myocardial infarction or ischemia, Cushing's disease, a history of steroid therapy, current drug or alcohol abuse, neurological treatments potentially affecting CNS.

All patients were treated with AD treatment by serotonin and norepinephrine reuptake inhibitors (SNRI) venlafaxine with a dose of 150—375 mg. The duration of acute treatment of a depressive episode was the time interval between a patient's admission and the stabilization of acute depressive symptomatology based on clinical examination by specialist-psychiatrist.

Clinical global impression–severity (CGI-S score) was performed by the attending physician with a 7-point CGI questionnaire (0-normal–7-extremely ill) at regular weekly intervals throughout the hospitalization period. The CGI is a brief assessment tool in psychiatry that measures illness severity, global improvement or change and therapeutic response.[16] This instrument provides the clinician's view of the patient's global functioning and it is used for the assessment of improvement in daily life complex functioning of the patients consisting of several activities important for quality of life, e.g. self-management, workload, family functioning etc. The CGI-S patient score on admission was 4—7. The stabilization of acute depressive symptomatology was defined by achieving a CGI-Improvement (CGI-I) score of 2 or less (2-much improved, 1-very much improved). The severity of external stress factors was evaluated using the 43-item Social Readjustment Rating Scale (SRRS) questionnaire.[17] This scale was created by Holmes and Rahe in the late 1960s as a tool for predicting the probability of developing a stress-related disorder. This questionnaire assigns a value to a life changing unit (e.g. death of spouse, divorce, personal injury or illness). Acute stress is usually defined as an abrupt, short-lasting (seconds to hours timescale) and isolated perturbation, whereas chronic stress is recurring, persisting for several hours a day for weeks, months or longer.[18] The-

refore, we used the SRRS questionnaire for assessment of the long-lasting stress factors whose consequences persist until the patient's admission. The scoring took place at the time of admission of the patient in the form of a moderated interview, which examined the individual items of the questionnaire. Only the presence of those stress factors that occurred within the year prior to hospitalization was considered in the evaluation. Stress factors considered as a result of depressive symptoms, such as reduced appetite, change in social habits, or medical examinations for psychosomatic problems were not taken into account. The assessment of the presence of external long- lasting stress factors was made by two case independent expert psychiatrists who had to agree on the resulting score. As a result of the SRRS score, patients were divided into two groups. The first group of depressive patients without the presence of long-lasting stress factors consisted of patients with a SRRS score of less than 30, while the second group of depressive patients with the presence of long- lasting stress factors consisted of patients with a SRRS score of 30 or more. The 30-point threshold was arbitrarily determined because of the fact that patients with this maximal value had a history of long- lasting stress factors with minimal traumatizing effects (e.g., change in habits, social activities, conditions), while the life of those with a higher score had more traumatic potential (from trouble with the boss through to the death of a close friend to the death of a spouse).

The study was approved by the Ethics Committee of the Jessenius Faculty of Medicine in Martin, the Comenius University in Bratislava, Slovakia. All the procedures performed in our study were in accordance with the 1964 Helsinki declaration. All patients participating in this study signed an informed consent with MR examination and study enrollment.

Procedures

Volumetric measurements of patients were performed twice: on the first day of admission to acute psychiatric hospitalization, and the second time on the day of regression of depressive symptoms according to a CGI improvement score of 2 or less. The time between the first and second measurements represents the time of hospitalization which lasted at least 14 days.

MRI data acquisition

The subjects were scanned by using a 1.5T Siemens Symphony scanner equipped with an 8- channel head coil. T1-weighted sagittal images were acquired using a 3D magnetization- prepared rapid gradient echo (MPRAGE) sequence with the following parameters: TR = 2080 ms; TE = 3.93 ms; TI = 1100 ms; FOV = 250 mm; flip angle = 15°; matrix size = 256 × 256, 192 slices; resolution = 1.0 × 1.0 × 1.0 mm^3.

Imaging processing

The T1-weighted structural images of all participants were processed with the FreeSurfer image analysis suite (version 5.3.0, http://surfer.nmr.harvard.edu). The ''recon-all'' standard procedure estimated the volume of brain regions using an automated segmentation process.[19] Regions of the hippocampus were considered in the following analysis. Before the recon-all pipeline, the images were visually inspected for excessive motion artifacts. No manual corrections were applied. All subjects used in this study were successfully processed in recon-all. Volume change is the difference in hippocampal volume after treatment and hippocampal volume before treatment.

Statistical analysis

The data was analyzed using R,[20] version 3.6.1, with the aid of the libraries robustbase,[21] car,[22] beeswarm.[23] The data was visualized by a boxplot overlaid with swarmplot. Dependence between a pair of variables was visualized by crossplot. Normality of data was assessed by the Quantile–Quantile plot with the 95% bootstrap confidence band. Normality was also tested by the Shapiro Wilk test. Wherever the test resulted in the rejection of the normality of the data, the Wilcoxon two-sample test was used to test the equality of the population medians. If the hypothesis of the normality was found tenable, the two sample *t*-test was used to test the equality of the population means. This procedure was used to compare hippocampus volumes before and after treatment; to compare the change in the volume of the hippocampus (the difference in volume after treatment and volume before treatment in hippocampus) between the groups of depressive patients without a presence of long-lasting stress factors and depressive patients with a presence of long-lasting stress factors. The relationship between the patient's stress score and the change in volumes of hippocampus were evaluated using a robust regression model.

Due to the fact that age and gender could represent physiological factors influencing hippocampus volume, the association between the difference of the size of hippocampus with the age, gender and venlafaxine dose of patients was assessed by the robust linear regression model with the interaction term. The interaction term allowed for different regression lines for male, female patients. For statistical significance, we considered the value $p \leq 0.05$.

Results

Changes in hippocampus

The studied MDD group (n = 30) included 18 women and 12 men aged from 18 to 74 years (54.8 ± 13.7 yrs). According to results of stress score in SRRS questionnaire, the MDD patients were divided into 2 groups: without presence of long-lasting stress factors (group 1), and with presence of long-lasting stress factors (group 2). All patients were right-handed. The duration of acute treatment ranged from 14 to 107 days (34.9 ± 24.9 days).

The MDD patients without the presence of long-lasting stress factors (group 1) showed nonsignificant trend towards decreased hippocampal volume after AD treatment in comparison to period before AD treatment (p = 0.123). In contrast, the MDD patients with the presence of long-lasting stress factors (group 2), the hippocampal volume was nonsignificantly higher after AD treatment compared to hippocampal volume before starting AD treatment (Table 1).

Table 1 Hippocampus volumes before and after treatment.

	Before treatment	After treatment	p value
Group of all patients	8085 ± 1176	8071 ± 1168	0.753
Group 1	7895 ± 1202	7771 ± 1164	0.123
Group 2	8195 ± 1179	8245 ± 1165	0.156

Group 1-the group of depressive patients without a presence of long-lasting stress factors, Group 2-the group of depressive patients with a presence of long-lasting stress factors. Data are expressed as average values in mm^3 ±SD.

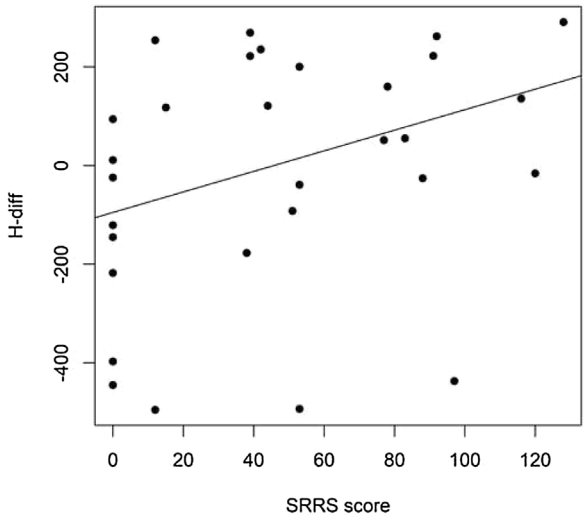

Figure 1 A significant correlation between score obtained in Readjustment Rating Scale questionnaire (SRRS score) and the change in volume of the hippocampus (H-diff). Black dots represent value of score obtained in Readjustment Rating Scale questionnaire score along with value of the change in volume of the hippocampus for a single depressive patient.

Linear regression model regarding the size of hippocampus with age and gender revealed that dependence was non-significant (p-values above 0.5, not shown) in the group of all patients, as well as in the both groups (with and without the presence of long-lasting stress factors).

The effect of long-lasting stress factors

Regression analysis revealed significant positive relation between stress factors and volumetric hippocampus change during AD treatment ($t = 2.299$, $p = 0.029$) indicating the higher SRRS score being associated with an increase in the hippocampus (Fig. 1). In addition, the hippocampal volume was significantly lesser in the MDD patients without long-lasting factors (group 1) compared to the MDD patients with long-lasting factors (group 2) ($p = 0.047$, Fig. 2, Table 2).

Discussion

The major findings of the study were as follows: (1) in the whole patient group, no significant differences were found in hippocampal volumes before treatment and after treatment; (2) with respect to stress factors, the change of hippocampal volume was significantly increased in the MDD group with presence of long-lasting factors, and significant positive relation was found between stress factors and volumetric hippocampus change during AD treatment. Several mechanisms are supposed.

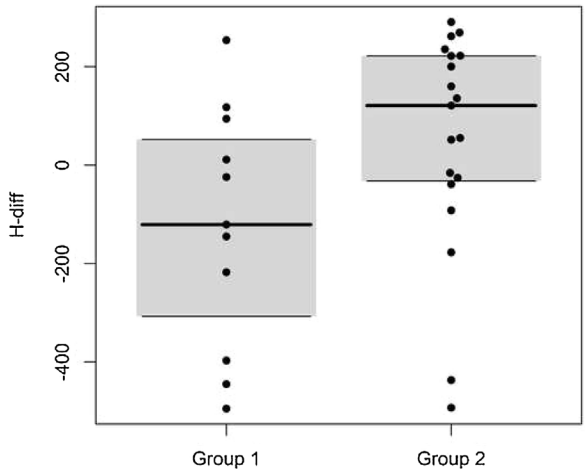

Figure 2 A significant difference in the change of volume of the hippocampus (H-diff) between the group of depressive patients without a presence of long-lasting stress factors (Group1) and the group of depressive patients with a presence of long-lasting stress factors (Group 2). Solid dots represent the values of change in volume of hippocampus for a particular depressive patient.

Table 2 Changes in hippocampus volume in depressive patients without a presence of long-lasting stress factors (group 1) and with a presence of long-lasting stress factors (group 2).

	Group 1	Group 2	p value
H diff	−124.46 ± 244.78	49.58 ± 224.93	0.047

In the case of the hippocampus, experimental studies demonstrated the increase of neurogenesis as a result of AD treatment[24,25,26] and after electroconvulsive therapy.[27,28] Similarly, experimental studies revealed that antidepressant treatment such as imipramine could restore the total number of cells in the hippocampus impaired by social defeat stress in mice,[29] and this treatment increased the number of hippocampal neurons in genetic rat depressive model characterized by impaired cell proliferation.[30] In humans, recent study revealed larger hippocampal tail volume after AD treatment (including venlafaxine) in the MDD patients compared to controls that is positively related to clinical remission. Thus, the hippocampal tail volume is proposed as a potentially useful biomarker of sensitivity to AD treatment.[31] Regarding neuropsychological changes, the meta-analysis reported that antidepressants could decrease the hypersensitivity to negative stimuli by decreasing hippocampus hyperactivation via a regulation by dorsolateral prefrontal cortex.[32] To the best of our knowledge, in human studies only one study supported an increase of hippocampal volume after long-term AD treatment lasting 3 years.[8]

In contrast, other studies revealed no significant changes of hippocampal volume after short-term AD treatment until one year.[33,34] Thus, we suggest that duration of AD treatment could play an important role in our study. Specifically, the duration of acute treatment in our patients was 14–107 days; thus, it seems that acute short-term duration of SNRI treatment is not sufficient to evoke significant changes of hippocampal volume in the whole patient group. In other words, we suggest that a longer time of venlafaxine treatment is needed for detection of detectable changes in hippocampus volume.

Further, the stress could represent important pathomechanism leading to abnormalities of the hippocampal volume in response to AD treatment. We firstly revealed significant positive relationship between SRRS score and the change in volume of the hippocampus. Further, the MDD group with long-lasting stress factors showed significantly increasing hippocampal volume during AD treatment compared to the MDD patients without stress factors.

The animal studies indicate several positive effects of the venlafaxine on hippocampus affected by chronic mild stress and depressive disorder. With respect to stress, recent studies emphasized the role of growth factors such as brain derived neurotrophic factor (BDNF) in neurogenesis in brain regions including hippocampus. Specifically, the BDNF decrease was observed in hippocampus of rats, which were exposed the chronic unpredictable stress.[35] From this perspective, Demirdas et al.[36] concluded that the venlafaxine prevents of decrease of the BDNF which is observed in depression-induced rats. Therefore, it seems that venlafaxine could play an important role on stress-related changes of hippocampal volume. More specifically, according to Duman's molecular and cellular theory of depressive disorder,[37] the volume of the hippocampus decreases by disrupting negative feedback on the hypothalamus-pituitary-adrenal axis (HPA) resulting in an increase of the cortisol levels associated with toxic effect especially on CA3 pyramidal hippocampal cells. Further, prolonged stress causes HPA dysregulation with increased levels of glucocorticoids leading to a decrease of hippocampal volume, disruption of hippocampal neurogenesis and increase extracellular glutamate in hippocampus.[38] Excess of glutamatergic transmission in the hippocampus may worsen cell damage and induce cell death which ultimately resulting in a reduction of hippocampal volume under the prolonged stress condition.[39] In this aspect, experimental studies revealed stimulative effect by venlafaxine on hippocampal cell proliferation,[40,41] and venlafaxine treatment fully ameliorated the effects of chronic unpredictable mild stress on the specific kinase (mTORC1) in signaling cascade of depressive processes in the brain of mice.[42] Moreover, the venlafaxine treatment results in decrease of overexpression of hippocampal S100B protein (calcium-binding protein B) in rats, which is increased in stress circumstances and depression.[43] Based on these studies, we suggest complex pathways leading to protective effect of the venlafaxine on stress-related abnormalities of hippocampal volumes associated with MDD.

Additionally, the venlafaxine has been shown to be effective and well tolerated in the short-term treatment of posttraumatic stress disorder.[44] Hence, the venlafaxine might have a better effect on stress-linked MDD by potentially more rapid acting through HPA stress cascade, growth factors and subsequent improved neurogenesis. Conversely, the decrease in hippocampal volume found in depressive patients without a presence of stress factors during AD treatment could reflect potential weaker effect of venlafaxine on hippocampus that is in contrast clinical stabilization of acute depressive symptomatology. This assumption requires further research related to long-term and longitudinal assessment of venlafaxine treatment on hippocampus volume in major depression.

Limitations of the study

The limitations of the study include a relatively small number of patients. Therefore, it is necessary to validate our results in a large group of subjects with respect to gender. Moreover, our results cannot be applied to another types of AD treatment other than venlafaxine. Additionally, this study was focused on the acute effect of venlafaxine, not on the long-term treatment, and the hippocampal volumetric measurements in depressive patients prior to treatment were not compared with the control group. Further study focusing on other structures using the MRI could explain and clarify the important link between AD treatment and its effect on the brain structures.

Conclusion

Our study revealed different response in hippocampal volume to AD treatment by venlafaxine depending on presence of long-lasting stress factors, i.e. the hippocampal volume increased only in the depressive patients with presence of stress factors. It seems that venlafaxine appears to be more suitable and preferential choice of antidepressant treatment for depressive patients with stress history. Further research is needed to elucidate pathways linking major depression, antidepressant treatment and hippocampus volume with respect to long-lasting stress factors detectable in MDD etiopathogenesis.

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Ethical consideration

The study was approved by the Ethics Committee of the Jessenius Faculty of Medicine in Martin, the Comenius University in Bratislava, Slovakia. All the procedures performed in our study were in accordance with the 1964 Helsinki declaration. All patients participating in this study

signed an informed consent with MR examination and study enrollment.

Conflict of interest

The authors have no conflict of interest to declare.

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