

Effects of high-frequency repetitive transcranial magnetic stimulation (rTMS) on spontaneously hypertensive rats, an animal model of attention-deficit /hyperactivity disorder

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INTRODUCTION

- Attention deficit hyperactivity disorder (ADHD) is characterized by inattention, hyperactivity and impulsivity. The presently accepted pathophysiology of ADHD involves the abnormal function of monoamine neurotransmitters such as dopamine or norepinephrine in the right prefrontal cortex area. As the aetiology of ADHD is yet unknown, the search for an effective treatment using drugs or non-invasive psychosocial therapies is still ongoing.
- This study aimed to examine the therapeutic effectiveness of TMS as a non-pharmacological therapy of ADHD to spontaneously hypertensive rats (SHRs), which is an ADHD animal model. In addition, the behavioural change and the change of catecholamines and BDNF in the brain were measured.

METHOD

- Male SHR/Izm (n = 26) and Wistar-Kyoto (WKY)/Izm (n = 8) rats of postnatal day (PND) 39 weighing 150-180 g were used as subjects and kept in groups of 2-3 animals per cage.
- The experiment was carried out for 3 weeks (19 days) with an alternation of 5 days of treatment and 2 days of rest. The rats were divided into the WKY, Sham, MPH, and TMS groups. The open field test, Y-maze test, and elevated plus-maze test was conducted to evaluate changes in behavioural symptoms.
- Animals were etherized and decapitated on the last day and the expression of BDNF and catecholamines (dopamine, noradrenaline, serotonin) were analyzed by western blotting and HPLC, respectively.

RESULTS

- In the open field test, the MPH group moved less distance ($p = 0.057$) than the Sham group. When the 10-min distance was divided into 2 5-min tracks, the TMS group covered less distance than the Sham group in the latter 5 min ($p < 0.05$).
- In the Y-maze test, in the third week, the MPH group showed a significant improvement in spontaneous alternation compared to the Sham group ($p < 0.05$). The TMS group, however, showed no statistically significant change throughout the experiment.
- BDNF expression in the prefrontal cortex of the MPH group was similar to that in the Sham group. BDNF concentration was higher in the TMS group than the Sham group, but without statistical significance.
- The average concentration of noradrenaline in the TMS group was significantly lower than in the Sham and MPH groups ($p < 0.05$). The average concentration of serotonin was significantly lower in the WKY group than in the Sham, MPH, and TMS groups ($p < 0.05$), but no difference was found between these 3 groups for SHR. The average dopamine level was significantly higher in the MPH group than in the WKY group ($p < 0.05$).

CONCLUSION

- High-frequency rTMS treatment to SHRs resulted in decreased noradrenaline concentration and elevated BDNF expression in the prefrontal cortex.
- The TMS group's behavioural pattern over time (10 min in the open field apparatus) was similar to that of the control WKY group which implies TMS group has adapted to the apparatus, leading to less hyperactive locomotor activity.
- Treatment of the animals with this protocol for longer sessions might elicit distinct modifications in both neurochemical analysis and behavioural symptoms.

Figure 1. Measured locomotor activity (s) in the open field test in the first (A, D), second (B, E), and third (C, F) weeks.

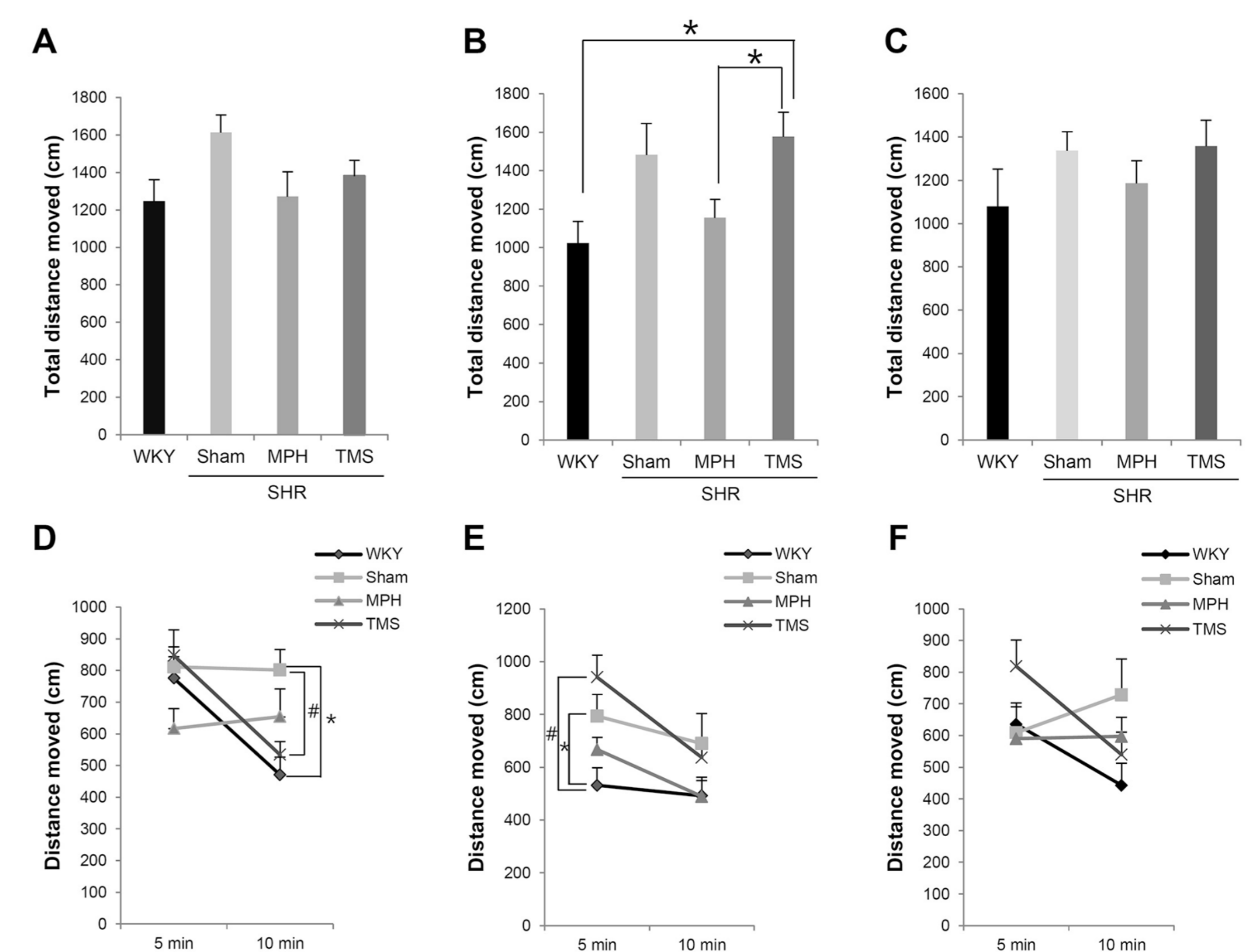


Figure 2. Western blot analysis of BDNF in the prefrontal cortex.

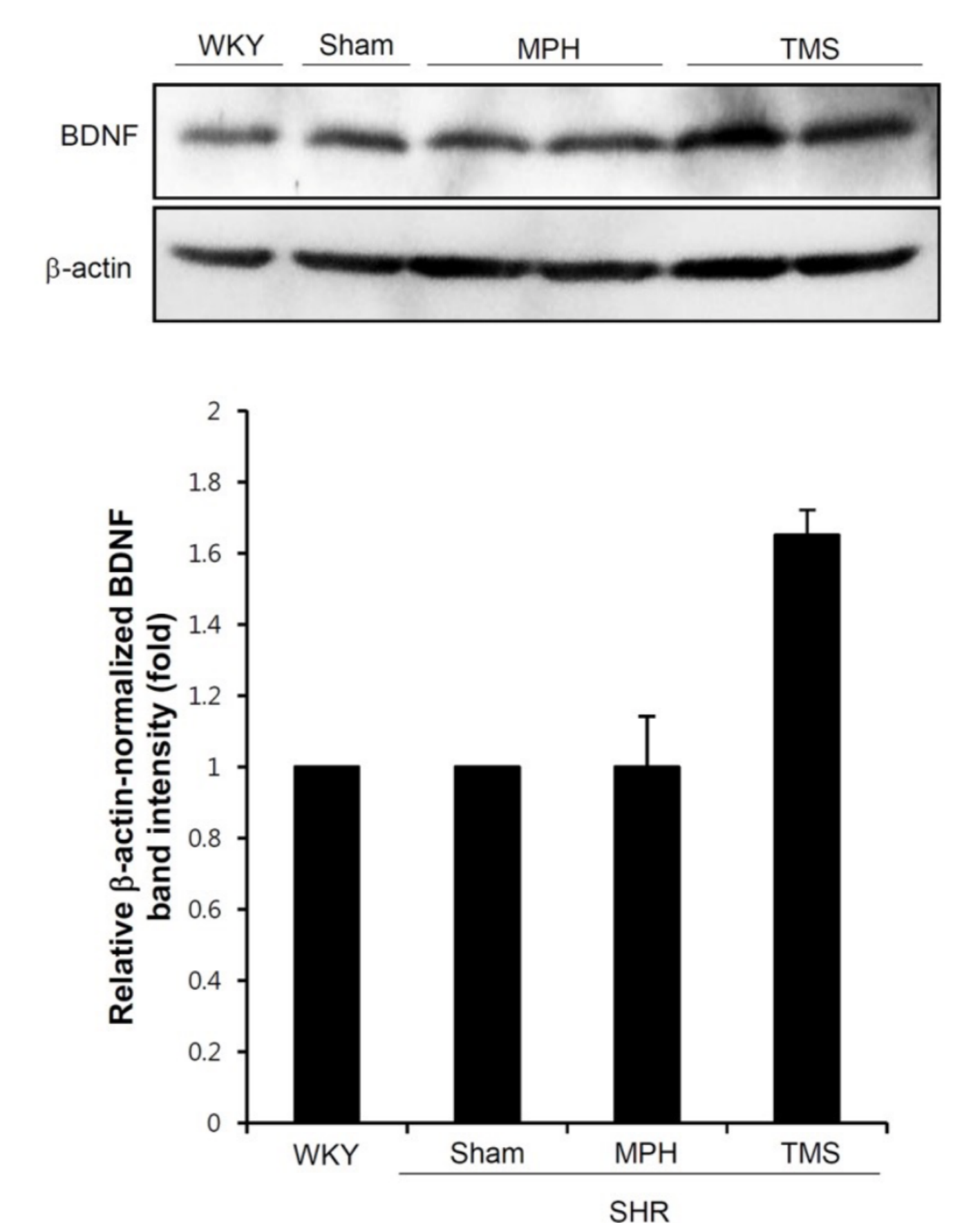


Table 1. The concentration of catecholamines in the prefrontal cortex

| | Noradrenaline | Serotonin | Dopamine |
|------|--------------------------|---------------------------|--------------------------|
| WKY | 1.36 ± 0.08 | 0.08 ± 0.005 | 0.01 ± 0.01 |
| Sham | 1.61 ± 0.04 [#] | 0.11 ± 0.01 [#] | 0.06 ± 0.03 |
| MPH | 1.60 ± 0.06 [#] | 0.12 ± 0.01 [#] | 0.19 ± 0.07 [#] |
| TMS | 1.42 ± 0.05 [*] | 0.11 ± 0.005 [#] | 0.01 ± 0.01 |

The table values represent the mean (ng/mg in tissue) ± SEM. [#]p < 0.05 vs. WKY; ^{*}p < 0.05 vs. Sham

WKY: Wistar-Kyoto rats, SHR: Spontaneously Hypertensive Rats, MPH: SHRs treated with methylphenidate, TMS: SHRs treated with repetitive Transcranial Magnetic Stimulation, BDNF: Brain-derived neurotrophic factor

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