

Abnormal Sympathetic Lateralization in Depression: Asymmetry of the Biological Clock?

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Abstract: The suprachiasmatic nuclei (SCN), a paired structure in the hypothalamus controls the circadian rhythms of sleep-wake, endocrine, motor activity, and autonomic nervous system in mammals. Major depression, a common mood disorder, shows abnormal circadian cycles, however, the chronobiologic mechanisms involved are still unknown. Previous studies in animals show that the right/left SCN controls the ipsilateral sympathetic activity. To have an appreciation of the sympathetic activity in right-handed humans, we measured the electrodermal activity (EDA) in both wrists in five healthy and five major depression subjects. Healthy subjects showed higher right side activity compared to left ($R > L$). Depressed patients, showed the contrary ($R < L$). These findings open the question of whether each half of the body's sympathetic activity depends on the ipsilateral SCN in humans. Also, the question was raised if abnormal asymmetries between right and left SCN could underlie depression's circadian disorders. This exploratory research allows introducing new approaches to mental and chronobiologic disorder's study in living humans.

Key words: Electrodermal activity, splitting, circadian rhythm, depression, mood disorder.

1. Introduction

Depression is a disorder that not only involves higher brain functions producing negative and pessimistic self-feelings, lowering the attention, the intellectual capacity and the memory, but also affects physiologic body functions that depend on the activity of the biological clock, the SCN in the hypothalamus. Depressed patients show abnormal circadian cycles of sleep, endocrine and autonomic/sympathetic activity [1-4]. However, the underlying mechanism is still unknown.

Studies in animals showed that right and left synchronic activity of the SCN controls the metabolic and visceral functions allowing the body to adapt to the changing requirements of the environment. The SCN controls the circadian changes of sleep-wake, motor, autonomic and endocrine activity, through the hours of the day. An exciting investigation in mice

demonstrated that the abolition of daylight cycles (constant light, L/L or dark D/D) produced desynchronization (antiphase activity) between right and left SCN, and loss of circadian rhythms [5, 6].

Practical concerns, like the small size and profound location of the SCN inside the brain, may difficult functional studies of this structure in living humans limiting the research in this field. With the intention to study the activity of the right and left SCN separately, we look for a parameter that could reflect each side of the human circadian system.

The SCN governs the autonomic/sympathetic system allowing our body to respond rapidly and properly in stress situations. The sympathetic fibers rise the sweat glands changing the electro conductivity of the skin that can be registered by a wearable electro dermal activity (EDA) watch. Previous investigations with retrograde tracers in rodents show the origin of the sympathetic fibers in the ipsilateral SCN [7]. Other studies demonstrated the ipsilateral activation of the electrodermal activity during the lateralized stimulation of limbic areas in humans [8]. Both works

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suggest a similar organization between rodents and humans.

To have an appreciation of the bilateral SCN activity, we registered the bilateral EDA in five depressed and five healthy subjects.

2. Materials and Method

2.1 Subjects

Five major depression patients and five healthy subjects were asked to participate in the study (Table 1). All signed Informed Consent. The study procedure was according to the Ethical Principles of the Declaration of Helsinki.

2.2 Technique

We registered the sympathetic activity with a Q

sensor Affectiva® Watch. Patients wear the watch in the right and left wrist simultaneously, during 5 daytime hours continuously.

2.3 Method

To have a measurement of the lateralization of the electrodermal activity, we calculate the right/left ratio (average of right wrist EDA/average left wrist EDA) for each subject. We use a one tailed *t* student test to compare both groups.

3. Results

We found a statistically significant difference of right/left EDA ratio between the Healthy Group (1.38 ± 0.2) and Depression Group (1.1 ± 0.4) ($p < 0.05$) (Fig. 1).

Table 1 Demographic characteristics of the subjects (EDA ratio: right/left ratio of the electrodermal activity).

Sex	Age	Hand preference	Condition	EDA ratio
Male	49	Right	Healthy	1.68
Female	45	Right	Healthy	1.25
Female	19	Right	Healthy	1.54
Female	16	Right	Healthy	1.22
Female	13	Right	Healthy	1.21
Male	47	Right	Depression	0.68
Female	32	Right	Depression	1.92
Female	70	Left	Depression	1.04
Female	22	Right	Depression	0.88
Female	27	Right	Depression	0.99

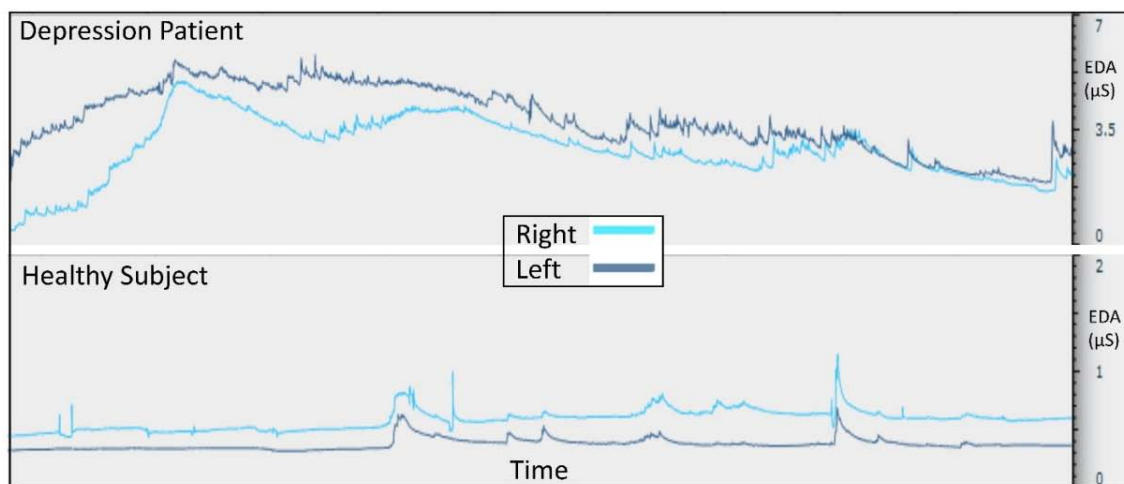


Fig. 1 Registers of the EDA in a depressed patient (upper) and a healthy subject (bottom).

In depression, the right wrist EDA (light blue) is lower than left (grey).

In the healthy subject, we can see the different lateralization (right EDA is higher than left).

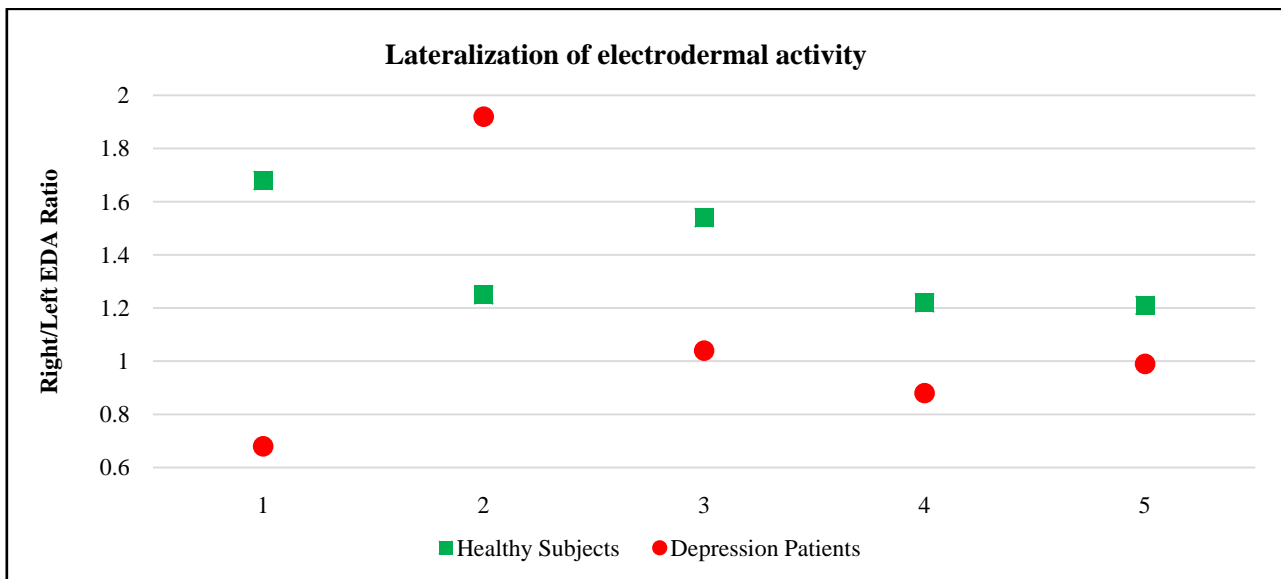


Fig. 2 The lateralization of the EDA is significantly different between depressives (red) and healthies (green) ($p < 0.05$).

4. Discussion

We found opposite lateralization of bilateral EDA between both groups: left predominance over right in depression and the contrary in healthy subjects (Fig. 2).

These results are in accordance with previous studies of bilateral EDA in healthy [9, 10] and depressed subjects [11, 12] showing abnormal lateralization of the sympathetic activity in depression.

The EDA depends on the sympathetic activity. Studies in animals showed that the sympathetic activity of each half of the body depends on the right and left SCN activity correspondingly [7]. Circadian rhythms depend on the normal and synchronic function of right and left SCN [6, 13]. The abnormal lateralization of sympathetic activity found in depression, suggests that the circadian dysfunctions of these patients could depend on a different lateralization of the SCN. The findings of right/left SCN antiphase activity in concordance with disruption of circadian rhythms in animal models [14], allow proposing a similar mechanism for human's circadian disorders in depression. Bilateral EDA would correspond to SCN activity in real time. This measurement may allow testing the effectivity of different stimuli to restore the normal lateralization of

the paired SCN. Simultaneous EDA measurements in both wrists could be useful to monitor and control the circadian system in humans.

The results of the present investigation propose a new understanding of sympathetic asymmetries from a chronobiologic point of view. This paper introduces a novel approach to circadian disorders pathophysiology in humans that consider the importance of mutual SCN interaction, also, raises new paradigms about the contribution of the chronobiologic and autonomic system to depression.

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