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Changes in Regional Cerebral Blood Flow of A Depressed Patient Before and During Musical Hallucinations: A Case Report

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ABSTRACT

Musical hallucinations (MHs) are a type of auditory hallucination in which music is perceived despite a lack of actual sound. Few reports have described longitudinal neuroimaging findings in different conditions before and during MHs. This report describes a depressed patient whose regional cerebral blood flow (rCBF) was assessed using single-photon emission computed tomography (SPECT) before and during MHs. A 72-year-old depressed woman was admitted to our hospital. During the treatment period, she experienced MHs. Then MHs disappeared with treatment of depression or following improvement in the mood. SPECT scans were performed to assess the levels of rCBF in several brain areas before and during MHs. During MHs, rCBF was increased in the basal ganglia, thalamus, amygdala, and parietal lobes. This report suggests that increased rCBF in multiple brain areas, especially in the basal ganglia and thalamus, might be related to the pathophysiology of MHs in depressed patients.

Keywords: *Musical Hallucinations, Depressive Disorder, Regional Cerebral Blood Flow, Single Photon Emission Computed Tomography (SPECT)*

Introduction

Musical hallucinations (MHs) are a specific type of auditory hallucination in which the auditory perception comprises songs, rhythm, harmony, and melody in the lack of actual sound (Golden and Josephs, 2015). MHs can cause patients significant distress, i.e., concentration difficulties, insomnia, impaired quality of life, anxiety and/or depression, and fear that they are dementing or otherwise psychiatrically ill (Coebergh *et al*., 2015). Thus, it is important to examine the etiology of MHs. Actually, MHs have been associated with hearing impairment, neurologic diseases, brain lesions, drug effects, and psychiatric diseases including mood disorders (Golden and Josephs, 2015; Muraosa *et al*., 2020). Although the pathophysiological process of MHs is not fully understood, neuroimaging studies have been conducted to investigate the mechanisms of MHs. Bernardini, *et al*. (2017) reviewed neuroimaging studies that have examined MHs. Their results suggest that several brain areas including the superior temporal sulcus, basal ganglia, orbitofrontal cortex, and precuneus are likely to be involved in MH

production. However, most of these studies were case reports describing neuroimaging assessment conducted at a single time point. Few reports have described longitudinal neuroimaging findings obtained under different conditions with and without MHs (Kasai *et al*., 1999; Izumi *et al*., 2002; Shoyama *et al*., 2010). Therefore, more such case studies are warranted to elucidate the pathophysiology of MHs. This report describes a depressed patient whose regional cerebral blood flow (rCBF) was assessed using single photon emission computed tomography (SPECT) before and during MHs.

Case Report

The patient was a 72-year-old woman who had developed major depressive disorder in her 40s and who had experienced several major depressive episodes. She had been remained in remission on pharmacological treatments using paroxetine 20 mg/d and mirtazapine 30 mg/d. She had never experienced psychotic symptoms such as hallucinations or delusions. She had no history of neurologic disease, use of illegal drugs, or alcohol abuse. She received amlodipine 5 mg/d, atorvastatin 10 mg/d, and vonoprazan 10 mg/d for the treatment of hypertension, hyperlipidemia, and chronic gastritis, respectively. These drugs for physical diseases were unchanged throughout the present course of treatment. Written informed consent for reporting her clinical course was obtained from her. This report was approved by the Ethical Review Committee of Yamagata University Faculty of Medicine.

On November 2020, she complained of depressed mood, decreased appetite, difficulties in starting activities, and suicidal thoughts. She was admitted to our hospital because of a relapse of major depressive disorder. On admission, she scored 36/60 and 28/30, respectively, on the Montgomery Åsberg Depression Rating Scale (MADRS) and the Mini-Mental State Examination. Her treatment using paroxetine and mirtazapine was switched to that using venlafaxine 37.5 mg/d, and this drug was gradually increased to 225 mg/d.

During January 2021, when she took venlafaxine 225 mg/d, she heard “Latin American music”, “humming music”, “Hawaiian music”, and “Japanese traditional folk songs”. Her MHs were exacerbated at night in quiet places. She was aware that the music was hallucinated. She scored 33/60 on the MADRS.

Findings obtained from laboratory blood tests, brain magnetic resonance imaging, and electroencephalography were unremarkable. An otolaryngologist examined her and found that she had mild presbycusis but did not need treatments.

[99mTc]-ethyl cysteinate dimer SPECT scans (Hayashi *et al*., 2021) were performed twice in December 2020 (before MHs, Fig. 1A) and in January 2021 (during MHs, Fig. 1B) to rule out neurodegenerative disorders or acute cerebrovascular diseases. Imaging data of SPECT were statistically

analyzed using the easy Z-score imaging system (Fujifilm Toyama Chemical Co., Ltd., Tokyo, Japan). Z-scores were calculated using statistical parametric mapping 8 and the eZIS. A Z-score map of SPECT image was extracted from reference to the mean and standard deviation (SD) of 40 age-matched normal controls (Matsuda *et al*., 2007). A voxel-by-voxel Z-score was calculated and evaluated as follows: Z scores = ([control mean] - [individual value]) / (control SD) (Matsuda *et al*., 2007). To compare the levels of rCBF increase or decrease in each region of interest before and during MHs, voxel-based stereotactic extraction estimation (Fujifilm Toyama Chemical Co., Ltd., Tokyo, Japan) using Z-score calculated by the eZIS data was performed; the differences of Z-score were displayed. rCBF during MHs was increased in the right basal ganglia, right thalamus, left amygdala, and bilateral parietal lobes (Fig. 2A), although no decrease of rCBF was detected during MHs (Fig. 2B).

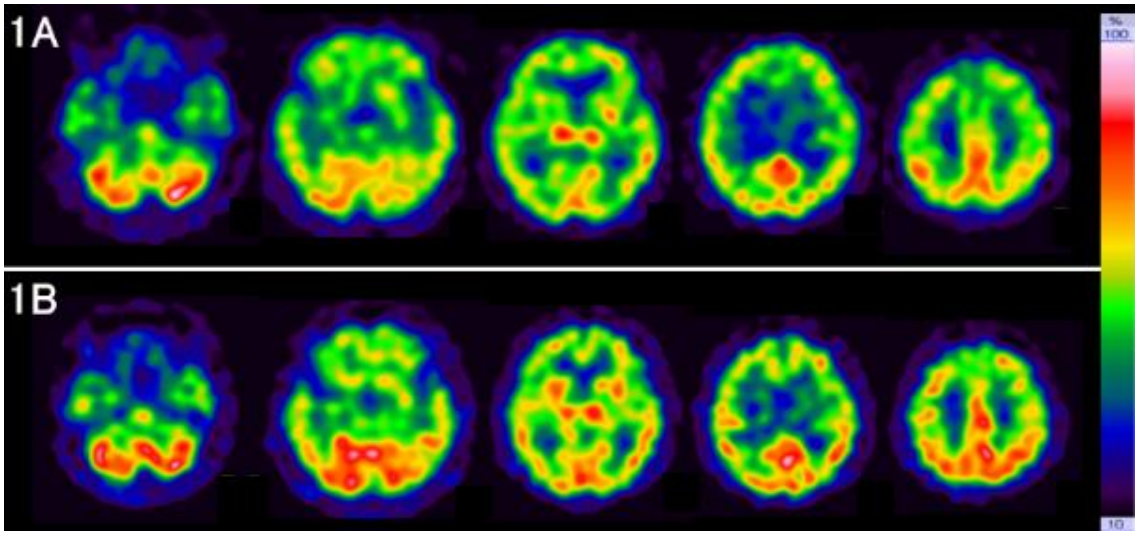

Figure 1: SPECT images before MHs (1A, upper) and during MHs (1B, lower). MHs, musical hallucinations; SPECT, single photon emission computed tomography.

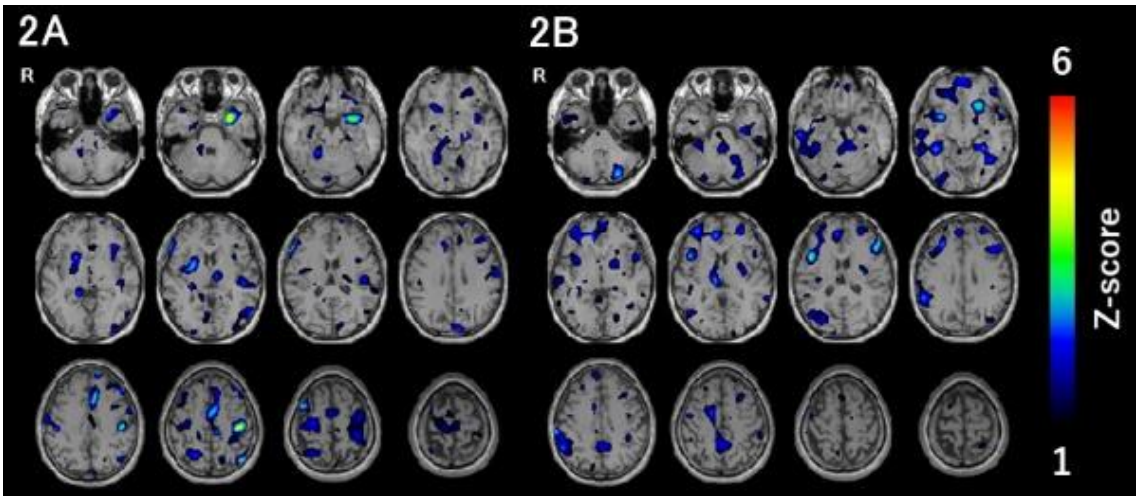

Figure 2: Increase (2A) or decrease (2B) of rCBF during MHs for each region of interest compared to that before MHs. MHs, musical hallucinations; rCBF, regional cerebral blood flow.

At the end of January, because of no apparent improvement in the treatment using venlafaxine, this drug was switched to maprotiline from 25 mg/d to 50 mg/d, but again her symptoms of depression and MHs did not change. In the beginning of March 2021, augmentation therapy using paroxetine 20 mg/d and lithium 400 mg/d was performed, then her mood improved gradually to yield a score of 10/60 on the MADRS. In accordance with her mood, MHs also disappeared completely. She was discharged at the end of March 2021. Throughout the episode, the patient was treated according to standard pharmacotherapy (Labbate *et al*., 2009).

Discussion

Earlier reports indicate that several etiological factors such as hearing impairment, neurologic diseases, brain lesions, drug effect, and psychiatric diseases, are linked to MHs (Golden and Josephs, 2015; Muraosa *et al*., 2020). The present case did not have apparent psychotic disorders, neurologic diseases, history of illegal drug use, or alcohol abuse. Although she had mild hearing impairment, treatment was not necessary for it. Her MHs emerged when depression was moderate to severe. Subsequently, they disappeared after depression improved. Therefore, in this case, it is likely that MHs were related to depression, although the possibility that her MHs were caused by the antidepressants, i.e., venlafaxine and maprotiline, cannot be excluded entirely.

In the present case, rCBF during MHs was increased in the basal ganglia, thalamus, amygdala, and parietal lobes compared to that before MHs, although no rCBF decrease was detected in any brain area during MHs. Three case reports have described longitudinal neuroimaging findings obtained in different conditions with and without MHs (Kasai *et al*., 1999; Izumi *et al*., 2002; Shoyama *et al*., 2010). Izumi, *et al*. (2002) described that rCBF during MHs was increased in the basal ganglia and lower frontal areas in a depressed patient with hearing impairment. Shoyama, *et al*. (2010) reported that rCBF during MHs was increased in the basal ganglia, thalamus, and hippocampus. It was decreased in the neocortical regions, angular gyrus, and cerebellum in a patient with depression accompanied by chronic pain disorders. These cases (Izumi *et al*., 2002; Shoyama *et al*., 2010) show agreement with findings obtained in the present case in terms of increased rCBF in the basal ganglia, and to a lesser extent, the thalamus. Kasai, *et al*. (1999) reported increased rCBF of the superior temporal areas and inferior gyri during MHs in a patient without evident psychiatric or neurological diseases. Therefore, results suggest that rCBF in the basal ganglia and thalamus is increased during MHs in patients with depression.

Grahn (2009) suggested that patients with Parkinson's disease, which is characterized by progressive cell death in the basal ganglia, have impaired ability to discriminate differences in rhythms compared to healthy controls. Neuroimaging studies showed that the activity of the basal ganglia and

thalamus is related to the perception and production of rhythms (Grahn, 2009; Penhune *et al*., 1998; Teki *et al*., 2011). Results of a study using functional magnetic resonance imaging also revealed increased connectivity between the thalamus and amygdala in relation to creative musical experience (Bashwiner *et al*., 2020). These study results suggest that the basal ganglia and thalamus play important roles in the perception and creativity of music. Moreover, they indicate the possibility that increased rCBF in these regions might be related to the pathophysiology of MHs.

Conclusion

This report describes a depressed patient whose regional cerebral blood flow (rCBF) was assessed using single-photon emission computed tomography (SPECT) before and during musical hallucinations (MHs). During MHs, rCBF was increased in the basal ganglia, thalamus, amygdala, and parietal lobes. Results suggest that increased rCBF in multiple brain areas, especially in the basal ganglia and thalamus, are related to the pathophysiology of MHs in depressed patients.

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Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relation that might be construed as a conflict of interest.

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