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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 ($16.92 \pm 9.13^\circ/s$) of the reflex in the depressed group as compared with the control group ($43.77 \pm 16.04^\circ/s$). 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. © 2006 IBRO. Published by Elsevier Ltd. All rights reserved.

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

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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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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-photoc 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-photoc stimuli).

Non-photoc 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-photoc 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; Mrosovsky, 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)

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 Tonnie's 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 $12.71 \pm 4.78^\circ/\text{s}$ of angular velocity, significantly lower than $43.5 \pm 14.27^\circ/\text{s}$ of the control group ($P < 0.01$). At 30 °C LE stimulation, depression group showed a mean of $24.38 \pm 11.39^\circ/\text{s}$, significantly lower than $41.6 \pm 14.32^\circ/\text{s}$ 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 $14.71 \pm 8.04^\circ/\text{s}$ in depression group that was significantly different to $41.64 \pm 16.16^\circ/\text{s}$ 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.

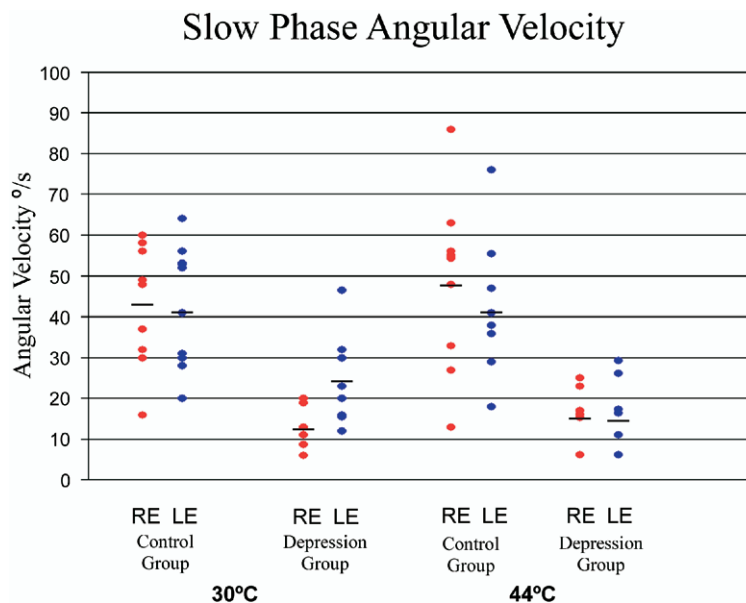


Fig. 1. The slow phase angular velocity of the depression group at 30 °C and 44 °C is significantly lower than that of the control subjects.

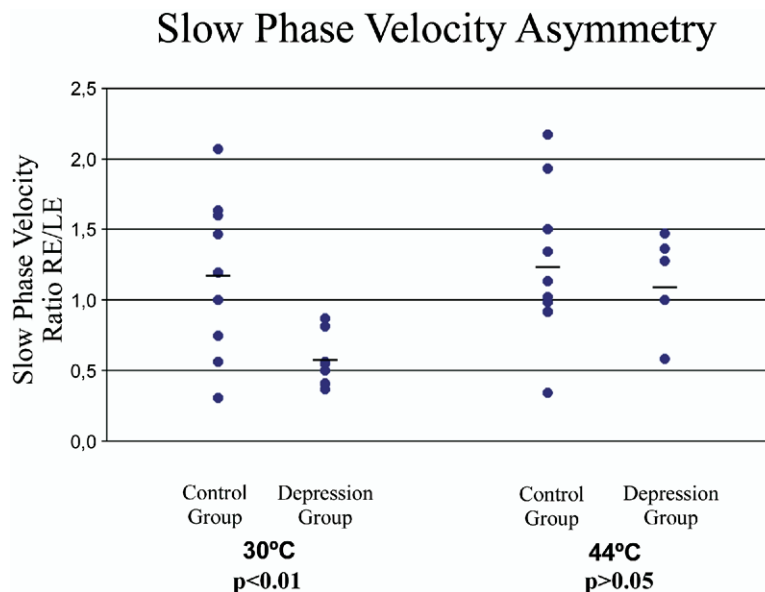


Fig. 2. When we compared control subjects and depression patients we detected asymmetry at 30 °C and 44 °C. The degree of asymmetry was measured according to the RE/LE ratio of the SPV.

The magnitude of asymmetry was measured by calculating an angular velocity ratio from the RE to the LE (RE/LE) in each subject. The SPV ratio at 30 °C stimulation was 0.56 ± 0.19 in depression group and 1.18 ± 0.57 in control group ($P < 0.01$). No significant variation in the SPV ratio was detected in the depression group, 1.16 ± 0.32 , and the control group, 1.22 ± 0.55 at 44 °C stimulation, nor were significant differences found in the groups' fast phase velocities ratios at 30 °C and 44 °C stimulation (Fig. 2).

The manual preference was not significantly different between both groups, with one left-handed and seven

right-handed in the depression group. The control group was composed by two left-handed and eight right-handed (Table 1). We did not find any relation between hand preference or sex and the asymmetries of the VOR. Also we did not find any relation between age and velocities or asymmetry of the reflex.

Saccadic arc decomposition during calibration was found in four of the depressed people, and dysrhythmic nystagmus was detected in five of the patients in that group (Fig. 3). The members of the control group did not present dysrhythmic nystagmus and calibration was normal (Fig. 4).

Table 1. Experimental subject characteristics and velocity of slow phase

Subject	Age (y)	Sex	Handedness	RE 30 °C	LE 30 °C	RE 44 °C	LE 44 °C
CGS 1	20	F	Left	37	31	33	36
CGS 2	21	F	Right	48	64	55	41
CGS 3	21	F	Left	32	20	63	29
CGS 4	22	F	Right	60	41	48	47
CGS 5	23	M	Right	58	28	13	38
CGS 6	23	F	Right	16	52	56	29
CGS 7	30	M	Right	49	30	27	18
CGS 8	32	M	Right	56	56	54.4	55.4
CGS 9	46	F	Right	49	41	48	47
CGS 10	68	F	Right	30	53	86	76
DGS 1	19	F	Left	11	20	16	16
DGS 2	25	M	Right	20	23	17	29
DGS 3	28	M	Right	11	30	23	18
DGS 4	29	F	Right	13	32	—	—
DGS 5	31	M	Right	13	16	15	11
DGS 6	32	F	Right	19	46.6	25	17
DGS 7	39	F	Right	8.7	15.4	6	6
DGS 8	43	M	Right	6	12	6	6

Subject characteristics, indicating angular SPV (°/s) elicited by stimulation of each ear with water at 30 °C and 44 °C. CGS, control group subject; DGS, depression group subject.

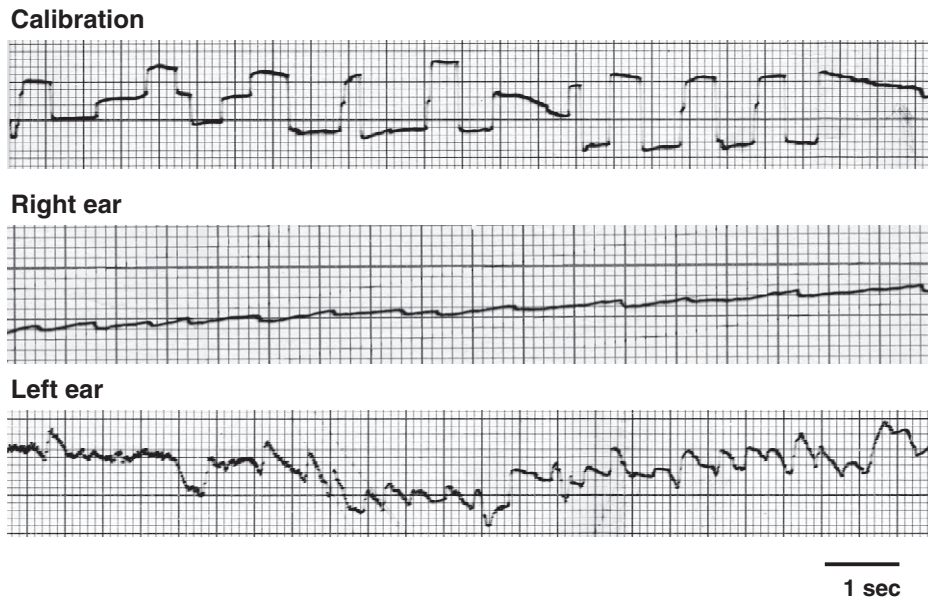


Fig. 3. Depression patients show an abnormal calibration (upper image) for 30 °C RE stimulus nystagmus (middle) and 30 °C LE stimulus nystagmus (bottom). Note the differences between RE and LE.

DISCUSSION

The results show a bilateral decrease in SPV with 30 °C and 44 °C stimuli in depressed people. SPV of nystagmus depends on the activity of the vestibular nuclei. A bilateral decrease in this nucleus activity suggests functional alterations at that site. Afferents to vestibular nuclei come from vestibular nerves and raphe nuclei (Halberstadt and Balaban, 2003; Horowitz et al., 2004; Kishimoto et al., 1991; Licata et al., 1995). References to raphe nuclei alterations in depression in the literature suggest that this nucleus could be the origin of vestibular nucleus hypoactivity.

We also detected an abnormal asymmetry of the VOR in depressed subjects. This is only evident at 30 °C stimulation, slow phase angular velocity. The VOR is generated in the external semicircular canal labyrinth of the inner ear. Hot water (44 °C) stimulates the activity of ciliary receptors and the vestibular nerve transmits this stimulation to ipsilateral vestibular nuclei in the brain stem. Cold water (30 °C) inhibits the activity of ciliary receptors. Vestibular nerve synapses in the ipsilateral vestibular nuclei, where SPV of the nystagmus is integrated, send this information to the corresponding motor

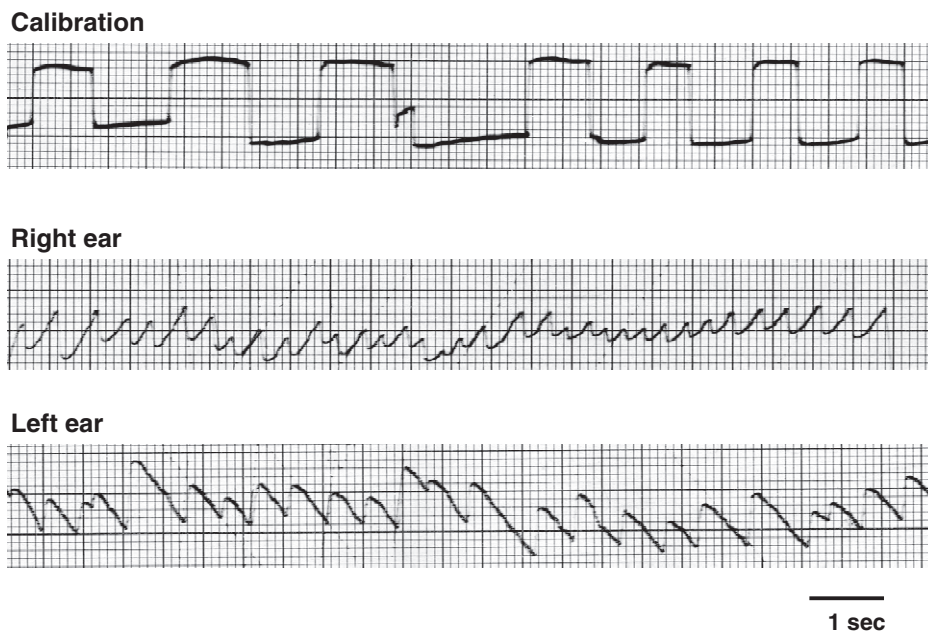


Fig. 4. These results for a control subject show normal calibration (upper image), 30 °C LE stimuli (middle) and 30 °C RE stimuli nystagmus (bottom). Note the symmetry of the nystagmus between RE and LE.

ocular nucleus (III and VI cranial nerves nucleus), thereby generating slow eye movement in the corresponding side. The velocity of the slow phase of the nystagmus depends on vestibular nuclei activity. Rapid compensatory eye movement (fast component of the nystagmus) to the opposite side is generated by the paramedian pontine reticular formation. We did not find a significant difference between fast phase asymmetry in depressed patients and control subjects. Pontine reticular formation that integrates this fast compensatory phase of nystagmus is not significantly compromised in this illness. Saccadic arc decomposition and dysrhythmic nystagmus support other findings of prefrontal and cerebellar vermis disturbances in these patients (Malaspina et al., 1994; Sweeney et al., 1998).

Our results show SPV asymmetry only at 30 °C stimulation. We believe that this is due to a right vestibular nuclei dysfunction that consists of minimal activity which cannot be decreased using an inhibitory afference from right vestibular nerve (30 °C water stimulation). This explains why the SPV of the nystagmus, which depends on vestibular activity, is diminished at 30 °C in right side stimulation in these patients. Meanwhile, 44 °C RE stimulation, which is excitatory, can enhance vestibular nuclei activity and camouflage differences in right-left activity.

Vestibular nuclei activity depends on the modulation that they receive from their afferents. These may be numerous and include vestibular nerves, raphe nuclei (Halberstadt and Balaban, 2003; Horowitz et al., 2004; Kishimoto et al., 1991; Licata et al., 1995) and SCN (Horowitz et al., 2004). The results of this study show a decrease in right vestibular nuclei activity in depressed patients, which suggests that one of the structures that gives afferents to vestibular nucleus may be dysfunctional in depression.

There are no data available on peripheral vestibular dysfunction in depressed subjects, but there is certainly evidence of alterations in raphe nuclei in depression (see introduction). The origin of right raphe nuclei dysfunction could be afferents to vestibular nuclei.

Vestibular dysfunction in these patients has to be studied. At this moment we can hypothesize that there is a dysfunction of raphe nuclei that affects both, SCN and vestibular function, or that a primary SCN dysfunction is the origin of the vestibular hypoactivity (Horowitz et al., 2004).

Several kinds of studies have been conducted in order to register abnormal asymmetries in depressed patients, however references in literature about anatomical findings have not been conclusive (Vakili et al., 2000; Bremner et al., 2000; Mervaala et al., 2000; Pillay et al., 1998; Kumar et al., 2000), neither functional studies (Allen et al., 2004; Alves et al., 2006; Bruder et al., 2005; Debener et al., 2000; Diego et al., 2001; Deckersbach et al., 2006; Flor-Henry et al., 2004; Knott et al., 2001; Passynkova and Volf, 2001). In the present experiment we did not obtain simultaneous registers of brain activity, so we wonder if the asymmetry we detected in our patients at the brain stem level is a manifestation, or not, of a more global functional encephalic asymmetry.

Experimental evidences in split hamsters, elicited by constant light conditions, show antiphase activity between left and right SCN (De la Iglesia et al., 2000). Stress in humans is closely related with depression in a cause-effect relationship (Neigh and Nemeroff, 2006; Nemeroff and Vale, 2005; Bale and Vale, 2003). We suggest that the asymmetry we found in vestibular activity in the depressed group could be a manifestation of the same kind of asymmetry that was found in split hamsters. We really wonder if stress, CRH or cortisol (as constant light is also probably a stressful condition) (Vernikos-Danellis et al., 1970), is by itself sufficient stimulus to make right and left SCN to work in an antiphase way. This question needs to be answered on next experiments.

We therefore propose that right SCN dysfunction could explain circadian alterations in hormonal secretion, wake-sleep cycle changes, locomotor disturbances and decreases in right vestibular nuclei activity.

With these ideas in mind, we further propose that depression probably involves a dysfunction in SCN, raphe nuclei and vestibular nuclei on both sides and particularly on the right side. Future research may be able to tell us which part of this structure is compromised first. This study cannot provide that information because of the structures' reciprocal modulations. This opens a new field of study. In fact, research on SCN-raphé nuclei-vestibular nuclei is now being conducted on animals (Halberstadt and Balaban, 2003; Licata et al., 1995; Fuller et al., 2002; Murakami et al., 2002), but not on humans.

This is the first time that an electrophysiological parameter, that reflects different right and left side activity at the brain stem level, has been recorded in depression. The study of the VOR in depressed subjects showed a very specific response pattern that consists of bilateral decreased SPV with a characteristically lower velocity in RE stimulation at 30 °C. This pattern could be helpful in the diagnosis and monitoring of depression and could be used as a biological marker for the disease.

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