

## News Release

### Title

### Researchers discover psychosomatic mechanism in the brain

### Key Points

- **Researchers discovered a psychosomatic central neural pathway transmitting psychological stress signals from the cerebral cortex to the hypothalamus.**
- **Genetic lesion or optogenetic inhibition of this pathway eliminated a variety of sympathetic and behavioral responses to psychosocial stress.**
- **This pathway is a potential target for treating stress-related disorders.**

### Summary

A research team led by Professor Kazuhiro Nakamura and Designated Assistant Professor Naoya Kataoka (Department of Integrative Physiology) at Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu, MD, PhD) discovered a psychosomatic neural pathway linking the circuit processing stress and emotion with the system controlling vital functions.

Psychosomatic responses are widely known as a variety of body's responses to psychological stress and emotion. However, it has long been unknown how stress and emotion signals in the brain affect the central circuit systems controlling vital functions, such as the autonomic nervous system.

The researchers discovered a central neural pathway that transmits stress signals from the dorsal peduncular cortex and dorsal tenia tecta (DP/DTT), an unexplored medial prefrontal cortical area, to the dorsomedial hypothalamus (DMH), a hypothalamic center controlling the sympathetic nervous system. Genetic lesion or optogenetic inhibition of this pathway eliminated psychological stress-induced increases in body temperature, heart rate and blood pressure, as well as suppressed avoidance behavior from stressors.

These findings demonstrate that the discovered DP/DTT→DMH pathway mediates central psychosomatic master signaling to drive a variety of autonomic and behavioral stress responses by connecting the corticolimbic emotion system to the hypothalamic motor control systems. This discovery potentially contributes to the development of novel strategies for treating psychosomatic disorders, such as panic disorder, post-traumatic stress disorder and psychogenic fever.

Their findings were published in the online edition of the journal *Science*.

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## Research Background

Psychological stress and emotions affect the regulations of vital functions to elicit various responses, which are called psychosomatic responses. For instance, psychological stress increases body temperature, heart rate and blood pressure by activating the hypothalamic brain area controlling the sympathetic nervous system. However, it has been an open question how stress and emotion signals in the brain activate the hypothalamic autonomic center. Addressing this question would significantly contribute to understanding the etiologies of many psychosomatic disorders.

## Research Results

The researchers sought for brain neuronal groups that transmit psychological stress signals to the dorsomedial hypothalamus (DMH), which controls the sympathetic nervous system. They discovered a group of DMH-projecting excitatory neurons in the dorsal peduncular cortex and dorsal tenia tecta (DP/DTT), an unexplored medial prefrontal cortical area, in rats. These neurons were found to transmit stress signals to the DMH and thereby, activate the sympathetic nervous system to increase brown adipose tissue thermogenesis, heart rate and blood pressure.

Genetic lesions of DP/DTT→DMH projection neurons suppressed brown adipose tissue thermogenesis and hyperthermia evoked by exposure of the rats to social defeat stress, an animal model of psychosocial stress (Fig. 1A and B). On the other hand, the lesioned rats exhibited intact regulation of normal body temperature. *In vivo* optogenetic inhibition of DP/DTT→DMH projection neurons also strongly inhibited stress-induced increases in body temperature, heart rate and blood pressure (Fig. 1C and D). These results indicate that the transmission of psychological stress signals mediated by the DP/DTT→DMH pathway is essential to drive sympathetic stress responses, while this pathway does not contribute to the basal maintenance of homeostasis.

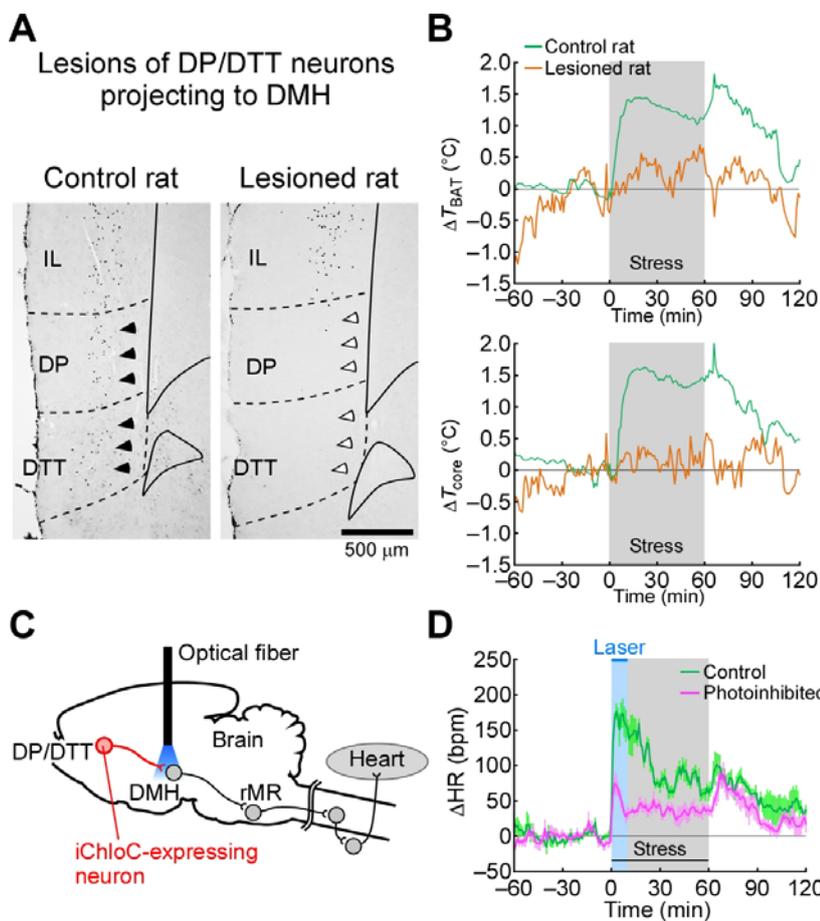
Stressed animals usually exhibit avoidance behavior from the stressors. However, the test rats in which the DP/DTT→DMH pathway was optogenetically inhibited did not show avoidance, but did interact with the stressor rats that had attacked the test rats during social defeat stress beforehand (Fig. 2). This finding shows that the DP/DTT→DMH pathway also drives avoidance behavior from stressors, as well as sympathetic stress responses.

In addition, the DP/DTT was found to receive stress signal inputs from multiple emotion-related forebrain regions, indicating that the DP/DTT integrates stress and emotion signals from the forebrain regions and transmit the integrated psychosomatic signal to the DMH to drive the variety of sympathetic and behavioral responses (Fig. 3).

## Research Summary and Future Perspective

The researchers discovered an important brain neural pathway mediating psychosomatic responses. Retrogradely tracing the neural pathway from the DP/DTT may lead to

elucidation of the scientific entity of what we call “stress” and “emotion”. Also, the present findings will contribute to understandings of the etiologies of stress-related disorders involving aberrant psychosomatic responses, such as panic disorder, post-traumatic stress disorder (PTSD) and psychogenic fever. The DP/DTT→DMH pathway may particularly be a good target for treating such disorders because this pathway does not contribute to basal homeostasis of the body.



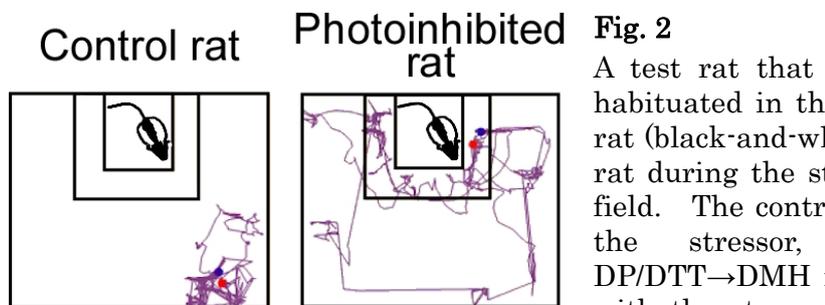
**Fig. 1**

A: Genetic lesions of DP/DTT→DMH projection neurons (black spots). Compared with the control rat (left), neurons in the DP/DTT area (arrowheads) disappeared in the lesioned rat (right).

B: Social defeat stress (gray) increased temperatures of brown adipose tissue ( $\Delta T_{BAT}$ ) and body core ( $\Delta T_{core}$ ) in the control rat, but not in the lesioned rat.

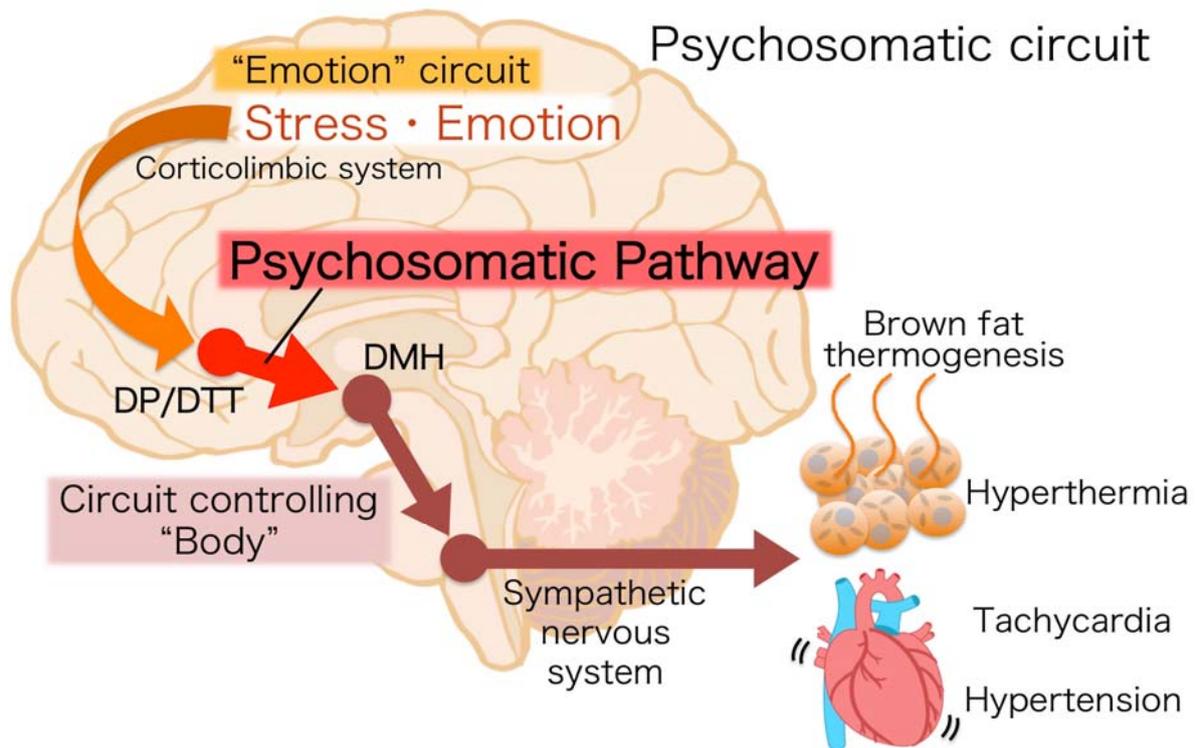
C: *In vivo* optogenetic inhibition of DP/DTT→DMH neurons transduced with the photosensitive chloride channel, iChloC.

D: Photoinhibition of DP/DTT→DMH neurons for 10 min suppressed the increase in heart rate (HR) induced by social defeat stress.



**Fig. 2**

A test rat that had received social defeat stress habituated in the test field, and then the stressor rat (black-and-white rat) that had attacked the test rat during the stress was caged and placed in the field. The control test rat (left) stayed away from the stressor, whereas photoinhibition of DP/DTT→DMH neurons (right) actively interacted with the stressor rat. Behavior of test rats was traced for 10 min.



**Fig. 3**

Psychosomatic neural circuit in the brain. The brain has the corticolimbic circuit system processing emotion and stress as well as the circuit system controlling the body (vital functions) through the autonomic (sympathetic and parasympathetic) nervous system. The neural pathway linking the two circuit systems has been unknown. The researchers discovered the psychosomatic pathway (red) from the DP/DTT to the DMH that links the two systems.

### Publication

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A central master driver of psychosocial stress responses in the rat.

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