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# ASYMMETRIES OF VESTIBULAR DYSFUNCTION IN MAJOR DEPRESSION

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**Abstract—Depression is characterized by alterations in the circadian secretion of hormones, sleep and motor activity, all of which are regulated by suprachiasmatic nuclei (SCN). The vestibular system in the inner ear registers the amount of motor activity. To test the integrity of this motion sensitive system in depression, we studied the vestibulo-ocular reflex (VOR) in depressive patients who were not taking medication and healthy control subjects, which allowed us to investigate each ear and its corresponding nerve centers. Ocular reflex movement depends on vestibular nuclei activity, and we found that at 30 °C stimulation the right vestibular system in depressive patients has approximately half the activity of the left side. Significant asymmetry was not detected in control subjects. We also found a significant decrease in the slow phase (16.92±9.13°/s) of the reflex in the depressed group as compared with the control group (43.77±16.04°/s). The vestibular nuclei of the right and left sides are hypoactive. Specifically, the right vestibular nucleus is hypoactive in depressed people and can easily be measured using VOR. These results support the abnormal asymmetries hypothesis of depression and suggest that these asymmetries also exist at the level of the brain stem or neuronal centers that are afferents to right vestibular nuclei, like SCN or raphe nuclei.**


**Key words: depression, nystagmus, raphe nuclei, SCN, vestibular nuclei, VOR.**

Depression is an important mood illness with a very high prevalence. Though its physiopathology has not been clarified, researchers suspect that suprachiasmatic nuclei (SCN) play an important role. Changes in hormonal secretion that depend on SCN activity have been widely described in depression literature. One of the most consistent findings is an altered cortisol secretion pattern (Zobel and Yassouridis, 1999; Peeters et al., 2004) with excess secretion that does not suppress with dexamethasone (Georgotas et al., 1986; Nelson and Davis, 1997). Blunted thyroid stimulating hormone response rate (Sarandol et al., 2003; Howland, 1993), altered glucose tolerance and growth hormone hypersecretion (Linwkowski, 2003) also have been reported. In addition, the sleep architecture is disturbed. Frequent findings that suggest circadian system dysfunction in depression include anticipated rapid eye movement (REM) episodes, enhanced density of REM sleep (Kupfer and Thase, 1983), insomnia or excessive sleepiness, and a decrease in locomotor activity (Asnis et al., 1983).

Circadian rhythms can be entrained by photic and non-photic stimuli. The role of light in the retinohypothalamic tract has been studied extensively over the past few years. It is clear that a decrease in environmental light can induce depression, particularly the seasonal type, which responds to light therapy. There is a need for further study of afferences to SCN other than light (non-photic stimuli).

Non-photic afferences to the SCN are more extensive and complex and their physiology is not completely understood. However, it is widely accepted that raphe nuclei are one of the most important non-photic inputs to SCN and the intergeniculate leaflet. Retrograde labeling techniques could confirm projections from raphe nuclei to SCN in rats, which would allow us to confirm that it receives inputs from dorsal raphe nuclei, median raphe nuclei and raphe magnus (Hay-Schmidt et al., 2003).

Functional regulation of SCN by raphe nuclei also has been demonstrated in the literature (Muscat et al., 2005; Ehlen et al., 2001; Glass et al., 2003; Dudley et al., 1999; Meyer-Bernstein and Morin, 1996, 1999; Mintz et al., 1997; Colbron et al., 2002; Collin et al., 2000; Blasiak and Lewandowski, 2003; Greenwood et al., 2005; Mrosovvsky, 1996; Hastings et al., 1998).

Clinical studies in humans suggest that raphe nuclei could play an important role in regulating SCN activity. Antidepressants known as selective serotonin reuptake inhibitors diminish depressive symptoms, including circadian alterations. Postmortem studies have revealed structural anomalies in raphe nuclei (Becker et al., 1994, 1995), a decrease in the number of neurons in the raphe nuclei in depressed patients (Baumann et al., 2002) and increased tryptophan hydroxylase in dorsal raphe nuclei in depressed people who committed suicide (Boldrini et al., 2005). Reduced brain serotonin transporter also has been described in living depressed patients (Malison et al., 1998).

In short, there is evidence to suggest a dysfunction of raphe nuclei in depression that can induce circadian alterations in a specific type of depression. On the other hand, raphe nuclei dysfunction could be a manifestation of SCN dysfunction and not its origin.

Several studies in animals indicate there are anatomical (Halberstadt and Balaban, 2003; Horowitz et al., 2004) and functional (Kishimoto et al., 1991; Licata et al., 1995)

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*Abbreviations:* LE, left ear; RE, right ear; REM, rapid eye movement; SCN, suprachiasmatic nuclei; SPV, slow phase velocity of the nystagmus; VOR, vestibulo-ocular reflex.

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relationships between vestibular nuclei and raphe nuclei. Researchers also have demonstrated that vestibular activity regulates circadian system (Murakami et al., 2002), medial vestibular nucleus projects, polysynaptically to SCN and monosynaptically to intergeniculate leaflet (Horowitz et al., 2004).

The purpose of this study is to analyze the vestibular system activity in patients with major depression by recording the vestibulo-ocular reflex (VOR).

## EXPERIMENTAL PROCEDURES

This study was conducted on eight patients with major depression using Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994) criterion. Patients were selected by a psychiatrist. The sample included four women and four men with an average age of 30.6±15.4, who had no history of vestibular pathology and were not undergoing pharmacological treatment. The control group consisted of 10 healthy voluntary people. It was composed of seven women and three men with average ages of 30.7±7.6, who had no history of vestibular pathology and were not undergoing pharmacological treatment. The participation of patients and healthy volunteers was according to international ethical standards.

A VIII pair examination was conducted and each labyrinth was stimulated separately with 30 °C and 44 °C water. Ocular movements were recorded in the skin, with three silver registration electrodes, using conducting gel; one in each eye, near the external angle and the third in a central point in the front. Electrical signals were processed by electronystagmography (ENG-ICS N-3-1 Tonnies d-465 T25T). Each subject was seated with his or her head inclined to 30° and wore an eye mask. All subjects underwent 400 ml/min irrigation for 30 s in each ear using an alternating stimulation technique. Ocular movements were measured 60–90 s after the stimulation began. The calibration of the polygraph for the registration paper was 1:2 (1 mm=two grades of ocular movement). The velocity of paper displacement was 10 mm/s. Eye movements to the right side of the patient are seen as upwards displacements of the polygraph needle, left movements as downwards displacements. The pendent of the traces reflects the velocity of the eye movements. For calculation of the velocities of slow and fast phases for each different temperature stimulus register, we used an average of the most clear and representative traces (four or five measurements per stimulus). Calculation was made manually measuring the pendent of the traces.

All the registers of control and depressed group were taken during the morning, between 9 and 11 AM, by the same person and using the same equipment.

The variables analyzed were slow and fast phase angular velocity at 30 °C and 44 °C stimulation in the right ear (RE) and left ear (LE). Quantitative analysis of symmetry was done using the left/right angular velocity ratio (RE/LE) of the slow and fast phases in each subject. The significance of the differences observed was tested using the Mann-Whitney *U* test.

## RESULTS

We detected a statistically significant decrease in the velocity of the slow phase (SPV) of the nystagmus in patients. At 30 °C stimulation of the RE depression group's mean was 12.71±4.78°/s of angular velocity, significantly lower than 43.5±14.27°/s of the control group ($P<0.01$). At 30 °C LE stimulation, depression group showed a mean of 24.38±11.39°/s, significantly lower than 41.6+14.32°/s of the control group ($P<0.05$). Stimulation at 44 °C also showed lower slow phase velocities in the depression group. RE at 44 °C in the depression group was 15.43±7.41, and in the control group it was 48.34±20.31 ($P<0.01$). LE stimulation at 44 °C showed 14.71±8.04°/s in depression group that was significantly different to 41.64±16.16°/s of the control group ($P<0.01$) (Fig. 1).

The fast phase velocity (FPV) was significantly lower in patients at 30 °C in the RE with a mean of the angular velocity of 126.3±52.1 compared with 202.7+68.9 of the controls ($P<0.05$). No significant differences were found in 30 °C LE and 44 °C right and LE stimulation.

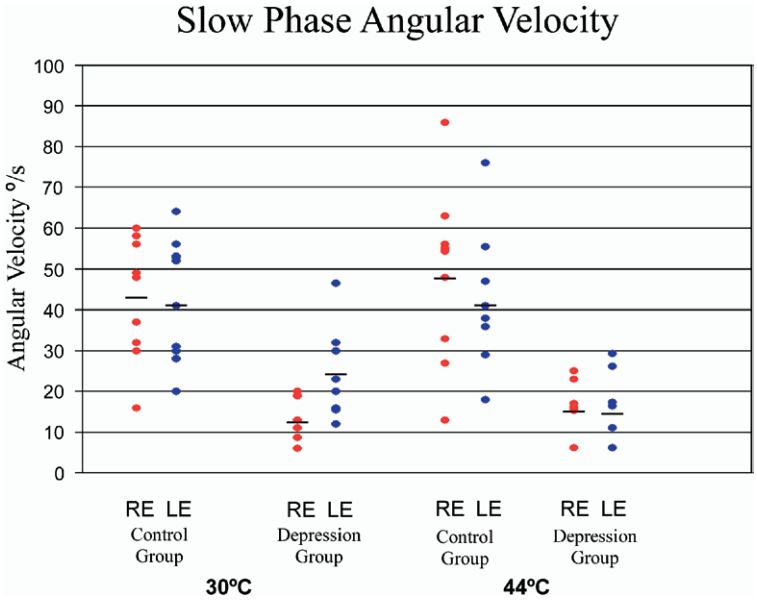


**Fig. 1.** The slow phase angular velocity of the depression group at 30 °C and 44 °C is significantly lower than that of the control subjects.