Chapter

Characteristic Profiles of Heart Rate Variability in Depression and Anxiety

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Abstract

This chapter on heart rate variability (HRV) presents a view based on our published data that HRV profiles in depression and anxiety show differences and can be used for the differentiation of these two disorders in clinical practices. Characteristic HRV profiles in depression and anxiety are revealed by measurements incorporating task load. Analysis of two frequency-domain HRV parameters, low frequency (LF) and high frequency (HF), together with heart rate (HR) itself measured at rest (Rest), during the task load (Task), and at rest after the task (After) enables the evaluation of the autonomic regulation in response to behavioral changes with different stress levels. LF is the heart rate modulation related to blood pressure changes to stabilize circulation. HF is related to breathing rhythm and reflects parasympathetic activity. It has been indicated that LF, HF, their ratio LF/HF and HR in depression and anxiety show characteristic dysregulations during Rest, Task and After. These HRV profiles are useful for understanding the pathophysiology of the disorders.

Keywords: heart rate variability, baseline and reactivity, autonomic dysregulation, depression, anxiety

1. Introduction

Depression and anxiety are frequent mental disturbances that seriously affect human life. They are commonly encountered in clinical practices, but comorbidity is often and differentiation of depressive and anxiety states is important with respect to therapeutic processes [1]. Psychiatric diagnosis at present is mostly based on psychological and behavioral assessments [2]. Additional use of objective measures as biomarkers to evaluate the symptoms and to make the differential diagnosis will be useful for the adequate treatment of depression and anxiety. A biomarker is defined as an indicator of biological and pathogenic processes or responses to exposure and intervention and is classified as molecular, histological, radiographical, or physiological index [3]. Various types of biomarkers for depression and anxiety have been studied, including genetic, biochemical, hormonal, imaging, and electrophysiological measurers, and some studies tried to use them to differentiate depression and anxiety [4]. Among physiological measures, the present chapter

focuses on heart rate variability (HRV) that has been utilized for analyzing autonomic activities to characterize and differentiate depression and anxiety.

2. Autonomic biomarkers of psychiatric disorders

Autonomic measures are interesting because some of the clinical symptoms of depression and anxiety are related to autonomic disturbances. In depression, appetite decreases, and weight loss is frequent. Bowel movement is also unstable. In anxiety, the patients report palpitation and cardiac discomfort without electrocardiographic abnormalities. Perspiration also increases. These somatic symptoms of depression and anxiety can be generated by autonomic dysregulations, supporting the feasibility of autonomic measures as biomarkers for depression and anxiety.

Although autonomic dysregulations are frequent in depression and anxiety, the methods for objective evaluation of autonomic symptoms are limited. Physiological indices of autonomic activity include pupil size, salivary amylase, gut movement, skin conductance, heart rate, and HRV. Among them, HRV has been intensively utilized in the analysis of autonomic function in depression and anxiety [5, 6]. HRV is easily measured by analyzing the electrocardiogram or pulse oximetric plethysmogram. A measurement takes only a few minutes and is less stressful for the patients. The measurement devices are small and portable and can be installed in regular clinical offices or in non-medical places. HRV is useful and convenient to characterize the autonomic dysregulations found in depression and anxiety.

3. Heart rate variability (HRV) measurement for evaluation of autonomic activity

HRV is a variation of inter-heartbeat intervals (**Figure 1**). The heart beats constantly but the rhythm is not regular. The heartbeat slows and accelerates, and the inter-heartbeat interval varies. It has been known that the heartbeat rhythm is composed of multiple components with different frequency ranges [7].

In HRV analysis, heartbeats or pulse beats are first identified conventionally by peak detection (**Figure 2**). The inter-beat interval trend made of the sequence of peak-to-peak intervals is processed by frequency analysis to yield the power spectrum of HRV. The power spectrum can reveal the presence of multiple heart rate rhythms with different frequencies ranges; high frequency (HF), low frequency (LF), very low frequency (VLF), and ultra-very low frequency (UVLF). HF and LF components are often used for the evaluation of autonomic activities in mental disorders, and

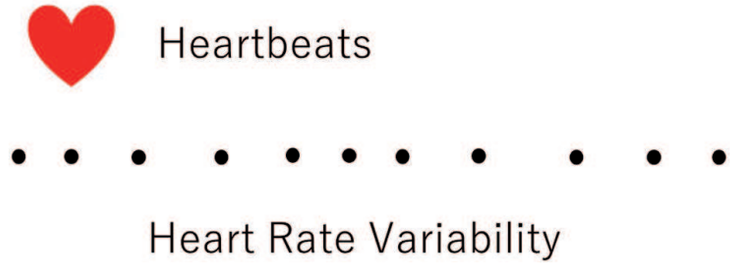

Figure 1.
Inter-heartbeat intervals increase and decrease presenting the heart rate variability (HRV).

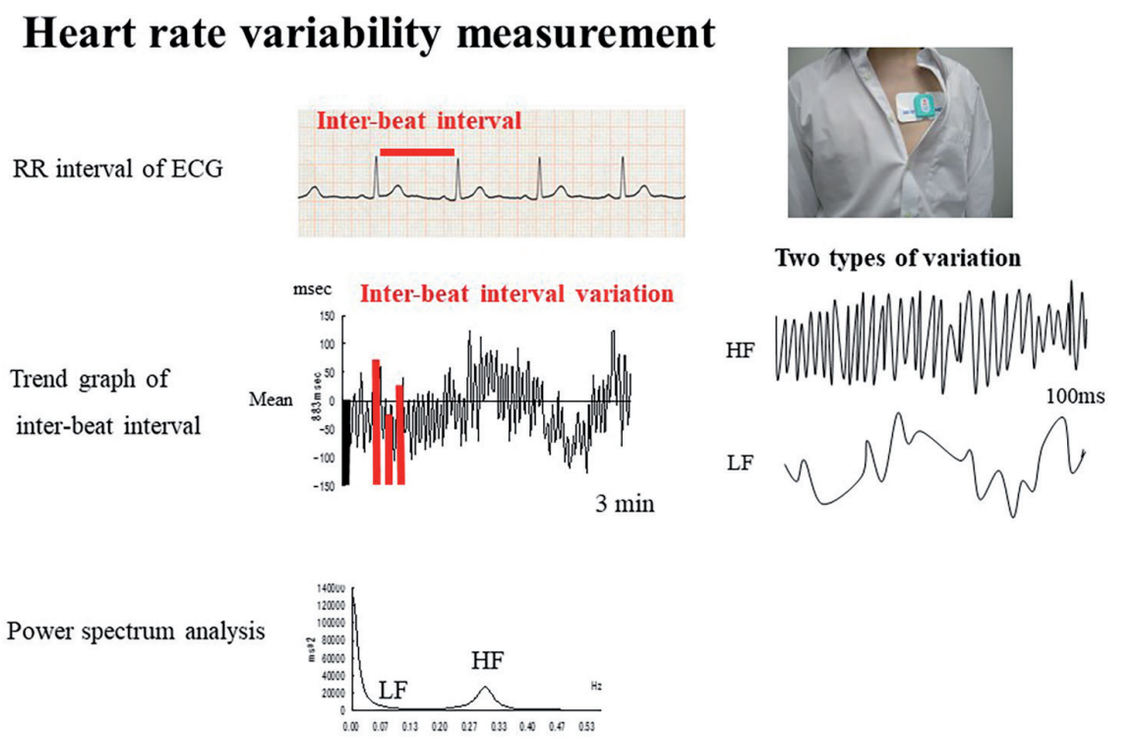

Figure 2.
The methods for heart rate variability (HRV) measurement. RR intervals of electrocardiogram (ECG) are used for creating the RR interval trend graph, which contains both low and high-frequency components (LF and HF). The power spectrum of the trend graph is used to calculate LF and HF by integrating the power in the range designated for LF and HF (0.04–0.15 Hz, 0.15–0.4 Hz, respectively).

their physiological bases have been clarified. The frequency ranges of HF and LF are usually set at 0.15–0.4 Hz and 0.04–0.15 Hz, respectively.

The rhythm of the HF component is related to breathing. Inspiration is accompanied by an increase in heart rate, and expiration by a decrease (**Figure 3**). This modulation is inhibited by the administration of anticholinergic agents such as atropine and is considered to be dependent on parasympathetic activity [8]. The physiological significance for the coupling of breathing rhythm and heart rhythm is not clarified but would be related to the maintenance of constant blood flow under the fluctuation of intrathoracic pressure during breathing activity.

LF component of HRV is generated under the control of baroreceptor [9], and is intimately related to blood pressure fluctuation. When the blood pressure is recorded continuously, the systolic peak fluctuates with an interval of about 10 to 20 seconds. This fluctuation is known as Mayer wave (**Figure 4**). Accompanying this blood pressure fluctuation, heartbeats also vary. When the systolic blood pressure is high, the inter-beat interval is long. When the blood pressure is low, the interval is short (**Figure 4**). It is a homeostatic control to stabilize the blood flow by adjusting the heart rate in response to the changes in blood pressure. Both sympathetic and parasympathetic systems are involved in generating the LF variation.

These observations indicate that HF variation controls the blood flow during various breathing rhythms. LF variation on the other hand stabilizes the blood flow during various activities that accompany changes in blood pressure. Both HF and LF variations serve as safety systems to avoid abrupt changes in blood flow in response to alterations of breathing and somatic condition, respectively. Blood pressure is adjusted automatically, but breathing is modified both unconsciously and consciously. Conscious control of breathing is observed not only during respiration

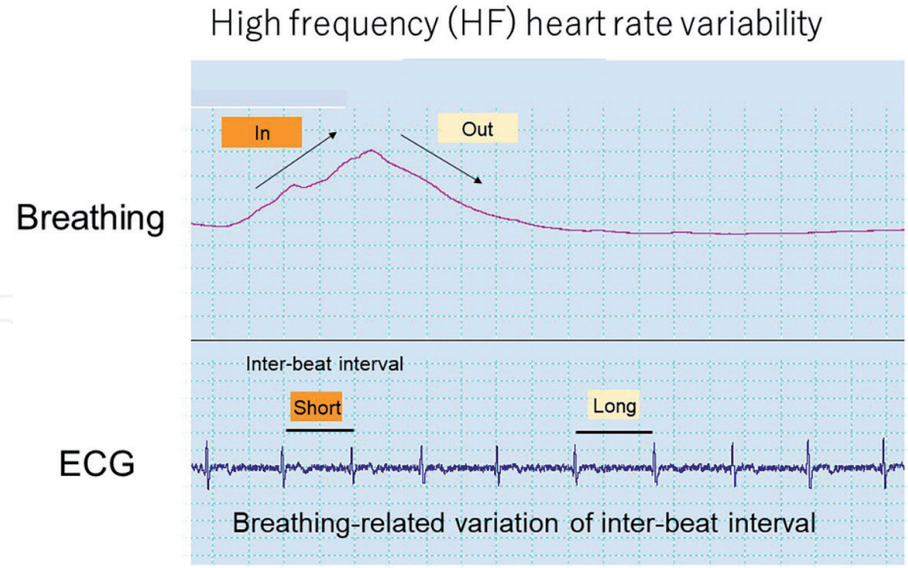

Figure 3.
High frequency (HF) heart rate variability related to breathing. Inspiration (In) is accompanied by shortening of inter-beat interval measured with R-R interval of electrocardiogram (ECG). Expiration (Out) is accompanied by its elongation.

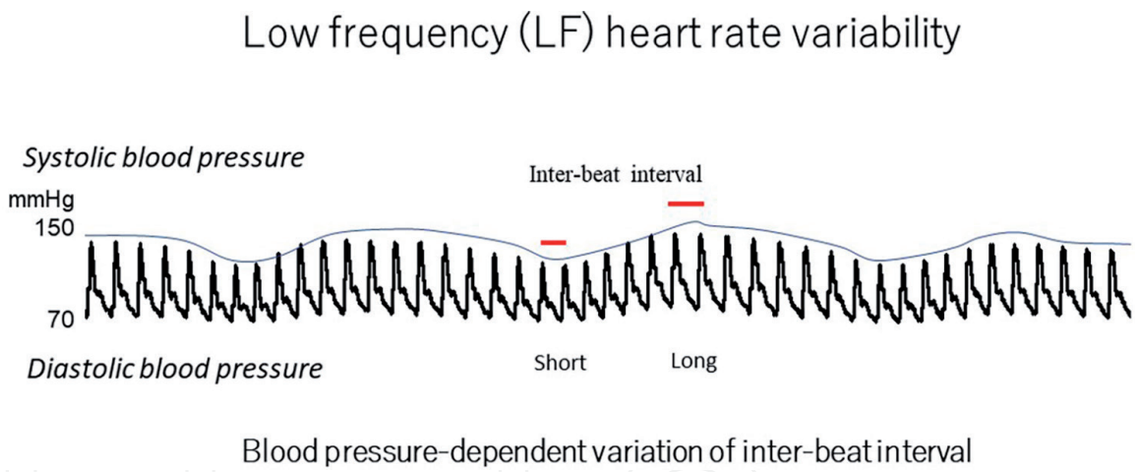

Figure 4.
Low frequency (LF) heart rate variability is dependent on blood pressure. Continuous measurement of blood pressure indicates systolic peaks fluctuate, generating Mayer wave. In response to Mayer wave, inter-heartbeat intervals vary. When the blood pressure is high, the inter-beat interval is long. When the blood pressure is low, it is short.

but during various activities including speaking, singing, and shouting. In various conditions, the HF and LF safeties will be switched on or off to adjust the blood flow and to meet the physiological demand.

HRV is controlled by the autonomic nervous system; sympathetic and parasympathetic. HF variation is large when the parasympathetic system is activated. Interpretation of LF changes in terms of sympathetic or parasympathetic changes is complex because LF variation is controlled by both sympathetic and parasympathetic systems. LF/HF ratio is sometimes used as a parameter representing sympathetic activity, although it is not recommended in some studies [9]. LF/HF can be used to evaluate the balance between breathing-related autonomic activity and blood pressure-dependent autonomic activity.

4. Measurements at rest and during the task load

In the studies on HRV in depression and anxiety, the data at rest condition have been frequently used to analyze the autonomic activity. And in some studies, the data were also recorded during task load or stress. An introduction of task load or stress enables the evaluation of autonomic responsiveness to the load. Random number generation task has been used for the task load in our studies. Random number generation is related to frontal cortical function. In the task, the subject makes a series of digit numbers (0–9) in random order at the speed of 1 Hz [10].

We propose to record HRV at rest (Rest), during task load (Task), and at rest after the task (After) (**Figure 5**). **Figure 5** shows sample data of a normal healthy subject. HF decreases, and LF/HF and HR increase during the task load. These changes of HRV are possibly related to the autonomic modulation in response to the task load and reflect both physical and mental adjustment to stress. Introduction of task load to the assessment of HRV has been found informative on analyzing the autonomic dysfunction of mental disorders [11]. The present chapter is intended to summarize that the Rest, Task, and After scores of HRV are differently altered in depression and anxiety.

Our previous study [12] has indicated the importance of analyzing the change from the rest data to that during the task load. Task/Rest ratio of the HRV indices is

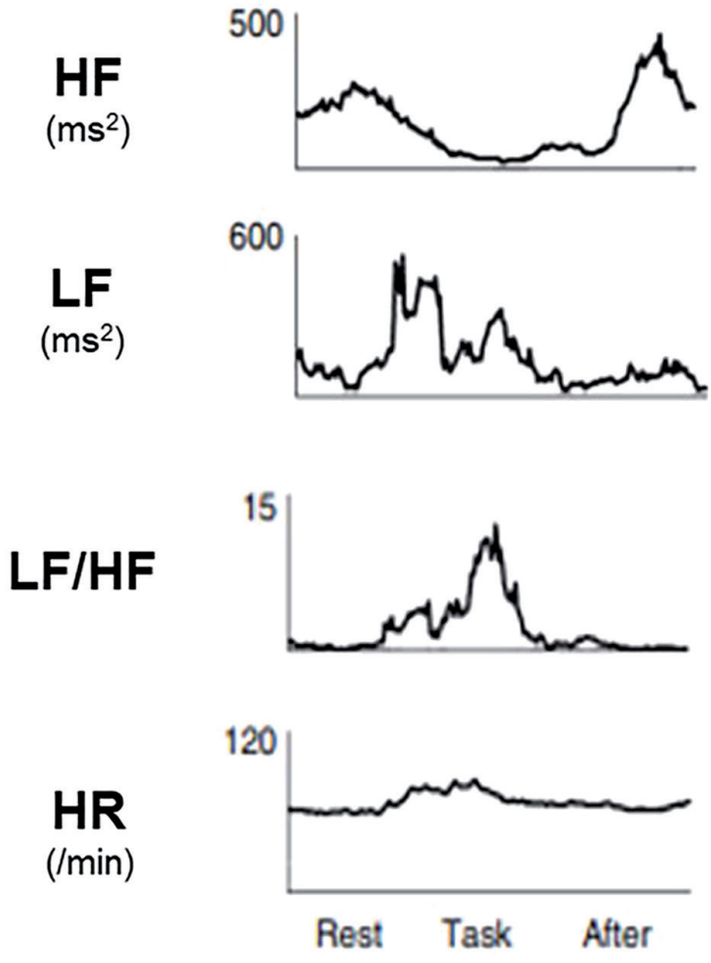

Figure 5.
A sample data of heart rate variability indices at the initial rest period (Rest), during the task load (Task), and during the rest period after the task (After).

used for this purpose, especially for evaluating depressiveness and anxiety. In this study on normal subjects, subjective depressiveness and anxiety were scored by questionnaires; Self-rating Depression Scale (SDS) and State-Trait Anxiety Inventory (STAI) [12]. It has been revealed that the Task/Rest ratio of HF index is significantly correlated with both SDS and STAI scores, confirming the importance of Task/Rest ratio in evaluating depression and anxiety. Below are the HRV profiles of depression and anxiety showing different patterns in the Rest-Task-After paradigm.

5. Characteristic HRV profiles in depression

Figure 6 presents the characteristic HRV profiles at the baseline rest condition (Rest), during the task load (Task) and during the rest condition after the task (After) in the control healthy subjects, in the patients with major depressive disorder (MDD) and in the patients with a general anxiety disorder (GAD). The HRV profiles of MDD and GAD were used in the present chapter to represent that in depression and anxiety. The schematic diagrams are made based on our published data [13]. The data in each measurement condition are connected by lines to clarify the characteristic profiles. LF data are connected by dashed lines to indicate that the inter-subject differences are large not only in the healthy subjects but in the patients with MDD and GAD.

The healthy HF pattern takes the form of a V shape and the healthy LF/HF and HR patterns have inverted V shapes. HF decreases, and LF/HF and HR increase during Task, and they return to the original level at After. This indicates that the breathing-related control of heart rate reflecting parasympathetic activity decreases during Tasks in healthy subjects. It is interesting that inhibition of parasympathetic activity during task load is observed in this paradigm. The parasympathetic inhibition during task load should be a healthy response of the autonomic system to stressful events. LF responses are not consistent. HF and LF react to stressful events differently. HR behaves similar to LF/HF.

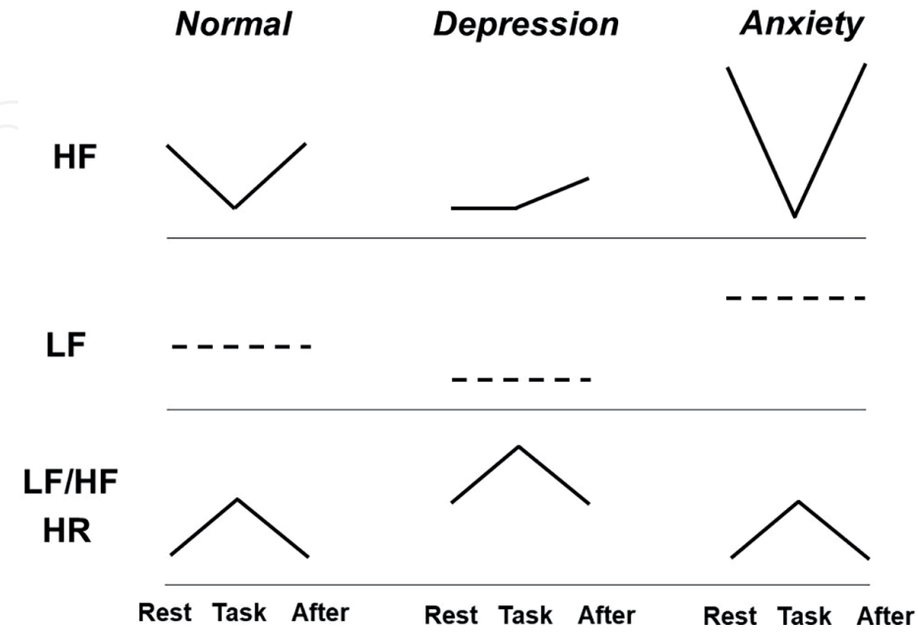

Figure 6.
Schematic diagrams of heart rate variability profiles in major depressive disorder (MDD) and generalized anxiety disorder (GAD). Detailed descriptions are found in the text.

In depression, HF at the resting state is low, indicating the underactivity of parasympathetic system. Parasympathetic underactivity is found not only in depression but in cardiovascular, neurological, and other psychiatric disturbances. In ischemic heart disorder and diabetic neuropathy, the peripheral autonomic nerve function is disturbed. In dementia and epilepsy, organic changes of the brain lead to autonomic alteration. In depression, functional changes of the responsible brain areas should involve the central autonomic system to generate HRV changes.

In addition to baseline change of the parasympathetic activity reflected in low HF, response of HF to the task load is disturbed in depression, making Task/Rest ratio high. Parasympathetic activity cannot be switched off during the task indicating the difficulty in modifying the autonomic activity in response to alteration of arousal level or attention. Unresponsiveness of HF is found not only in MDD [11] but in normal subjects with high depressiveness and anxiety [12]. Subjective scores for depressiveness and anxiety were correlated with Task/Rest ratio of HF in normal controls. Depressiveness and anxiety may be related to parasympathetic unresponsiveness to stress.

Depression is also accompanied by an increase of HF during the rest period after the task load. The rebound-like increase starts after the end of the task and lasts for several tens of seconds. The functional significance of this transient change of HF may be related to excessive excitation of the parasympathetic system after suppression during the task load. Overall, depression is accompanied by continuous suppression together with the uncontrollability of the parasympathetic system.

As for LF, a reduction in the baseline level is observed in depression. But the rebound-like increase is present at the resting state after the task load possibly because LF reflects both sympathetic and parasympathetic activity. LF/HF and HR are higher in depression than in control. Parasympathetic underactivity is also responsible for these changes. It is interesting to observe that LF/HF and HR increase in response to task load although HF and LF are unchanged during the task load. Individual differences during the task load may account for this discrepancy.

6. Characteristic HRV profiles in anxiety

On the other hand, the patients with GAD show an elevation of both HF and LF when they are free of a panic attack or severe phobic symptoms. In contrast to the HRV profile in depression, the parasympathetic system is activated, and breathing-related and blood pressure-dependent modulation of heart rate is enhanced. The elevation of HF and LF at the resting state may be considered as a regulation of autonomic activity to cope with anxiety-related changes. When the regulation does not work, panic attack may occur. During panic attacks and exacerbation of anxiety symptoms, HF decreases and LF/HF increases, reflecting parasympathetic inhibition [6]. But when the anxious state is ameliorated, HRV indices return to the original level [13].

The elevated HF in GAD reacts to the task load by decreasing as in the normal control. Reactivity of parasympathetic activity is maintained in anxiety patients. The elevated LF can contribute to the stabilization of blood flow when the fluctuation of blood flow is large. Such fluctuation would be present during the time of stress. LF elevation may be the sign of an increased control of stress-induced circulatory changes. HRV profiles in GAD can be the result of autonomic accommodation to the anxious state.

7. Conclusions

The present chapter described the different profiles of HRV found in MDD and GAD, and tried to delineate the functional significance of the findings in terms of autonomic activity. It is interesting to use HF and LF indices to evaluate the pathophysiology of mental disorders based on the physiological mechanisms underlying HRV.

Although depression and anxiety coexist frequently, the patterns of autonomic dysregulation show differences when viewed from HRV analyses. Depression is mainly accompanied by parasympathetic inhibition and unresponsiveness. In anxiety, augmentation of parasympathetic activity is present during the condition when the symptoms are controlled. When phobic symptoms appear, parasympathetic activity lowers and the autonomic balance is lost. Then the autonomic dysregulation in anxiety becomes similar to that of depression.

It should be important to understand the differences and similarities to evaluate the pathophysiology of depression and anxiety in clinical practices. Differentiation of depressive and anxious conditions using HRV measures can be useful for adequate pharmacological, psychological, and behavioral therapies [14].

Conflict of interest

The author declares no conflict of interest.

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