Repeated tactile stimulation promotes hippocampal neurogenesis and reduces depression-like behaviors

CHAN Jackie, Ngai-Man[1], LAI Cynthia Yuen-Yi[1,*], PO Kevin, Kai-Ting[1], LAU Benson, Wui-Man[1,*]

Affiliation:
1: Rehabilitation Sciences, The Hong Kong Polytechnic University, HKSAR, PRC
*: Co-Corresponding author
†: Equal contribution

Backgound

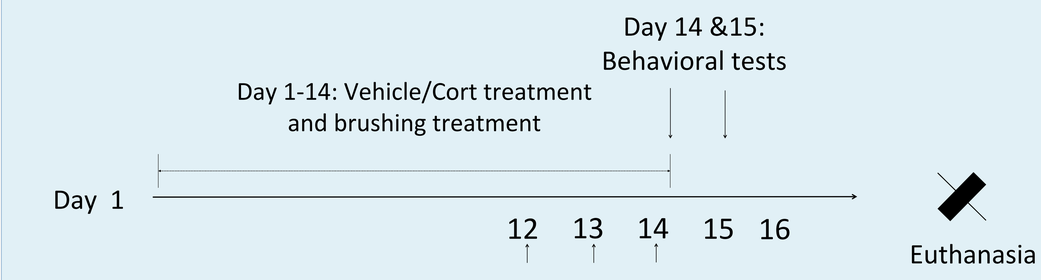
There are studies reported the effectiveness of tactile stimulation on clinical studies. For instance, a human study showed that after receiving a tactile stimulation treatment (Wilbarger's protocol) the subjects showed a decrease in salivary corticosterone level. However, there is a lack of evidence to support the pro-neurogenic role of tactile stimulation. The anxiety level in burnt patients was decreased after massage therapy. Pre-clinical studies demonstrated that manual stimulation of whisker-pad or facial muscles of rats promoted functional regain and nerve regeneration, which suggests that tactile stimulation could promote neuroplasticity and behavioral recovery. Tickling, a manipulation which induces the appetitive vocalization of rats, was shown to be a pro-neurogenic factor, which supports that tactile stimulation may be a positive neurogenesis regulator. However, as tickling will induce positive emotion in rats, this may be a confound when interpreting the tactile stimulation as the key regulator. A recent study discovered that provision of altering tactile stimulation via changing texture of cage floor could promote cell proliferation in the spinal cord, while consistent application of tactile stimulus promotes neuronal differentiation. Collectively, the findings from other research groups indicate the therapeutic effect of tactile stimulation, while the underlying mechanisms remain to be determined. Neurogenesis, in this case, serves as a potential target of tactile stimulation and key player in the tactile stimulation therapy.

Objective of study

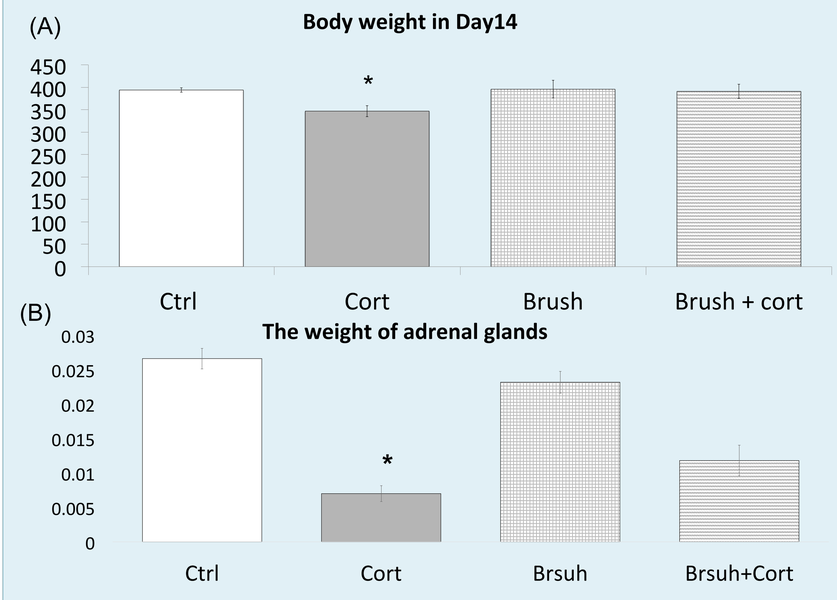
To test whether repeated tactile stimulation increases hippocampal neurogenesis and affect affective behaviors under control and anxiety conditions caused by hypercortisolemia

Experimental design

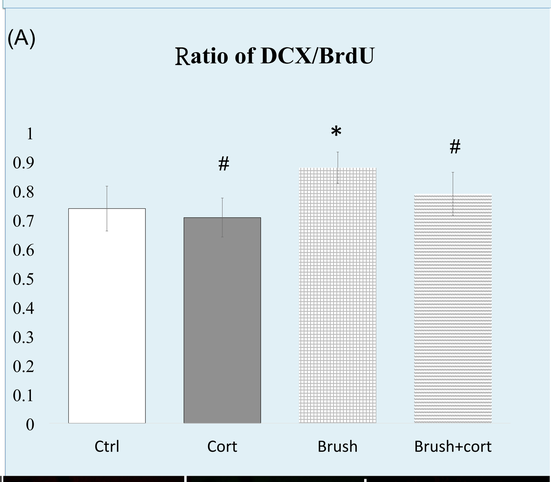
Animals are divided into 4 groups (n=8 per group): 1) Control group with daily handling and vehicle injection; 2) Cort group with daily high dose corticosterone treatment (40 mg/kg, subcutaneous injection); 3) Brush group with daily tactile stimulation and 4) Brush+cort group with corticosterone treatment and brushing. The duration of treatment will be 14 days. Affective and neurogenesis impairment will be induced by corticosterone treatment and the potential therapeutic effect of brushing will be determined. After treatment for 2 weeks, animals will be subjected to behavioral tests at day 14 and 15, followed by sacrifice at day 16.

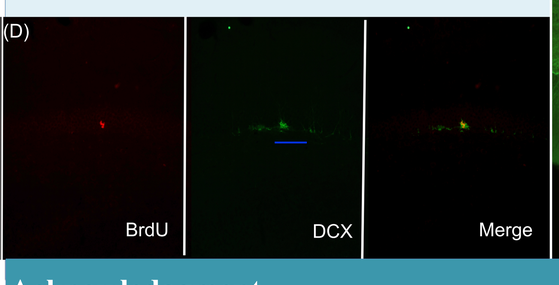


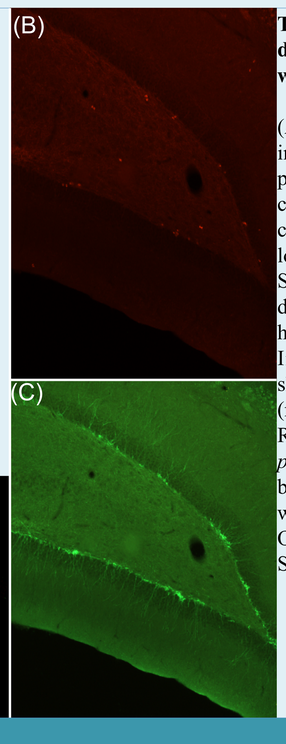
Results



Body weight gain and the weight of adrenal gland after treatment.
(A): Brushing increased body weight in co-treatment group compared to cort group. (B): Corticosterone significantly suppressed body weight gain and the growth of adrenal glands in both cort-treated group and co-treated group. Result was performed in mean±SEM. *: $p<0.05$, One-way ANOVA with LDS post hoc test.







The evaluation of neuronal differentiation rate by double-labeling with DCX/BrdU markers.

(A): The neuronal differentiation rate is indicated by the percentage of BrdU-positive cells expressing DCX-positive cells. The number of co-labeling positive cells in cort-treated group is significantly lower than brush and co-treatment group. Significant increased number of neuronal differentiation in brush group, which higher than control. (C-D): Immunofluorescent photomicrographs showing the co-labeling of cells with BrdU (red) and DCX (green) in dentate gyrus. Result was performed in mean+SEM.#: $p<0.05$ when cort group is compared to brush and co-treatment group. *: $p<0.05$ when brush group is compared to control. One-way ANOVA with LSD post hoc test. Scale bar: 100μm.

Acknowledagment

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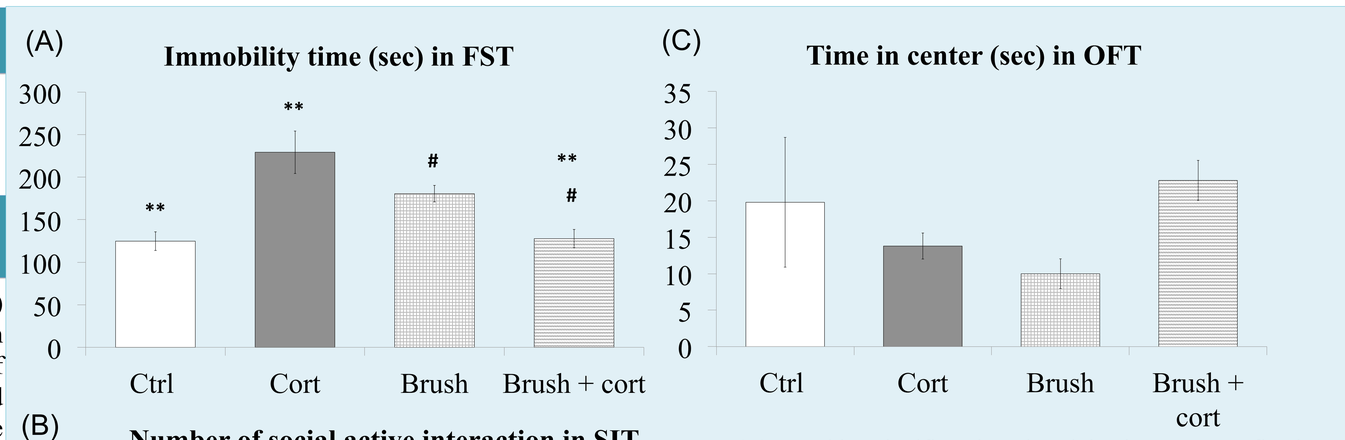
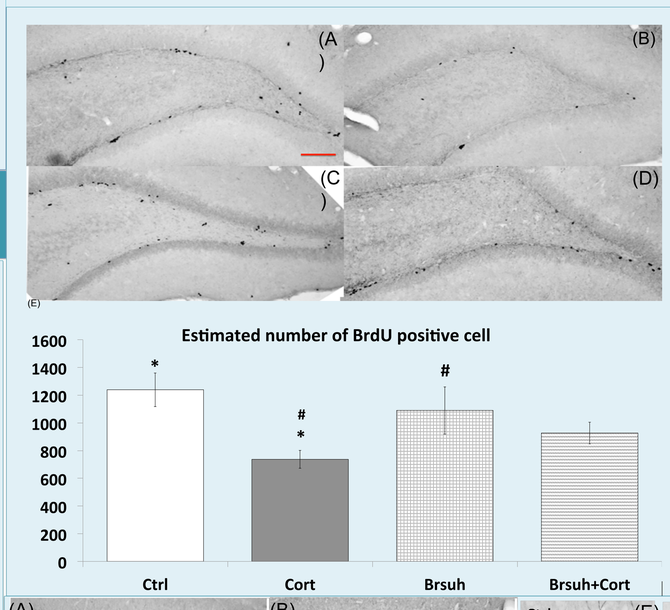
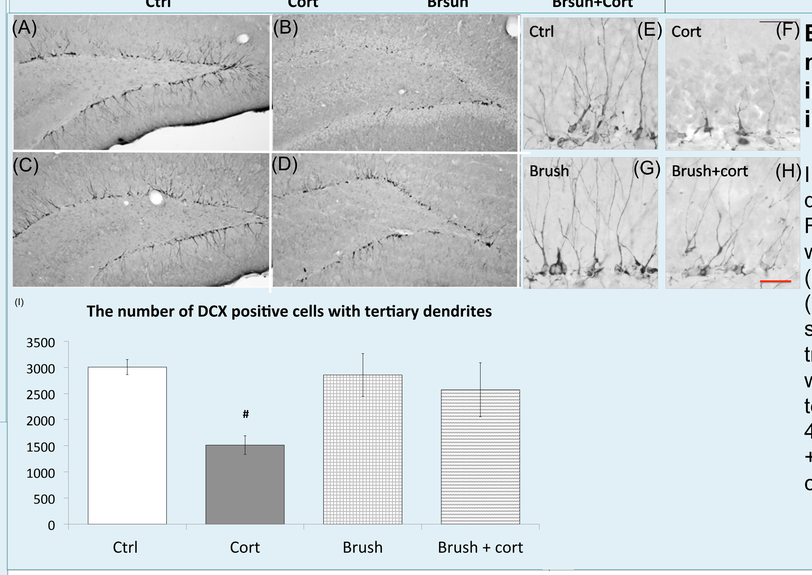


(A): Brushing significantly reduced the time spent on floating in the forced swimming test. (B): Co-treatment group shows significantly increased number of social interaction higher than cort group and no difference to control group. (C): Anxiety-like behavior is indicated by the number of time spent in the central arena, which showed no difference between groups. Results were expressed in mean±SEM,*:$p<0.05$ and **:$p<0.01$, when compared to control group,#:$p<0.05$ when co-treated group compared to brush group. One-way ANOVA with LSD post hoc test.



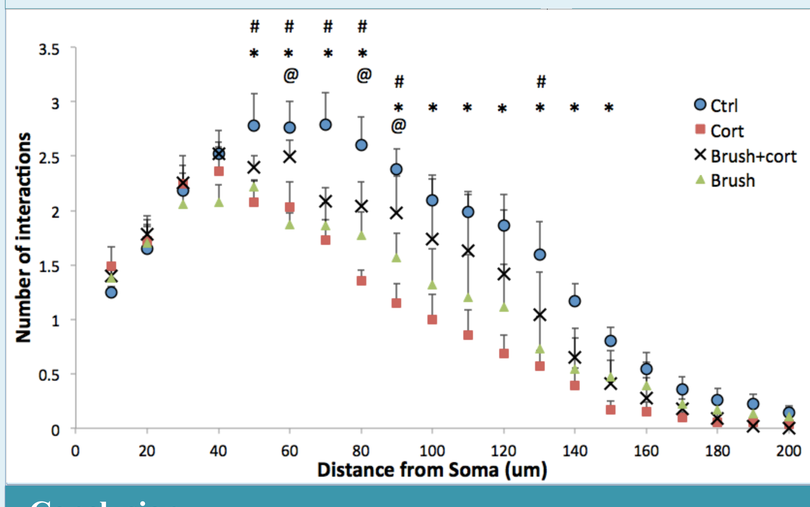
Brushing enhances cell proliferation in hippocampus.

(A): Control group animals had significantly higher number of BrdU-positive in the dentate gyrus. (B): Corticosterone treated group showed suppression effect while significantly decreased number of proliferative cells, (C) Brush group showed no different to control group and (D): co-treated animals showed that the number of BrdU-positive cells in the dentate gyrus is increased by brushing. (E) Showing the mean of number of positive BrdU was counted in each group. Values expressed in mean±SEM, *:$p<0.05$ when compared to control group,#: $p<0.05$ when compared to brush group. One-way ANOVA with LSD post hoc test. Scale bar: 100μm.



Brushing reversed the suppression of neurogenesis induced by corticosterone and increased number of dendritic maturation of immature neurons in hippocampus.

Immunostaining photomicrographs show the doublecortin positive cells (DCX) in dentate gyrus. Representative photomicrographs of DCX-positive cells were divided into control (A& E) group, corticosterone (B& F) group, brushing (C& G) group and co-treatment (D& H) group. (I): Corticosterone significantly suppressed hippocampal neurogenesis, while co-treatment with brushing potentially reversed the change with increased the number of DCX positive cells with tertiary dendrites. (A-D): 100X magnification; (E-H): 400X magnification. Result was performed in mean +SEM. #:$p<0.05$ when cort-treated group is compared to control. One-way ANOVA with LSD post hoc test.



Brushing promotes dendritic maturation of new neurons induced by corticosterone.

(A): Sholl analysis showed that the dendritic complexity of immature neurons (distance from soma 50μm to 150μm) is significantly lower in corticosterone group when compared to the control. The number of intersection in co-treated group (distance from soma 90μm to 160μm) showed increased by brushing and no different to control. Result was performed in mean+SEM.*:p< 0.05 when corticosterone group compared to control. #: $p<0.05$ when brush group is compared to control. @: $p<0.05$ when co-treated group is compared to cort-treated group. One-way ANOVA with LSD post hoc test.

Conclusion

This study provides evidence for differential effect in both normal experimental animals and animals with suppressed neurogenesis. Brushing treatment could reverse the suppression effect of neurogenesis induced by high dose corticosterone and reduces the depression-like and anxiety-like behaviors. The present study provides evidence for the use of tactile stimulation to relieve anxious and depressed behavior . Further study on the molecular mechanism underlying the effect of brushing will provide a clear picture whether neurogenesis is necessary for the therapeutic effect.