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A neural network confirms that physical exercise reverses EEG changes in depressed rats

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ABSTRACT

The use of an artificial neural network (ANN) system to differentiate the EEG power density spectra in depressed from normal rats was tried. The beneficial effects of chronic physical exercise in reducing the effects of stress and therefore depression was also to be tested in animals by the same method. In this study, rats were divided into 4 groups, subjected to (i) chronic stress (D group); (ii) chronic exercise by treadmill running (EO group); (iii) exercise with stress (ES group) and (iv) handling (C group). The prefrontal cortical EEG, EMG and EOG were recorded simultaneously on paper and the digitized EEG signals were also stored in the hard-disk of a PC-AT through an ADC. After filtering the digitized signals, the EEG power spectra were calculated by an FFT routine. Three successive 4 s artefact-free epochs were averaged. The REM and NREM sleep periods as well as the awake period signals were analyzed separately. The FFT values from each of the 3 states, in the 4 groups of animals were tested by an ANN with 30 first layer neurons and a 2nd layer of a majority-vote-taker. The ANN could distinguish the depressed from the normal rats' EEG very well in REM (99%) sleep, NREM (95%) sleep and awake (81%) states. In most of the cases it identified the exercised rats' EEG as normal.

Keywords: EEG power spectra, depression (rats), artificial neural network, (chronic physical) exercise, sleep–wake cycle

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INTRODUCTION

Depression is one of the common underdiagnosed diseases in clinical psychiatry[1]. Electroencephalography (EEG), in its conventional form, is not routinely useful in the definitive diagnosis of any specific idiopathic condition like depression[2,3].

EEG reflects the electrical activity of the brain during the various states of sleep and wakefulness. REM (Rapid eye movement, fast or paradoxical) sleep and SWS (Slow wave sleep, non-rapid eye movement or NREM sleep or synchronized sleep) and awake states can be differentiated by simultaneous recording of EEG, EMG (electromyogram) and EOG (electro-oculogram)[4]. Manual scoring of different sleep stages takes a great deal of time and effort. To overcome that, artificial neural networks (ANN) have been used in automated staging of sleep[5]. Instead of analyzing only the frequency and amplitude changes, obtaining power spectra by fast Fourier transform (FFT) of EEG signals conveys more information. This can be used more efficiently by ANN[6]. Computerization has led to more sophisticated use of EEG, even in affective disorders, where perceptual processes are significantly distorted[7]. In endogenous depression, short REM latency, increased REM frequency, and an early temporal distribution of REM sleep are noted[3,8].

In most cases, before experimenting with human beings, it is customary to test the validity of results in other animals. Now animal models of depression are available[9–11]. The stress-dependent Katz[12] animal model of depression appears to fulfill the requirements of predictive, face and construct validities[10]. Earlier, an ANN has been successfully used for identifying EEG power spectra, of the REM sleep state, in depressed rats[13].

Exercise has been found to be effective in combating stress, in both human beings and other animals[14,15]. This study was planned to investigate whether an ANN could detect the EEG power spectra changes, if any, caused by regular exercise along with chronic stress.

METHODOLOGY

Subjects

The recordings from 36 normal male albino rats (littermates of 200–300 g weight, age 12–14

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weeks) of Charles Foster strain, maintained at 12:12 hours of light:dark schedule at 23 ± 1°C, with food and water *ad lib*, have been taken.

Apparatus

Cortical EEG, EMG, EOG have been recorded through an 8-channel polygraph (Medicare, India). The polygraph has also been connected through a 12-bit ADC (Micronics, India) and recording has been done with it at a sampling frequency of 256-Hz, and stored in the hard-disk of a PC-AT (HCL, India). The digitized data has been filtered by a fourth order, cascaded, Butterworth, infinite impulse response (IIR) type digital filter developed by the author. The FFT of these has been performed by a program (in Turbo C) developed by the author, modified from Hutchings[16]. The data from these successive 4 s artefact-free epochs was averaged.

Procedure: stereotaxic implantation of electrodes

Electrodes were implanted, aseptically, on the rats anaesthetized with Pentobarbital (Loba Chemie, India) @ 35 mg/kg i.p. For grounding, midline frontal stainless steel screw electrode, of 1 mm. diameter, and 2 other bilateral screw electrodes, 2 mm. posterior to and 4 mm. lateral to the Bregma have been used for cortical EEG. Loop electrodes (2 for EOG from bilateral outer canthus muscles and 2 for EMG from bilateral cervical muscles) have been implanted. Their socket contacts had earlier been soldered to a 9-pin connector and the whole array has been fixed with dental acrylic. Following up, a minimum of 1 week has been allowed for handling and adapting to the recording chamber.

Experimental design

The rats have been divided into 4 groups:

(i) Handled and operated control (C group; $n = 5$).
(ii) Depressed (D group; $n = 15$)—subjected to chronic intermittent stress for 2 weeks.
(iii) Exercised only (EO group; $n = 5$)—subjected to treadmill running for 8 weeks.
(iv) Exercised+Stressed (ES group; $n = 11$)—subjected to treadmill running for 6 weeks, followed by 2 weeks of chronic stress and concomitant exercise as before.

Depression model

The D group has been subjected to chronic stress, as given in *Table 1*, one stressor per day, for two weeks. This method has been modified from Sobolosky and Thurmond[17]. On the 8th day, the electrodes have been implanted. Recording has been done on the 15th day.

Table 1 Chronic stressor schedule for depression

day	stressor
1.	Crowding for 24 h
2.	Electric shock of 0.75 mA for 15 s/min for 30 min
3.	Tail pinch by rubber damped forceps 1 cm away from the base for 1 min
4.	Water deprivation for 24 h
5.	Heat at 40°C for 5 min
6.	Day/Night Reversal
7.	Cold swim at 4°C for 5 min
8.	Electrode implantation
9.	Noise at 100 dB for 5 min
10.	Heat at 40°C for 5 min
11.	Electric shock of 0.75 mA for 15 s/min for 30 min
12.	Tail pinch by rubber damped forceps 1 cm away from the base for 1 min
13.	Food deprivation for 24 h
14.	Noise at 100 dB for 5 min
15.	Recording

Exercise regime

The exercised rats had to run on a treadmill (Uni-Insta, India) at the maximum speed of 20 m/min., for a maximum of 1 h per day, for 6 days a week, for 8 weeks at 0° inclination[18].

Neural network model

A neural network simulation program has been written in Turbo C and run on a PC-AT. Of the various algorithms available for ANN, the present paper has used multiple adaptive linear elements i.e., Madaline Rule-I with a first layer of 30 hard-limited (signum) adalines whose outputs purvey inputs to a second layer of single majority-vote-taker[19]. FFT values (from 1 to 30 Hz. at increments of 1 Hz.) have been used as input vector to the ANN because variations in Fourier transform with respect to frequency are less pronounced than the variations with respect to time. So, less number of samples hold as much information, thereby reducing the number of input neurons and greatly increasing the speed of the network. Also, there is no need for translation or time invariance. Madaline Rule-I has been implented since it is one of the simplest.

Moreover, the majority vote-taker element is quite fast acting; absolute correction has been used to reverse the output of the adaline to be completely adapted, so, only one iteration is required for adaptation. The other advantages of this rule are that the network can be newly trained each time whenever there is any change in the input pattern due to individual variations, and even if the number of neurons are increased, the training time increases slowly and not exponentially. During training and testing, all the input values have been divided by the maximum value in the input pattern vector, to make the network scale invariant.

Training

Initially small random values (−1 to +1) have been assigned to the weights and have been stored in

a file. During training, the file with the FFT values of REM or NREM sleep or awake state along with the actual condition (normal/depressed) is presented. The input values have been stored in an array $x[i][j]$. $W[i][j]$ is the weight connecting the ith input to the jth adaline. The linear output of the jth adaline $s[j]$ is sent to a hard limiter whose output response $o[j]$ is +1 if $s[j] \geq 0$ and −1 if $s[j] < 0$. The majority of these +1's and −1's have been found and compared to the desired output. If the desired majority is the same as the desired output, no adaptation is required. Otherwise weights have been adapted in accordance with alpha-least mean square rule, choosing the value of alpha as one, to result in absolute correction.

Testing

During testing, the file with the FFT values of different states, i.e. REM sleep, NREM sleep and awake are presented separately, to the ANN which reads the input values and finds the linear output of the adalines. The linear output is presented to the hard limiter whose output is either +1 or −1. The majority vote-taker finds the majority of positive or negative values and distinguishes the EEG power spectra of the particular state, in question, of depressed rats from the control ones. However, the FFT values of the EEG from the exercised groups of rats (which were not presented during the training sessions) were included for testing.

Testing protocol

The aim of the testing protocol was to determine the state (REM sleep/NREM sleep/awake) in which the ANN could distinguish the EEG power spectra best. During training, the EEG spectra from the exercised groups were not included. However, during testing, those were used to check whether they were identified as similar to the spectra of the control group or of the depressed group. A total of 1200 samples (600 for training and 600 for testing) of FFT values were used for testing. For each of the three states, the following protocol was followed. 200 samples were used for training and another 200 for testing. For training, 100 files from the C group and 100 files from the D group were chosen randomly. For testing, 50 files were chosen from each of the 4 groups randomly.

The REM, NREM and awake states were confirmed from simultaneous paper recordings of EEG, EMG and EOG.

RESULTS

The results are presented in *Table 2*. The best results were obtained in the REM sleep state recordings. Testing for the null hypothesis ($p_1 = p_2 = p_3$, where p_n is the proportion of incorrect to correct recognition by the ANN) for the 3 states yielded a value of the test statistic ($\chi^2 = 46.7784$, d.f. = 2) greater than the tabulated value even at $P < 0.001$. This indicates a highly significant difference between the recognition in the three states. To test for the difference between the two sleep states, a similarly calculated value ($\chi^2 = 5.4984$, d.f. = 1) was greater than the tabulated value at $P < 0.05$ but less than that at $P < 0.01$. So, there is a significant difference in recognition between the two sleep states at 5% level, but not at 1% level.

As the results show, in most of the cases, the exercised groups' EEG power spectra were identified as 'normal' and not as 'depressed'.

Table 2 Percent recognition of EEG power spectra in various states

		ANN classification		
(A) REM sleep state:				
Group	*n*	Normal	Depressed	% Correct
C	50	50	0	100
D	50	0	50	100
EO	50	50	0	100
ES	50	48	2	96
TOTAL	200	198 (correct)	2 (incorrect)	99
(B) NREM sleep state:				
Group	*n*	Normal	Depressed	% Correct
C	50	50	0	100
D	50	0	50	100
EO	50	50	0	100
ES	50	40	10	80
Total	200	190 (correct)	10 (incorrect)	95
(C) Awake state:				
Group	*n*	Normal	Depressed	% Correct
C	50	49	1	98
D	50	7	43	86
EO	50	40	10	80
ES	50	30	20	60
Total	200	162 (correct)	38 (incorrect)	81

DISCUSSION

The specific FFT changes in each state, along with their behavioural changes, due to exercise and/or stress, are beyond the scope of this paper. From the paper recordings, compared to the C group, a significant increase in the REM sleep frequency and duration, in the D group and a significant decrease of those in the exercised groups have been found. The opposite findings have been observed in case of NREM or SWS. Recent research has stressed on human slow wave sleep more than on REM sleep[20], albeit data on animal experiments are lacking. For correlating EEG findings with mental states, animal studies are helpful[21]. However, in the present study, REM sleep state recordings have been found to be more informative than NREM state, whereas the awake state has been the least indicative. In humans, awake state recordings will be more easily available.

The only reported previous work[13], known to the author, used REM sleep state recordings of EEG power spectra in depressed and control rats. There, testing with unknown samples gave an accuracy of 81% and with known samples (trained with all samples) the accuracy was 99.5%. However, in the present study, known samples (training files) were not used for testing, NREM sleep and awake states too were tested, and the

EEG effects of concomitant exercise and stress were also tested.

The accuracy of the identification may be improved by training and testing with more samples, as well as by varying the ANN architecture. Another ANN can be used for classifying the sleep stages, and taking continuous recordings and storing them in magnetic tapes for further analysis will also be helpful in determining the temporal variations of the various sleep stages.

This work is probably the first of its kind where an ANN has been employed to differentiate EEG power spectra in depressed and exercised animals. If similar encouraging results are also obtained from clinical experiments, then it will be a non-invasive, non-radiological and comparatively less expensive diagnostic and monitoring tool in depression. However, other clinical conditions with negative symptoms, like schizophrenia type II, have to be tested.

Computerized pattern recognition and clinical acumen, are however, not mutually exclusive and will only reinforce each other[22]. It is believed[23] that a human clinician must remain a necessary component of computerized diagnostic procedures to ensure a sufficient high level of diagnostic validity. It is also advocated[24] that computer-generated procedures for psychiatric assessment removes subjective bias from the interpreting process.

CONCLUSIONS

Automated monitoring of EEG power spectra in depression and noting the changes due to treatment can be of immense clinical help. Already some work is being done on quantifying the awake-EEG findings in depression[25]. ANN can become a very useful tool in this field also, as there would be more concurrence between the diagnosticians of various laboratories.

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