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Short communication

# Caffeine and modafinil given during 48 h sleep deprivation modulate object recognition memory and synaptic proteins in the hippocampus of the rat

M. Wadhwa, S. Sahu, P. Kumari, H. Kauser, K. Ray, U. Panjwani *

*Department of Neurophysiology, Defence Institute of Physiology & Allied Sciences (DIPAS), Defence Research and Development Organization (DRDO), Lucknow Road, Timarpur, Delhi, India*

## HIGHLIGHTS

- Sleep deprivation (SD) reduces novel object/location recognition memory scores.
- SD also decreases the expression of synaptophysin, synapsin I and PSD-95 protein.
- Caffeine and modafinil improve novel object recognition memory during SD.
- Caffeine/modafinil ameliorate the reduced synaptic protein expression during SD.

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## ABSTRACT

We aimed to evaluate the effect of caffeine/modafinil on sleep deprivation (SD) induced alterations in recognition memory and synaptic proteins. The data revealed a beneficial effect of caffeine/modafinil against deficit in the familiar object retrieval performance and object exploration ratio after 48 h SD. Caffeine treatment prevented the SD induced down-regulation of synaptophysin and synapsin I proteins with no change in PSD-95 protein in hippocampus. However, modafinil administration improved the down-regulation of synaptophysin, synapsin I and PSD-95 proteins in hippocampus. Hence, caffeine/modafinil can serve as counter measures in amelioration of SD induced consequences at behavioural and protein levels.

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## 1. Introduction

Hippocampus plays an important role regulating various memory performances, including recognition memory, the ability to discriminate novel from familiar stimuli. Novel objection recognition test (NORT) is a well-established method to study recognition memory function [1,2]. Both rapid eye movement (REM) sleep and slow wave sleep (SWS) increase scores of object recognition task [3]. SD impairs recognition memory as presented by a deficit in object exploration, discrimination and recognition (familiar and novel object as well as their respective location) [4].

Sleep favours synaptic plasticity as demonstrated by behavioural and molecular level changes in gene and protein expression [5,6]. Hippocampal recognition memory consolidation involves synaptic plasticity i.e. long term depression (LTD) and long term potentiation (LTP) [7]. This process is influenced by sleep deprivation [8,9]. SD reduces the expression (transcriptional and translational) of synaptic proteins in the hippocampus and may

*Abbreviations:* ANOVA, analysis of variance; BDNF, brain derived neurotrophic factor; BSA, bovine serum albumin; CA, cornu ammonis; DAB, 3,3′-diaminobenzidine; DG, dentate gyrus; EDTA, ethylenediaminetetraacetic acid; GAPDH, glyceraldehyde-3-phosphate-dehydrogenase; HC, hippocampus; HRP, horseradish peroxidase; IHC, immunohistochemistry; LTD, long term depression; LTP, long term potentiation; NaCl, sodium chloride; NMDA, *N*-methyl-D-aspartate; NORT, novel object recognition test; NP-40, nonyl phenoxypolyethoxylethanol; PBS, phosphate buffered saline; PBST, phosphate buffer saline containing Tween 20; PFA, paraformaldehyde; PMSF, phenylmethylsulfonyl fluoride; PSD-95, postsynaptic density-95; PVDF, polyvinylidene fluoride; REM, rapid eye movement; SD, sleep deprivation; SDS-PAGE, sodium dodecyl sulphate-polyacrylamide gel electrophoresis; SWS, slow wave sleep; Tris HCl, Tris hydrochloride; WB, western blotting.

* Corresponding author at: Applied Physiology Division, Defence Institute of Physiology and Allied Sciences (DIPAS), Defence Research and Development Organization (DRDO), Lucknow Road, Timarpur, Delhi 110 054, India. Fax: +91 11 23914790.
*E-mail address:* neurophysiolab.dipas@gmail.com (U. Panjwani).

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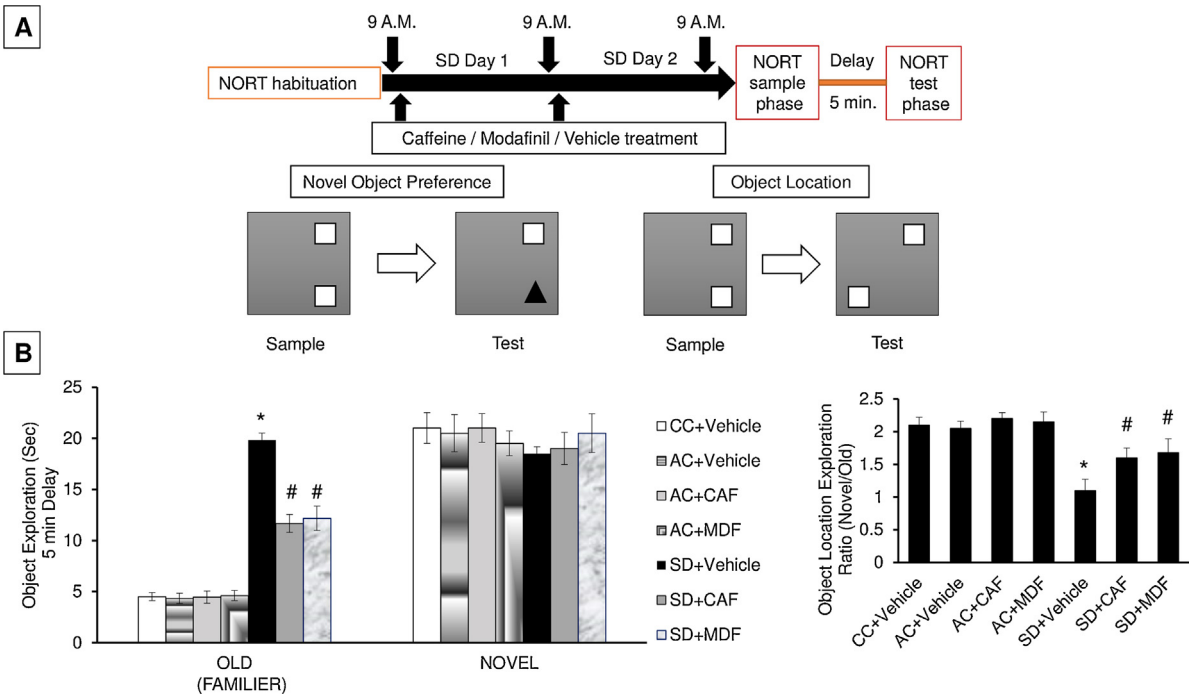


**Fig. 1.** Novel object/location recognition memory following 48 h SD and caffeine/modafinil treatment.
(A) Graphical presentation of short term memory in NORT, (B) Novel object preference test and novel location exploration ratio after 5 min delay. Values expressed as mean percentage of CC ± SEM. One way ANOVA followed by Tukey–Kramer Multiple Comparisons Test was applied for old and novel object exploration independently among different groups. Kruskal–Wallis test followed by Dunn post-test was applied for exploration ratio. $^{*}p < 0.05$ significantly different compared to CC and AC + Vehicle group, $\#p < 0.05$ significantly different compared to SD + Vehicle group.

modify the synaptic homeostasis which is also modulated by other factors like aging and stress [5,10,11].

Caffeine and modafinil are well known psychostimulants which are reported to ameliorate the SD mediated cognitive impairment [12,13]. Acute caffeine treatment has been shown to improve recognition memory which may be due to enhancement of brain derived neurotrophic factor (BDNF) expression in hippocampus [14]. It also attenuates the changes in PSD-95 density and immunoreactivity in hippocampal regions, preventing the synaptic deterioration [15]. Chronic modafinil administration improves recognition memory deficits in neurodegenerative disorders [12]. It ameliorates recognition memory deficits by up-regulating synapsin I expression in cornu ammonis (CA3) region of dorsal hippocampus [16].

Taken together, these findings provide a conceptual framework of caffeine and modafinil treatment for counteracting SD induced changes in synaptic proteins. Synaptic proteins (synapsin I, synaptophysin and PSD-95) are essential for synaptic processes, but there is little information about synaptic protein changes and object recognition memory impairment after SD. Therefore, the present study aimed to evaluate SD induced changes in both presynaptic (synapsin I and synaptophysin) and postsynaptic (PSD-95) protein expression, recognition memory performance. The role of caffeine and modafinil treatment was evaluated in counteracting the SD induced changes in recognition memory performance and synaptic protein expression.

## 2. Material and methods

### 2.1. Experimental animals

Adult male Sprague–Dawley rats (250–300 g) were used. Animals were housed in pairs with ad libitum access to food pellets (Lipton India Ltd., India) and water. A light/dark cycle of 12 h was maintained at controlled temperature (26 ± 2 °C) and humidity (50 ± 5%). Experiments were conducted according to standard guidelines for the "Care and Use of Animals in Neuroscience and Behavioural Research" (National Research Council, 2003) and guidelines of the Institutional Animal Ethical Committee. During the experiments, all attempts were made to minimise animal suffering. Behavioural studies (training as well as testing) were carried out during the light phase between 09:00 and 10:00 A.M.

### 2.2. Treatment

Caffeine (Sigma–Aldrich, USA, 60 mg/kg/day), freshly dissolved in sterile physiological saline solution was given orally. Modafinil (Modalert, Sun Pharma, India, 100 mg/kg/day, suspended in physiological saline) was administered orally. Caffeine and modafinil doses were based on previous reports [13,17,18]. The drugs were given twice (24 h apart) at the onset of light phase during the 48 h SD period scheduled between 09:00 and 09:30 A.M during the course of the experiment.

### 2.3. SD procedure

Animals were sleep deprived by an automated cage shaking stimulus [13]. The animals were kept single in transparent acrylic cages (35 cm × 35 cm × 60 cm, top open). The animal was tracked continuously using a camera positioned above the cages. The amplifier was switched on automatically by ANY maze interface (Stoelting Co, USA) if the animal remained immobile for more than 30 s and froze for more than 5 s, leading to cage shaking for 3 s using a pair of shaking pads positioned below the cages. ANY maze software was used to analyse the data.

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