Estimation of Chronic Stress by Measuring Sympathetic Sedation Time

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Abstract: Intermittent exposure to stressors disrupts the negative feedback mechanism of cortisol toward corticotropin-releasing hormones. In this study, this condition is referred to as chronic stress. Chronic stress causes a variety of recurring, long-term, incurable illnesses, such as major depression. Therefore, it is important to understand chronic stress on a daily basis. We propose a chronic stress estimation method using sympathetic sedation time measurements as a non-invasive, short-time, and highly accurate method. This method determines the degree of chronic stress according to the length of time until the sympathetic activity subsides after stressor loading. To verify the feasibility of the proposed method, we conducted an experiment comparing the sympathetic sedation times among a healthy group, middle group, and chronic stress group classified by the Quick Inventory of Depressive Symptomatology. We calculated sympathetic sedation time from the trend of change in RRV at calm after stressor loading due to a two-back task. As a result of the experiment, which consisted of nine participants, the sympathetic sedation time in the chronic stress group was longer than in the healthy and middle groups, supporting the feasibility of this method.

1 INTRODUCTION

Normally, when a person is exposed to a stressor, corticotropin-releasing hormone (CRH) is secreted from the hypothalamus. As a result, adrenocorticotropic hormone (ACTH) is secreted from the anterior pituitary gland, which promotes the secretion of cortisol from the adrenal cortex. Even though cortisol causes various stress responses, including hippocampal atrophy, it has a negative feedback mechanism for CRH and ACTH, and this feedback will eventually cause the stress response to disappear. However, intermittent exposure to stressors deteriorates the negative feedback function of cortisol (Fink, 2010; Contoreggi, 2015) (Fig.1). In this study, we define a condition in which the negative feedback function of cortisol deteriorates as chronic stress.

Chronic stress can cause a variety of illnesses. Chronically high levels of cortisol can cause hippocampal atrophy and impaired memory (Vachon-Presseau et al., 2013). In addition, it causes chronic high blood pressure and blood sugar levels, which can lead to diabetes. Chronically high levels of CRH due to the deterioration of the negative feedback

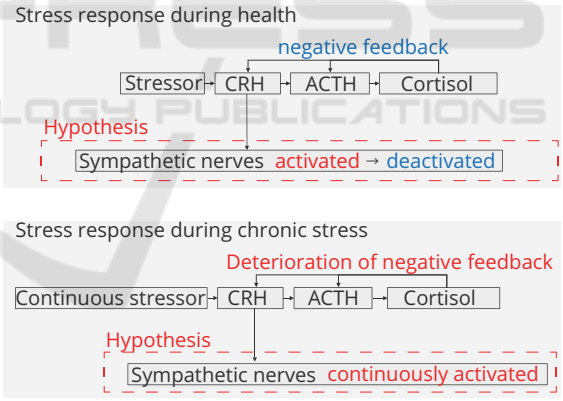

Figure 1: Stress response in healthy and chronic stress states.

mechanism of cortisol may promote fear conditioning by the amygdala and predispose individuals to post-traumatic stress disorder (Hashimoto et al., 2017). High CRH levels can also lead to high dopamine levels and impair cognitive function (Fink, 2010). If these diseases persist for a long period of time, they can lead to major depression. These diseases, including major depression, are prone to recurrence and have a long treatment period (Clinic, 2020). Moreover, high levels of cortisol exposure damages the hippocampal and prefrontal cortex nerves, and may

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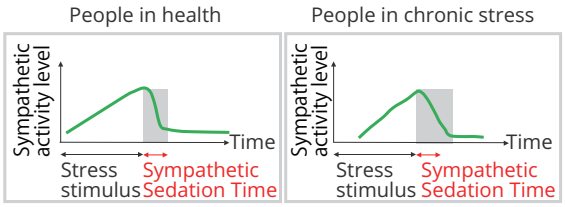

Figure 2: Estimation of chronic stress by measuring sympathetic sedation time after stressor.

not cause neurogenesis, depending on age and severity of the depression (Contoreggi, 2015; Van Wingen et al., 2012). Chronic stress conditions can cause various diseases that are prone to recurrence, have a long treatment period, and may not be completely cured. Therefore, we believe it is important to understand the chronic stress state on a daily basis to prevent these diseases.

The prior methods of chronic stress estimation can be broadly classified into two types. One method measures changes in behavior and cognition caused by chronic stress, and the other measures biological information related to the negative feedback mechanism of cortisol.

As a method for measuring changes in behavior and cognition, questionnaires, such as PSS-14, and the estimation of a chronic stress state from a change tendency of the pressure distribution on the seat surface of a chair are used (Katsunori, 2006; Cohen et al., 1983; Kuroha et al., 2019). In addition, chronic stress can be estimated by lifestyle change such as sleeping time collected from smartphones (Opoku Asare et al., 2019; Dogan et al., 2017; Rohani et al., 2018; Wang et al., 2018). PSS-14 is a questionnaire that consisting of 14 question items on a five-level Likert scale. It is assumed that the response is made by remembering the events within one month or one week, and the chronic stress state can be estimated in a short time. Since the answers in the questionnaire are subjective evaluations, there are difficulties of inaccurate answers if the participant does not answer seriously or if they are not aware of their own stress. In the method using the change in seat pressure, the chronic stress state can be easily estimated non-invasively by sitting on a chair for a long duration using a cushion equipped with a pressure sensor. In the method using smartphones, chronic stress can be easily estimated from information such as screen startup time and sleep time collected from them. However, the estimation accuracy is low in these methods because the biological reaction under chronic stress is not directly measured.

Two of the methods for estimating biological information with regards to the negative feedback mechanism of cortisol are the DEX/CRH test and salivary cortisol concentration measurement (Heuser et al., 1994; Hellhammer et al., 2009). In the DEX/CRH test, dexamethasone (DEX) is administered before bedtime, and the blood cortisol concentration when CRH is administered in the next morning is measured. Dexamethasone is a long-acting artificial cortisol. Healthy individuals have low cortisol levels even after CRH administration due to the negative feedback mechanism. On the contrary, under chronic stress, high cortisol is measured after CRH administration, thus, the chronic stress state can be measured. The challenge with this method is that it is invasive, requiring at least three injections of DEX and CRH administration, and cortisol collection. Another difficulty is that the load test time is up to several hours. Estimating by salivary cortisol concentration, another measurement method, can measure chronic hypercortisol status non-invasively. The challenges of this method is that the salivary hypercortisol status is caused not only by a decrease in the negative feedback mechanism of cortisol, but also by the diurnal variation of cortisol and acute stressors, thus, strict control is required for measurements. Another difficulty is that it takes several hours to analyze the salivary cortisol concentration.

Overall, the behavioral and cognitive changes due to chronic stress can be assessed non-invasively and quickly, but the accuracy is low. On the contrary, the method for measuring biological information with regards to the negative feedback mechanism of cortisol is highly accurate because it directly measures the biological reaction in a chronic stress state, but the measurement is long-term or invasive. Therefore, the purpose of this study is to design a non-invasive, fast, and highly accurate chronic stress measurement method and to evaluate its accuracy.

2 CHRONIC STRESS ESTIMATION METHOD BY MEASURING SYNPATHETIC SEDATION TIME

In this study, we propose chronic stress estimation by sympathetic sedation time measurements as a non-invasive, fast, and highly accurate chronic stress measurement method. A stressor is applied to an user, the time during which the sympathetic nerve activity subsides is measured, and the chronic stress state is estimated from this time duration. We believe that the sympathetic nerve activity sedation time is longer under chronic stress, as detailed below (Fig.2).

The negative feedback function of cortisol is dete-

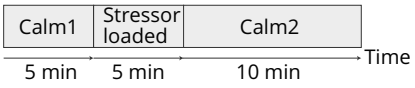

Figure 3: Proposal method procedure.

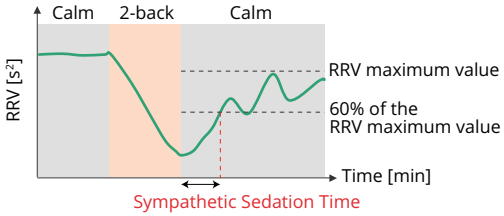

Figure 4: How to calculate sympathetic sedation time.

riorated under chronic stress. As a result, those with chronic stress are considered to have high CRH for a long time after stressor loading. CRH may promote sympathetic nerve activity. Habib et al. found that male rhesus monkeys orally administered with the CRH antagonist antaramine have reduced sympathetic nerve activity when confronted with other male individuals compared to placebo individuals (Habib et al., 2000). Therefore, we believe that under a chronic stress state, the sympathetic nerve activity activated by the stressor is difficult to sedate because CRH does not decrease after stressor loading(Fig.1).

Therefore, we believe that the chronic stress state can be estimated by loading the stressor on the user and measuring the time for the subsequent sympathetic nerve activity to subside. This method is expected to be highly accurate as it measures biological reactions related to the negative feedback mechanism. In addition, since it is a sympathetic nerve measurement, it can be measured non-invasively by a sensor, such as an electrocardiogram. The measurement time is approximately 30 min. This time is shorter than that of the DEX/CRH test and saliva cortisol concentration measurements, which is an advantage.

We describe the details of the proposed method. First, the user remains calm for 5 min to soothe sympathetic activity. During this time, respiratory control is performed to enhance the effect of calming. The respiratory cycle is set to 12 times/min as a sufficiently slow cycle to sedate the sympathetic nerves. Next, user is loaded the stressor for 5 min. Then, the user remains calm for 10 min. During this period, the sympathetic nerve activity is measured, and sympathetic sedation time is calculated. As sympathetic nerve activity changes depending on the respiratory cycle, it may be necessary to suppress the variation in sympathetic sedation time due to the respiratory cycle by controlling breathing during calming after the stressor. Therefore, the effect of sympathetic sedation time due to respiratory control during calming after the stressor was examined. The flow of the proposed method is described in Fig.3.

In this study, the required function of the stressor used in the proposed method was defined as causing a stress response that causes cortisol secretion. In addition, as a constraint condition, the load can be loaded within a short time of several minutes. We selected the two-back task as the stressor that satisfies these functions. Even though there are many variations of this task, we selected one in which recordings of numbers from one to five are played through headphones every second and a participant has to press the space key only when the number matches that read two prior.

In this study, we assumed that the sympathetic nerve was sedated when the R-R interval variability (RRV) at calm after the two-back task exceeded 60% of the maximum value of RRV at calm. The time taken until the sympathetic nerve was sedated for the first time after the two-back was defined as the sympathetic nerve sedation time (Fig.4). RRV is the variance of the interval between R waves during 1 min for electrocardiography and is a parasympathetic index. Since the sympathetic and parasympathetic nerves have an antagonistic effect, the sympathetic nerve appears to be sedated by the increase of RRV.

3 EXPERIMENT

3.1 Overview

To verify the possibility of estimating chronic stress by measuring the sympathetic sedation time, we recruited experimental participants and conducted an experiment. Assuming that the higher the degree of depression, the higher the degree of chronic stress, the participants were divided into three groups using the Quick Inventory of Depressive Symptomatology (QIDS), which is a diagnostic criterion for depression (Rush et al., 2003). The QIDS scores ranged from zero to five points in the healthy group, six to 10 in the middle group, and at least 11 points in the chronic stress group. The sympathetic nerve sedation time of each group was compared. In addition, as described in the previous chapter, the sympathetic nerve sedation time may change depending on the respiratory control, thus, the effect of the respiratory control at calm after the two-back task shown in Fig.3 was examined. This experiment is approved by the Ethics Review Board.

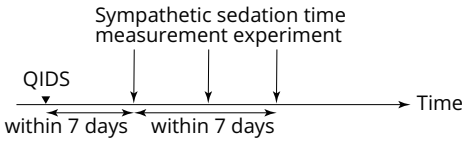

Figure 5: Experiment flow.

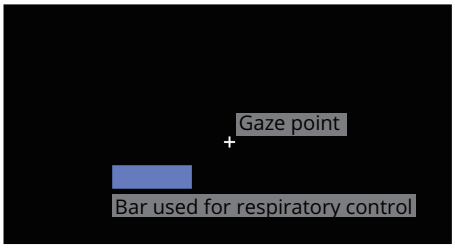

Figure 6: Point of gaze at calm.

3.2 Experiment Flow

First, the participants filled in the QIDS within one week prior to the sympathetic sedation time measurement experiment. Then, the participants were subjected to a sympathetic sedation time measurement experiment three times on different days. The three sympathetic sedation time measurement experiments differed only in the respiratory control conditions at calm after the two-back task. The first and last experiments for each participant were scheduled within seven days so that the chronic stress status of the participants did not change significantly between experiments. Since the sympathetic nerve sedation time changes depending on the diurnal variation of cortisol, the sympathetic nerve sedation time measurement experiment was performed from 15:00 to 17:00 when the diurnal variation of cortisol was small. In addition, to suppress fluctuations in the diurnal variation of cortisol, alcohol and caffeine intake, strenuous exercise, and staying up late the day before the experiment were prohibited. The flow of the experiment is shown in Fig.5.

In the sympathetic sedation time measurement experiment, the process described in the previous chapter was performed using a GUI.

1. **Calm1:** Participants were instructed to look at a cross gaze point for 5 min and rest to calm the sympathetic nerves (Fig.6). At that time, respiratory control was performed at a cycle of 12 times/min to enhance the effect of sympathetic nerve sedation. Respiratory control was performed according to the expansion and contraction cycle of the blue bar shown in Fig.6.
2. **2-Back Task (Stressor Loaded):** Participants were instructed to perform the two-back task for 5 min while looking at the same gazing point as in Calm1. This task involves the playing of a reading of any number from one to five through headphones every second, and participants press the space key when the number matches two numbers prior (Fig.7). Unlike Calm1, respiration was not controlled. This is because we believe that respiratory control reduces the ability to concentrate on the two-back task and reduces stress load.

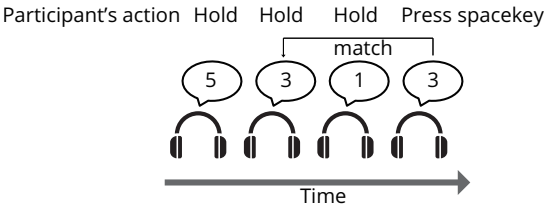

Figure 7: 2 Back task.

3. **Calm2:** To measure the sympathetic sedation time, participants were instructed to look at the gaze point for 10 min and calm. Three conditions were prepared for respiratory control as follows: no respiratory control, fast respiratory control (20 times/min), and slow respiratory control (12 times/min). Under the no respiratory control condition, the blue breathing control bar did not appear, participants were instructed to breathe naturally. Under fast or slow respiratory control conditions, participants were instructed to breathe according to the expansion and contraction cycle of the blue bar. Before the experiment, participants were told under which respiratory control conditions the experiment would be conducted. The order of these conditions was counterbalanced among the participants.

This process was performed by looking at the PC screens installed in the compartments separated by partitions. During this process, the electrocardiogram was measured and the R-R Interval (RRI) was calculated. Electrocardiogram was measured at 1000 Hz using biosignalsPlux. R waves were detected by first passing the electrocardiogram through a Butterworth filter from 0.05 to 26 Hz and then using the biosppy library(Carreiras et al., 15). Furthermore, the RRI variability (RRV) was calculated for each minute window and used as a parasympathetic nerve activity index. The time when RRV after the two-back task exceeded the threshold for the first time was defined as sympathetic sedation time. The threshold was set to 60% of the maximum value of RRV after the two-back task (Fig.4).

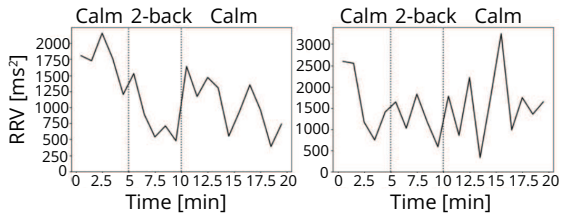

Figure 8: RRV time series of participants. The left side refers to the healthy group. The right side refers to the chronic stress group.

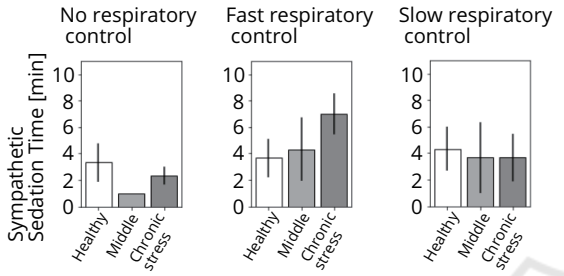

Figure 9: Sympathetic sedation time for each respiratory condition. The left side is under no respiratory control. The center is under fast respiratory control. The right is under slow respiratory control.

4 RESULTS

We recruited nine participants to this study. The QIDS classification revealed three healthy individuals (one male and two females in their 20s), three middle groups (three males in their 20s), and three chronic stress groups (three males in their 20s). The mean and standard errors of the QIDS scores were 3.33 ± 0.98 in the healthy group, 6.00 ± 0.00 in the middle group, and 13.66 ± 1.78 in the chronic stress group.

Fig.8 shows the RRV data of a participant in a healthy group under no respiratory control and that of another participant in the chronic stress group under no respiratory control. In the healthy participant (left), RRV increased immediately after the two-back task, that is, the sympathetic nerves were sedated immediately. On the contrary, in the chronic stress participant (right), RRV increased approximately 5 min after two-back (experimental time 15 min), that is, it took some time to sedate the sympathetic nerves.

Next, we calculated the mean and standard error of the sympathetic sedation time described in Chapter 3 for each respiratory control condition and participant group. The results are shown in Fig.9. In addition, the threshold values of sympathetic nerve sedation used when calculating the sympathetic nerve sedation time were 70% and 80% of the RRV maximum value, shown in Fig.10.

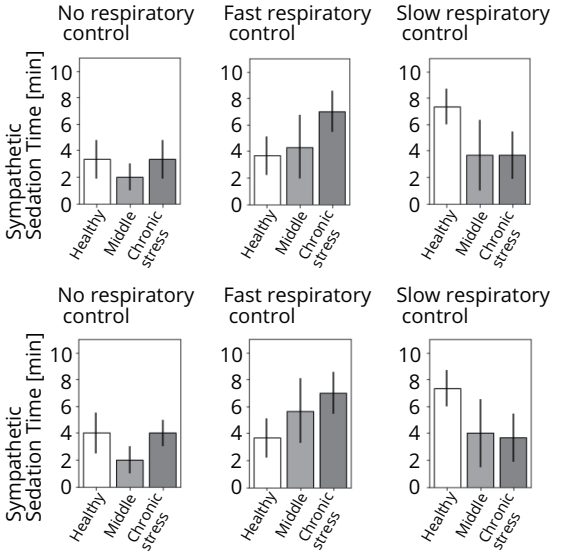

Figure 10: Upper row: Results when the threshold for sympathetic sedation is 70% of the maximum RRV value. Lower: 80%.

5 DISCUSSION

5.1 Respiratory Control

As shown in Fig.9,under no and slow respiratory control,the hypotheses of shorter sympathetic sedation time in the healthy group and longer sympathetic sedation time in the chronic stress group were not met. However, under fast respiratory control conditions, the hypothetical tendency was confirmed. A similar tendency was confirmed when the threshold for sympathetic sedation was set to 70% or 80% of the maximum RRV value (Fig.10).The hypothesis being met only under fast respiratory control was considered to be because this respiratory control at calm is also a stressor, and the sympathetic nerve sedation time is longer than that of no respiratory control in both the healthy and chronic stress groups. However, in the chronic stress group, the negative feedback function of cortisol was reduced, and the effect of prolonging the sympathetic sedation time by fast respiratory control was greater than that of other groups. The chronic stress state may be estimated from the sympathetic sedation time by performing fast respiratory control at calm after two-back. To make the feasibility verification of the proposed method more reliable, the following factors could be improved.

5.2 Sympathetic Sedation Time

In this verification, the sympathetic sedation time was calculated using only the RRV of the electrocardiogram as an index, but RRV is affected by the respiratory cycle as well as the sympathetic nerves. The results must be verified from various angles using other sympathetic nerve indexes, such as pupil diameter, electro dermal activity, etc. In addition, the sympathetic nerves were sedated when RRV after two-back exceeded 60% of the maximum value for the first time, but the threshold value of 60% is necessary for comparison with various threshold values of other sympathetic nerve indexes.

5.3 Stressor

In this study, the two-back task was selected as a stressor that secretes cortisol, but this task leads to a low amount of cortisol secretion (Henckens et al., 2011). Since the proposed method is intended to measure the decrease in the negative feedback mechanism of cortisol, the stressor needs to cause the secretion of cortisol. For example, the Trier Social Stress Test (TSST) results in the secretion of cortisol, but the process is very long and the second presentation shows acclimatization and significantly reduced cortisol secretion (Yao et al., 2016; Dhabhar et al., 1997; Wüst et al., 2005; Schommer et al., 2003). We need to design a cortisol-secreting stressor that can be presented in a short period of time and with little familiarity.

6 CONCLUSION

In this study, we propose chronic stress estimation through sympathetic sedation time measurements as a non-invasive, fast, and highly accurate method. In this method, a stressor is applied to an user, the time until the sympathetic nerve activity subsides is measured, and the chronic stress state is estimated from the length of time.

We recruited nine participants to this study. As a result, we confirmed that the sympathetic sedation time tended to be longer in the chronic stress group than in the healthy group by performing fast respiratory control after stressor loading. Moreover, we believe that the following improvements could make the demonstration of feasibility more reliable.

1. Multifaceted verification of whether the sympathetic nerve has sedated.
2. Optimal stressor design for sympathetic sedation time measurement.

After demonstrating the feasibility of chronic stress estimation by measuring sympathetic sedation time through the above improvements, we aim to design a wearable device that integrates a sensor for measuring sympathetic sedation time as well as a stressor presentation device. We believe that with the development of such devices, anyone will be able to identify their chronic stress state on a daily basis and prevent mental illnesses, such as major depression.

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