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Current Opinion in Behavioral Sciences

Resilience to stress and social touch

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Modern lifestyle and adversities such as the COVID-19 pandemic pose challenges for our physical and mental health. Hence, it is of the utmost importance to identify mechanisms by which we can improve resilience to stress and quickly adapt to adversity. While there are several factors that improve stress resilience, social behavior—primarily in the form of social touch—is especially vital. This article provides an overview of how the somatosensory system plays a key role in translating the socio-emotional information of social touch into active coping with stress. Important future directions include evaluating in humans whether stress resilience can be modulated through the stimulation of low-threshold C-fiber mechanoreceptors and using this technology in the prevention of stress-related neuropsychiatric disorders such as major depressive disorder.

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Current Opinion in Behavioral Sciences 2022, **43**:75–79

This review comes from a themed issue on **Body–brain interactions/affective touch**

Edited by **Annett Schirmer** and **Francis McGlone**

For complete overview of the section, please refer to the article collection, "Body–brain interactions/affective touch"

Available online 14th September 2021

https://doi.org/10.1016/j.cobeha.2021.08.011

Introduction

Modern lifestyle is associated with high levels of stress, especially in the work environment [1]. Additionally, there are social challenges facing humanity today such as the mental health crisis arising from the COVID-19 pandemic. SARS-CoV-2 and its hazardous variants have greatly increased the level of stress in our lives, mainly because they increased perceived threat and social isolation. As a consequence, mental illnesses such as major depressive disorder and anxiety disorders are becoming more prevalent [2]. In order to understand the relationship between resilience to stress and social touch, it is essential to first understand the neurobiological mechanisms of the stress response.

Stress is a concept that was coined by Hans Selye in the last century. This concept describes the way that the physiology of our body continually seeks to conform to environmental demands and adapt to them [3]. Through our sensory systems we perceive these environmental demands or stressors. Sensory information is translated into action potentials in the sensory organs and that information travels to the brain where the danger levels of stressors are evaluated [4]. When the integrity of the organism is threatened, brain structures such as the amygdala and the hypothalamus issue bodily changes and modulate the response to stress [5••]. One important component of this response engages the sympathetic nervous system leading, among others, to the release of adrenaline from the medulla of adrenal glands into the blood [6]. Adrenaline increases heart rate and blood circulation, preparing the body to cope with stress [6]. A second system to be recruited is the hypothalamic-pituitary-adrenal (HPA) axis, which is part of the slow response to stress [6]. This neuroendocrine axis translates the neuronal activity associated with stress into a hormonal message that is sent to the adrenal glands [6]. From the cortex of these glands, the main stress hormone (cortisol in humans and corticosterone in rodents), is released into the blood [6]. These hormones increase blood sugar and produce the energy needed to sustain bodily activity under adverse conditions [6]. There are several extra-hypothalamic systems that play a key role both in the generation and regulation of stress responses including, for example, the locus coeruleus and the endocannabinoid system [7].

Stress and the somatosensory system

Sensory systems play a fundamental role in stress since they are responsible for transmitting information from the environment to the amygdala in order to activate and deactivate stress responses. Without that information, the amygdala cannot evaluate the possibility of danger and modulate responses to stress accordingly [8]. Despite the importance of sensory systems in both inducing and inhibiting stress, their therapeutic potential has been left largely untapped.

One potential therapeutic application involves the somatosensory system and, more specifically, the cutaneous mechanoreceptors of the skin — also known as low-threshold mechanoreceptors (LTMs) [9]. These LTMs contain a class of unmyelinated C fibers that are called CLTM in non-human animals and C-Tactile (CT) afferents in humans [10]. These fibers prefer gentle, dynamically moving stimuli at velocities between 1–10 cm/s and are believed to convey affective touch between conspecifics [11]. The socio-emotional information from affective touch reaches an area of the brain called the posterior insula [12••]. This area is a multi-sensory hub and well connected with the anterior insula [13] and through this way it connects with other parts of the brain including the prefrontal cortex, anterior cingulate cortex, orbitofrontal cortex, and amygdala [14]. Therefore, affective touch could be a key factor to improve adaptation to stressors and promote resilience to stress. Note, however, that touch targeted towards other LTMs such as A-beta fibers and their projections to primary and secondary somatosensory cortex may also be relevant for stress.

Resilience to stress

Our early life experiences and associated epigenetic changes including, for example glucocorticoid receptor expression, remodel the brain circuits that modulate stress responses [15,16]. Just as a runner improves their performance through daily training, the biological mediators that regulate the response to stress improve their performance each time we are exposed to stressors and adapt to them. In the early 1970s, Norman Garmezy was the first to focus his attention on how humans cope with stress [17]. He observed that some children had an active way of coping with stress and were able to adapt faster [17]. Garmezy coined the term 'resilience' to explain this phenomenon and defined it as the ability to adapt quickly to adversity [17]. Resilience to stress is a biological-behavioral process that is continuously generated over time when we are exposed to stress and adapt to it [18•]. Simply put, resilience emerges from the learning generated from our life experiences with stress.

The concept of allostasis put forward by Bruce McEween can help elucidate this idea: stress pushes us away from the homeostasis or balance we have with the environment in which we live [5••]. Allostasis is related to the process of going back to homeostasis in which the physiological parameters necessary for the mediators of the stress response to function outside of homeostasis are generated [5••]. In this scenario, the performance of the sympathetic nervous system and the HPA axis demand an energy cost or allostatic load that allows adaptation to stress [5••]. Glucocorticoids, for example, cortisol and corticosterone, by the activation of glucocorticoid receptors, translate the effects of stress into changes in neuronal plasticity in brain structures that control the response to stress, such as the hippocampus and the medial prefrontal cortex [19]. Thus, stress hormones improve the performance of allostatic mediators, such as the sympathetic nervous system and HPA axis, when they are exposed to stressors again [5••]. This improves the coping response to stress, in turn, allowing a faster adaptation to stressors [19]. When adaptation to stress does not happen, an allostatic overload is generated which triggers an imbalance both in the release of glucocorticoids, as well as in the ratio between the glucocorticoid receptors and mineralocorticoid receptors [20•]. Mineralocorticoid receptors have a 10-fold higher affinity for corticosterone compared to glucocorticoid receptors. At the beginning of the stress response, mineralocorticoid receptors bind glucocorticoids in the cytoplasm of neurons, while glucocorticoid receptors are activated at the end of the stress response and participate in adaptation and recovery [20•]. At a pathological level, imbalance in the ratio between the glucocorticoid receptors and mineralocorticoid receptors triggers neuroinflammatory processes, mainly in the hippocampus, amygdala and medial prefrontal cortex, which impair the ability to cope with stress, increasing the susceptibility to stress-related neuropsychiatric diseases, such as mood disorders and neurodegenerative diseases like Alzheimer's disease [20•]. To prevent these mental illnesses, it is necessary to understand what behavioral factors can improve resilience to stress.

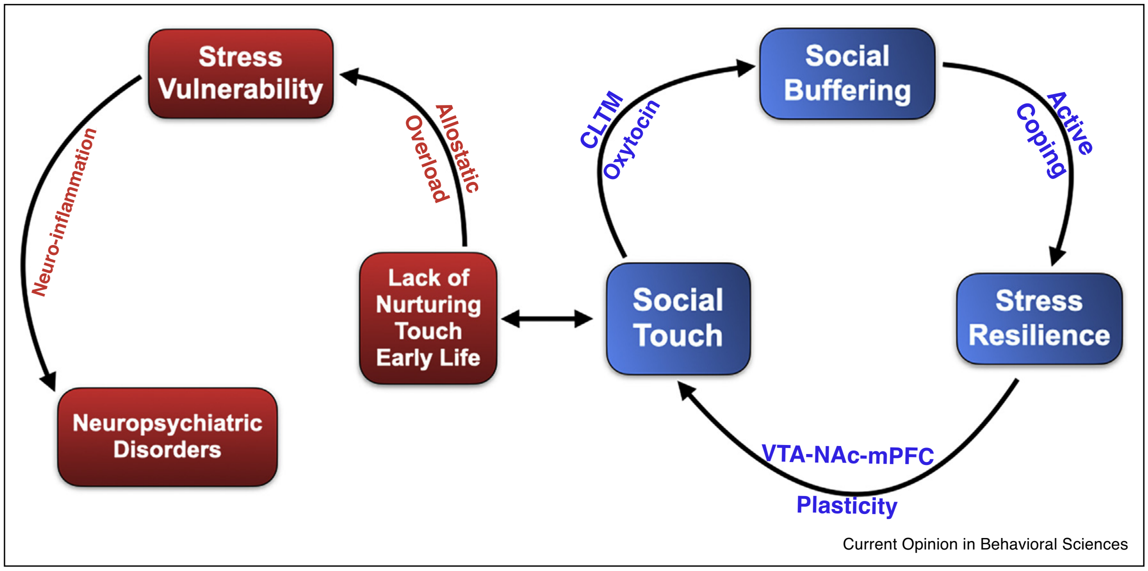
CLTMs and stress resilience

The main biological characteristic of resilience to stress is that the activity of the HPA axis is optimal for generating active coping with stress and achieving adaptation [5••]. Lower or higher levels of HPA axis activity generate allostatic overload and trigger the behavioral phenotype susceptible to stress [5••]. Research suggests that slow stroking, potentially engaging the CT system, can help to optimize HPA activity. In a recent study, the skin of rats was stroked at a slow (5 cm/s) or fast (30 cm/s) velocity before subjecting them to a chronic unpredictable mild stress paradigm [21••]. Interestingly, slow stroking seemed to dampen the HPA axis relative to fast stroking; in the slow stroking condition only, plasma corticosterone levels were similar to those obtained for non-stressed rats [21••]. At a behavioral level, slow stroking generated an anxiolytic effect in stressed animals and stimulated active coping, showing an increase in climbing and a decrease in floating behavior in the forced swim test [21••]. These results demonstrate that it is possible to modulate stress resilience through the somatosensory system in rats (Figure 1). Moreover, they agree with another study showing that gentle skin stimulation decreases the development of depressive-like behaviors and improves episodic memory in rats that were exposed to the chronic unpredictable mild stress protocol [22••].

Resilience and social behavior

Resilient rodents show active coping with social defeat stress, developing a social behavior like non-defeated rodents in social interaction tests [23]. Social behavior can modulate responses to stress via two mechanisms that are activated by social touch. The first mechanism is related to oxytocin; this hormone is synthesized in the paraventricular nucleus of the hypothalamus and social touch stimulates its synthesis and increases its plasma concentration [12••,24,25]. Thus one may speculate that CT afferents stimulated by social touch increase oxytocin release through neural connections between the posterior

Figure 1



Conceptual model to explain the cross-talk between social behavior and stress. Social touch is a key element of social behavior in mammals. Gentle stroking touch applied at optimal velocity of cutaneous low-threshold C-fiber mechanoreceptors (CLTMs) triggers oxytocin release and attenuates the effects of stress [12••,41], an important phenomenon related with social buffering. An active stress-coping strategy is associated with social buffering and stress resilience [35,36]. Enhances neuronal plasticity in the ventral tegmental area-nucleus accumbens-medial prefrontal cortex (VTA-NAc-mPFC) brain circuit further increasing motivation to develop social behavior in which social touch is included [37]. On the other hand, lack of nurturing touch in early life induces allostatic overload and stress vulnerability [5••,12••]. Increases of neuro-inflammation in brain areas that modulate stress responses triggers neuropsychiatric disorders such as major depression [20•].

insula and the paraventricular nucleus. There is also cross-talk between the oxytocin system and the HPA axis. Oxytocin can dampen the HPA axis which leads to a decrease in plasma corticosterone levels when rodents are exposed to stress [26] (Figure 1). In humans, intranasal administration of oxytocin was found to suppress the cortisol response to psychological stress and to attenuate emotional sensitivity after stress [27]. The second mechanism by which social touch may control stress responses depends on the insula and its complex connections to cortical and subcortical regions. The anterior part of the insular cortex has strong functional connectivity with the hippocampus and the medial prefrontal cortex [14]: when these areas of the brain are activated, they inhibit the HPA axis and the sympathetic nervous system thus decreasing the stress levels [6].

Notably, social touch is not only relevant for stress in mammals. It is also beneficial in fish where tactile stimulation was shown to reduce stress, fear, and aggression [28–30]. Thus, it appears that the mechanism by which touch modulates resilience to stress has been highly conserved in evolution. Indeed, fish apart from making direct physical contact, can detect conspecifics through vibrations of water currents. This sort of remote touch may be a precursor of and functionally similar to direct touch which features in the interactions of land-dwelling species [29].

Social buffering and stress

The tendency of social behavior to mitigate the effects of stress is known as 'social buffering' [31] (Figure 1). Thus, affiliative tactile stimulation is an important component of social buffering and through this mechanism can modulate resilience to stress (Figure 1). For example, negative feedback of the HPA axis increases after maternal licking and grooming of pups in animal models [32], while in humans CT stimulating touch reduces sympathetic arousal in preterm infants [33]. The evidence shown above supports the hypothesis that tactile stimulation of the skin can modulate resilience to stress.

Social behavior unrelated to tactile stimulation may also promote social buffering. Among other species, this was demonstrated in rodents and found to engage their highly developed olfactory system [34]. For example, autonomic responses to stress were ameliorated when voles perceived stress in the company of another vole as compared with alone [35]. Partners also improved the ability to cope with stress and allowed a better recovery from stressful situations [36]. Social buffering promotes an active stress-coping strategy characteristic of resilient animals [37,38]. In this way, throughout the duration of coping with stress, the excitability of the dopamine pathway connecting ventral tegmental area (VTA) with nucleus accumbens (NAc) (VTA-NAc-DA) increases [39] (Figure 1). This brain circuit plays an important role in the motivation to carry out a social behavior and serves as a natural reinforcer in some mammals [40] (Figure 1). There is a high density of oxytocin receptors expressed in the VTA-NAc-DA circuit which stimulates its functioning during stress [41,42] (Figure 1).

Conclusions and future directions

One of the most important evolutionary benefits of social behavior is social buffering, which allows the development of active coping and resilience to stress (Figure 1). In this context, the stimulation of C-LTMs improves resilience to stress in rats. Future experiments in humans are needed to establish a similar causal pathway for CTs and to evaluate their therapeutic potential in stress-related diseases such as major depressive disorder and anxiety disorder. This will become more and more relevant as challenges such as the COVID-19 pandemic increase the level of stress in our lives and heighten its impact on our mental health.

Author contribution

A. D.-S. designed and wrote the article.

Conflict of interest statement

Nothing declared.

Acknowledgements

This research was supported by DIUV-CI Grant № 01/2006. Thank you to Jeremy Reineck (University of California Santa Barbara, USA) for your excellent work in the English edition of this article.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Hassard J, Teoh K, Cox T, Dewe P, Cosmar M, Gründler R, Flemming D, Cosemans B, Van den Broek K: *Calculating the Costs of Work-Related Stress and Psychosocial Risks – A Literature Review*. European Agency for Safety and Health at Work; 2014 http://dx.doi.org/10.2802/20493.

2. Quittkat HL, Düsing R, Holtmann FJ, Buhlmann U, Svaldi J, Vocks S: **Perceived impact of covid-19 across different mental disorders: a study on disorder-specific symptoms, psychosocial stress and behavior**. *Front Psychol* 2020, **11**:586246.

3. Sapolsky RM: **Glucocorticoids, the evolution of the stress-response, and the primate predicament**. *Neurobiol Stress* 2021, **14**:100320.

4. Pérez-Valenzuela C, Terreros G, Dagnino-Subiabre A: **Effects of stress on the auditory system: an approach to study a common origin for mood disorders and dementia**. *Rev Neurosci* 2019, **30**:317-324.

5. •• McEwen BS, Akil H: **Revisiting the stress concept: implications for affective disorders**. *J Neurosci* 2020, **40**:12-21

A key review of the influence of allostasis concept to complement the stress. Together they are needed to understand the neurobiology of resilience to stress.

6. Herman JP, Nawreen N, Smail MA, Cotella EM: **Brain mechanisms of HPA axis regulation: neurocircuitry and feedback in context Richard Kvetnansky lecture**. *Stress* 2020, **23**:617-632.

7. Wyrofsky R, Reyes BAS, Van Bockstaele EJ: **Co-localization of the cannabinoid type 1 receptor with corticotropin-releasing factor-containing afferents in the noradrenergic nucleus locus coeruleus: implications for the cognitive limb of the stress response**. *Brain Struct Funct* 2017, **222**:3007-3023.

8. Fast CD, McGann JP: **Amygdalar gating of early sensory processing through interactions with locus coeruleus**. *J Neurosci* 2017, **37**:3085-3101.

9. Marshall AG, McGlone FP: **Affective touch: the enigmatic spinal pathway of the C-tactile afferent**. *Neurosci Insights* 2020, **15**:2633105520925072.

10. Cascio CJ, Moore D, McGlone F: **Social touch and human development**. *Dev Cogn Neurosci* 2019, **35**:5-11.

11. Zotterman Y: **Touch, pain and tickling: an electro-physiological investigation on cutaneous sensory nerves**. *J Physiol* 1939, **95**:1-28.

12. •• Walker SC, Trotter PD, Swaney WT, Marshall A, Mcglone FP: **C-tactile afferents: cutaneous mediators of oxytocin release during affiliative tactile interactions?** *Neuropeptides* 2017, **64**:27-38

An important review to understand how social touch regulates the release of oxytocin, the main hormone that regulates social behavior in all mammals. Neural circuits are described, both peripherally and centrally, which translate the activation of CLTMs located in the skin with the brain activity necessary to trigger social behavior.

13. Shura RD, Hurley RA, Taber KH: **Insular cortex: structural and functional neuroanatomy**. *J Neuropsychiatry Clin Neurosci* 2014, **26**:276-282.

14. Quadt L, Critchley HD, Garfinkel SN: **The neurobiology of interoception in health and disease**. *Ann N Y Acad Sci* 2018, **1428**:112-128.

15. Kantake M, Yoshitake H, Ishikawa H, Araki Y, Shimizu T: **Postnatal epigenetic modification of glucocorticoid receptor gene in preterm infants: a prospective cohort study**. *BMJ Open* 2014, **4**: e005318.

16. Fallon IP, Tanner MK, Greenwood BN, Baratta MV: **Sex differences in resilience: experiential factors and their mechanisms**. *Eur J Neurosci* 2020, **52**:2530-2547.

17. Garmezy N: **Resilience in children's adaptation to negative life events and stressed environments**. *Pediatr Ann* 1991, **20** 459–460, 463–466.

18. • Cathomas F, Murrough JW, Nestler EJ, Han MH, Russo SJ: **Neurobiology of resilience: interface between mind and body**. *Biol Psychiatry* 2019, **86**:410-420

A highly up-to-date review on the neurobiological bases of stress resilience. It ranges from the effects at the peripheral level as central to the resilience to stress.

19. de Kloet ER, de Kloet SF, de Kloet CS, de Kloet AD: **Top-down and bottom-up control of stress-coping**. *J Neuroendocrinol* 2019, **31**:e12675.

20. • de Kloet ER, Meijer OC, de Nicola AF, de Rijk RH, Joëls M: **Importance of the brain corticosteroid receptor balance in metaplasticity, cognitive performance and neuro-inflammation**. *Front Neuroendocrinol* 2018, **49**:124-145

A review to understand the fundamental role that glucocorticoid (GR) and mineralocorticoid (MR) receptors have in coping to stress and resilience to stress. MR:GR balance hypothesis is proposed to explain the aetiology of stress resilience.

21. •• Walker SC, Cavieres A, Peñaloza-Sancho V, El-Deredy W, McGlone FP, Dagnino-Subiabre A: **C-low threshold mechanoafferent targeted dynamic touch modulates stress resilience in rats exposed to chronic mild stress**. *Eur J Neurosci* 2020 http://dx.doi.org/10.1111/ejn.14951

An empirical study showing that social touch aimed at activating CLTMs improves resilience to stress in rats. It is shown how stroking regulates plasma corticosterone levels and coping with stress.

22. •• Costa R, Tamascia ML, Sanches A, Moreira RP, Cunha TS, Nogueira MD, Casarini DE, Marcondes FK: **Tactile stimulation of adult rats modulates hormonal responses, depression-like behaviors, and memory impairment induced by chronic mild stress: role of angiotensin II**. *Behav Brain Res* 2020, **379**:112250

An independent study supporting the study by Walker *et al.* [21••] and also provides new results of the effects of stroking on depressive behaviors and memory.

23. Toyoda A: **Social defeat models in animal science: what we have learned from rodent models**. *Anim Sci J* 2017, **88**:944-952.

24. Okabe S, Yoshida M, Takayanagi Y, Onaka T: **Activation of hypothalamic oxytocin neurons following tactile stimuli in rats**. *Neurosci Lett* 2015, **600**:22-27.

25. Tang Y, Benusiglio D, Lefevre A, Hilfiger L, Althammer F, Bludau A, Hagiwara D, Baudon A, Darbon P, Schimmer J *et al.*: **Social touch promotes interfemale communication via activation of parvocellular oxytocin neurons**. *Nat Neurosci* 2020, **23**:1125-1137.

26. Winter J, Jurek B: **The interplay between oxytocin and the CRF system: regulation of the stress response**. *Cell Tissue Res* 2019, **375**:85-91.

27. Flanagan JC, Fischer MS, Nietert PJ, Back SE, Maria MM, Snead A, Brady KT: **Effects of oxytocin on cortisol reactivity and conflict resolution behaviors among couples with substance misuse**. *Psychiatry Res* 2018, **260**:346-352.

28. Soares MC, Oliveira RF, Ros AFH, Grutter AS, Bshary R: **Tactile stimulation lowers stress in fish**. *Nat Commun* 2011, **2**:534-538.

29. Schirmer A, Jesuthasan S, Mathuru AS: **Tactile stimulation reduces fear in fish**. *Front Behav Neurosci* 2013, **7**:1-9 Article 167.

30. Mathuru AS, Schirmer A, Ng TPY, Kibat C, Cheng R-K, Jesuthasan S: **Familiarity with companions aids recovery from fear in zebrafish**. *bioRxiv* 2017:098509.

31. Kiyokawa Y, Hennessy MB: **Comparative studies of social buffering: a consideration of approaches, terminology, and pitfalls**. *Neurosci Biobehav Rev* 2018, **86**:131-141.

32. Suchecki D: **Maternal regulation of the infant's hypothalamic-pituitary-adrenal axis stress response: Seymour 'Gig' Levine's legacy to neuroendocrinology**. *J Neuroendocrinol* 2018, **30**: e12610.

33. Manzotti A, Cerritelli F, Esteves JE, Lista G, Lombardi E, La Rocca S, Gallace A, McGlone FP, Walker SC: **Dynamic touch reduces physiological arousal in preterm infants: a role for c-tactile afferents?** *Dev Cogn Neurosci* 2019, **39**:100703.

34. Takahashi Y, Kiyokawa Y, Kodama Y, Arata S, Takeuchi Y, Mori Y: **Olfactory signals mediate social buffering of conditioned fear responses in male rats**. *Behav Brain Res* 2013, **240**:46-51.

35. Lewis R, Wilkins B, Benjamin B, Curtis JT: **Cardiovascular control is associated with pair-bond success in male prairie voles**. *Auton Neurosci* 2017, **208**:93-102.

36. Beery AK, Kaufer D: **Stress, social behavior, and resilience: insights from rodents**. *Neurobiol Stress* 2015, **1**:116-127.

37. Young C, Majolo B, Heistermann M, Schülke O, Ostner J: **Responses to social and environmental stress are attenuated by strong male bonds in wild macaques**. *Proc Natl Acad Sci U S A* 2014, **111**:18195-18200.

38. Bravo-Tobar ID, Fernández P, Sáez JC, Dagnino-Subiabre A: **Long-term effects of stress resilience: hippocampal neuroinflammation and behavioral approach in male rats**. *J Neurosci Res.* 2021 http://dx.doi.org/10.1002/jnr.24902.

39. Douma EH, de Kloet ER: **Stress-induced plasticity and functioning of ventral tegmental dopamine neurons**. *Neurosci Biobehav Rev* 2020, **108**:48-77.

40. Steinman MQ, Duque-Wilckens N, Trainor BC: **Complementary neural circuits for divergent effects of oxytocin: social approach versus social anxiety**. *Biol Psychiatry* 2019, **85**:792-801.

41. Peris J, MacFadyen K, Smith JA, de Kloet AD, Wang L, Krause EG: **Oxytocin receptors are expressed on dopamine and glutamate neurons in the mouse ventral tegmental area that project to nucleus accumbens and other mesolimbic targets**. *J Comp Neurol* 2017, **525**:1094-1108.

42. Leng H, Zhang X, Wang Q, Luan X, Sun X, Guo F, Gao S, Liu X, Xu L: **Regulation of stress-induced gastric ulcers via central oxytocin and a potential mechanism through the VTA-NAc dopamine pathway**. *Neurogastroenterol Motil* 2019, **31**:e13655.