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EFFECTS OF THERAPEUTIC COOLING ON THE VISUAL EVOKED POTENTIALS OF MULTIPLE SCLEROSIS PATIENTS

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ABSTRACT
Nineteen MS patients' changes in cognitive performance test scores following a controlled period of head and torso cooling revealed improvement for most of the sample, but not for all, and a few actually performed worse. EEG visual evoked responses, in the form of scalp charge density time integrals revealed an inverse relationship between the degree of cognitive performance improvement and the 'normality' of this EEG data, as predicted by the Shauf-Davis model of neural conduction.

KEYWORDS: Multiple Sclerosis, Cooling Therapy, Visual Evoked Potentials, Electroencephalography, EEG.

INTRODUCTION
Nineteen MS patients, all instrumented for EEG and wearing a cooling vest, received carefully monitored cooling therapy for a one hour period. Before cooling and afterwards, all subjects were given a set of cognitive tests, the "Rao Test Battery" (Rao, 1994). Before cooling they were also given a series of visual stimuli in the form of a reversing black and white checkerboard pattern for recording of stimulus-gated EEG epochs.

One objective was to quantify the degree of improvement in multiple scoliosis (MS) patients' cognitive performance following therapeutic cooling. Externally applied cooling therapy has been used extensively to alleviate many of the symptoms of MS: to reduce perceived fatigue, reduce muscle tremor, and improve visual performance (Beenakker *et al* 2001, Feys *et al* 2005, Kinnman *et al* 2000, Ku *et al* 1999, Reynolds *et al* 2011, NASA/MS Cooling Study Group 2003, Syndulko *et al* 1996).

Another objective was to relate the cognitive performance results to plausible changes in neural activation in the visual pathway. There is evidence in the literature that MS is associated with conduction blocks in the visual pathway due to demyelination (Beatty 1993, Halliday 1981, Phillips *et al* 1983, Chiappa 1980, Riemslag *et al* 1985). This impairment has been associated with abnormal visual evoked potentials (VEPs), such as abnormalities in the shapes, latency, or amplitudes of particular peaks. (Beatty 1993, Giesser 1993).

In order to avoid subjective judgment of abnormality, as well as facilitate statistical analysis of inter-subject and pre-post differences, we employed a special EEG approach: VEPs were mathematically transformed into estimates of the whole scalp *charge density* pattern – hereafter referred to as VEQs (Q for charge). The resulting VEQs at occipital electrode Oz were then time-integrated over a 200 msec. period to produce *numerical measures* of the comparative "strength" of visual pathway activation. This also facilitated comparison with the mean VEQ of a 'control' group of 19 healthy subjects collected in the same manner as the MS group prior to cooling.

The general results of this research are summarized in Figure 1. It will be seen that, as might be expected, cooling facilitated a cognitive test score improvement for most of the MS patients; but the stronger their VEQ, the *less* their cognitive test score *improvement* following cooling. This finding is the focus of discussion in the final section of this paper, where it is related to the Shauf-Davis theoretical model of nerve conduction.

METHOD
Subjects: After extensive screening and interviews 19 participants with MS were selected (11 men and 8 women). Nineteen healthy subjects (12 men and 7 women) were also included in the study – solely for collection of 'normal' EEG data, explained above. The mean and standard deviation of the MS and healthy subjects' heights (cm), weights (Kg), and ages (Yr) are given in Table 1.

Table 1: Subject characteristics.

Subject Group	Height (cm)	Weight (kg)	Age (yr)
MS Female	163.0 ± 5.8	77.4 ± 13.8	52.0 ± 7.0
MS Male	177.8 ± 5.1	75.9 ± 7.0	47.7 ± 7.4
Healthy Female	165.7 ± 7.0	67.4 ± 10.5	42.9 ± 9.7
Healthy Male	180.6 ± 5.0	89.8 ± 10.9	43.0 ± 13.7

Cooling: All tests were conducted at normal room temperature with the subjects seated in an upright position. Each wore the Life Enhancement Technologies, Inc. (LET, Los Angeles, CA) active liquid cooling garment. After instrumentation and orientation the pre-cooling testing session consisted of 30 minutes for cognitive tests and collection of EEG data (only EEG for the healthy group). This was followed by a 60 minute cooling period, and then 30 minutes for post-cooling EEG and cognitive tests.

Thermal response measures

A U.F.I., Inc., (Morro Bay, CA) Biolog battery-powered ambulatory monitoring system was used to record the subject's body temperature, heart rate, and respiration during each seated test sequence. Four U.F.I. 1070 temperature transducers were placed on the subject-- for chest, forearm, calf, and rectal temperature. A standard Lead I ECG configuration was used to monitor heart rate. Respiration was monitored using an expandable piezoelectric strap placed around the chest. A Thermoscan, Inc. (San Diego, CA) hand-held infrared thermometer was used to take left and right ear canal temperatures. And a Becton Dickinson and Company (Franklin Lakes, NJ) digital thermometer was used to measure oral temperature.

Neuropsychological assessment tests

The "Brief, Repeatable Battery of Neuropsychological Tests" referred to as the "Rao test battery" (Rao 1994) was used to obtain a qualitative index of each subject's cognitive processing before and after cooling therapy. This test battery was developed by members of the Cognitive Function Study Group of the National Multiple Sclerosis Society for evaluating short-term changes in cognitive function in patients with MS. The brief, repeatable battery provides measures of sustained attention, concentration (Paced Auditory Serial Addition Test, Symbol Digit Modalities Test), verbal learning and delayed recall (Selective Reminding Test), and visual-spatial learning and delayed recall (10/36 Spatial Recall Test).

Each subject was given a thorough orientation overview, including practice trials for each individual test, prior to the pre-cooling test sequence. Scores on the individual elements of the Rao battery were combined into pre-cooling and post-cooling 'composite' scores for each subject.

Electroencephalography

After a training period to familiarize the subject with the EEG procedure described below, each subject was instrumented for EEG using the Physiometric, Inc. (Billercia, MA) eNET electrode cap. Nineteen electrode sites were utilized, corresponding to the International 10-20 system (Homan 1988). Just before cooling, while subjects were seated comfortably in front of a computer screen, continuous multi-channel EEG records were recorded on a Lexicor (Boulder, CO) NRS-24 system (3200x analog gain, 0.5 Hz high-pass filter, 60 Hz notch filter, for a maximum scalp Impedance of 5000 ohms). Analog data were digitized at a rate of 256 samples per second.

Visual stimulus

During the EEG recording subjects passively viewed a series of reversing black and white checkerboard patterns presented on a computer screen. The viewing distance and size of the display were controlled to assure that each checkerboard square subtended a visual angle of approximately 18 minutes of arc (as per Harter and White 1970). This pattern-reversal stimulus is commonly used to generate Visual Evoked Potentials (VEPs), which are frequently used for diagnostic evaluation of the extent of visual pathway impairment in MS patients (Halliday 1981, Chiappa 1980).

VEP Construction

Each pattern reversal, every half second, triggered a pulse that was sent to the Lexicor via a pair of Keithly, Inc. (Cleveland, OH) P-I/O-12 cards. These pulses marked the beginning of each stimulus-gated response. Subsequent to the experiment, the continuous recording was scanned and those stimulus-gated epochs that were free of eye-blink and other artifacts were averaged together to produce a *multi-channel* VEP for the subject. At least 50 epochs were included in each VEP.

Conversion of VEPs to VEQs

Continuous EEG records and VEPs constructed from them are time profiles of scalp *voltage* differences between scalp electrodes and a reference electrode. All VEPs were mathematically converted to *charge-density* profiles. The conversion procedure entails two steps: First, at each time sample point in the VEP, the shape of the scalp voltage surface is estimated by multiple regression analysis, using the X-Y grid locations of the electrodes as the independent variables. Then, at each electrode site, the Laplacian of this fitted surface (the sum of the second-partial spatial derivatives in the X and Y directions) is computed. Charge density is proportional to the (negative of) the Laplacian (Lorrain and Corson 1970). The stimulus-gated charge-density record thus produced for a particular electrode site is hereafter referred to as a VEQ.

VEQ data use

Being a function of the derivatives of the contours of the scalp voltage surface, the VEQs are independent of the voltage level of the common reference (Hjorth 1980, Nunez 1981), which may differ from one subject to another. However, the most important benefit of the transformation of VEPs into VEQs is the that latter are numerical data that can be *time- integrated*. Since there is considerable morphological variation in VEPs and VEQs for MS patients (Giesser 1993), we focused on the overall "strength" of the VEQ rather than the latency or amplitude of particular waveform features. As an index of the "strength" of the response to the visual stimulus we employed the absolute value of the time-integral of charge density at oZ during the period from 70 to 200 milliseconds following stimulus presentation. The anatomical projection of the visual pathway suggests that the most relevant data are obtained from the occipital electrodes; this is why we focused on the oZ electrode.

RESULTS

Thermal response to cooling therapy

All body temperatures of both the male and female MS subject groups cooled significantly ($P<0.05$) during the cooling period: rectal -0.4 to -0.6 °C, oral -0.6 to -0.8 °C, ear -0.3 to -0.4 °C, average skin -1.6 to -1.7 °C, and average body -0.6 to -0.7 °C. The average "core" cooling (-0.4 to -0.8 °C), represented by the rectal and oral temperatures, are well within the values (approximately -0.6 °C) shown by Watson (1959), Ku *et al* (1999) and the NASA/MS Cooling Study Group (2003) to improve the symptoms of MS patients.

The rectal, ear, and oral temperatures of both the male and female MS subject groups continued to cool during the recovery period, after the cooling garment was removed. The average skin and average body temperatures of the male and female MS subjects increased immediately after removal of the cooling garment.

Neuropsychological test response to cooling therapy

All but six of the nineteen MS patients tested (68%) improved their composite cognitive performance scores. Table 2 shows the number of male and female MS subjects who improved on each Rao test as a fraction, with the number improved as the numerator and the total number of subjects tested as the denominator.

Table 2: Fraction of MS Subjects Who Improved After Cooling.

Test	Males	Females
Selective Reminding	8/11	5/8
10/36 Spatial Recall	4/11	3/8
Symbol Digit Modalities	2/11	6/8
Paced Auditory Addition		
Three Second Interval	6/11	6/8
Two Second Interval	4/11	5/8

For those subjects whose performance improved, the average percentage gain in the composite Rao scores was 13.2% for women and 17.5% for men.

DISCUSSION

Figure 1 shows a scatter plot of patients' post-cooling *improvement* in Rao composite score versus their *pre-cooling* VEQ integral—as a fraction of the control group's grand average VEQ time-integral. Although the particular coefficients of the polynomial fit to this data are probably not important, the curve reveals a distinctive non-linear, but mainly inverse, relationship between the two variables.

(Note: p refers to MS patient; m = male, f = female.)

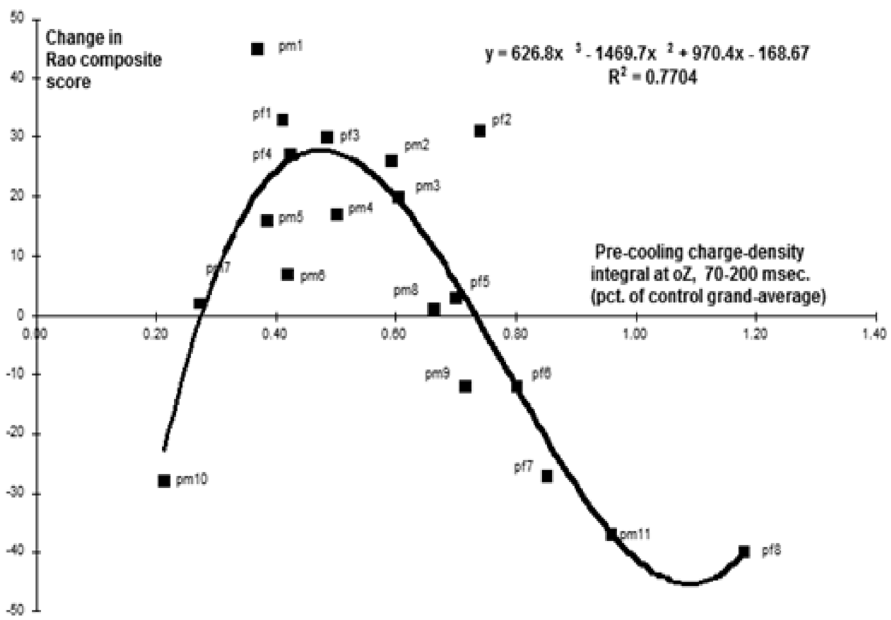

Figure 1: MS patients' post-cooling improvement in Rao composite score versus their pre-cooling VEQ integral.

There seem to be three groups – from left to right

A .) Patients whose VEQ integrals were less than 25% of normal had a decrease in their post-cooling Rao test score.

This pattern may be seen in the VEQ data itself; Figure 2 compares the actual VEQ traces for representative MS patients from the three groups.

B.) The patients who benefit most (in terms of the cognitive functions tested by the Rao battery) are those whose pre-cooling VEQ integrals are between 25% and 75% of normal.

C.) Those patients with the strongest VEQs (approximately above 75%, compared to the grand average of the healthy subjects) tend to benefit least from cooling. Indeed, their Rao scores may even be lower after cooling than before.

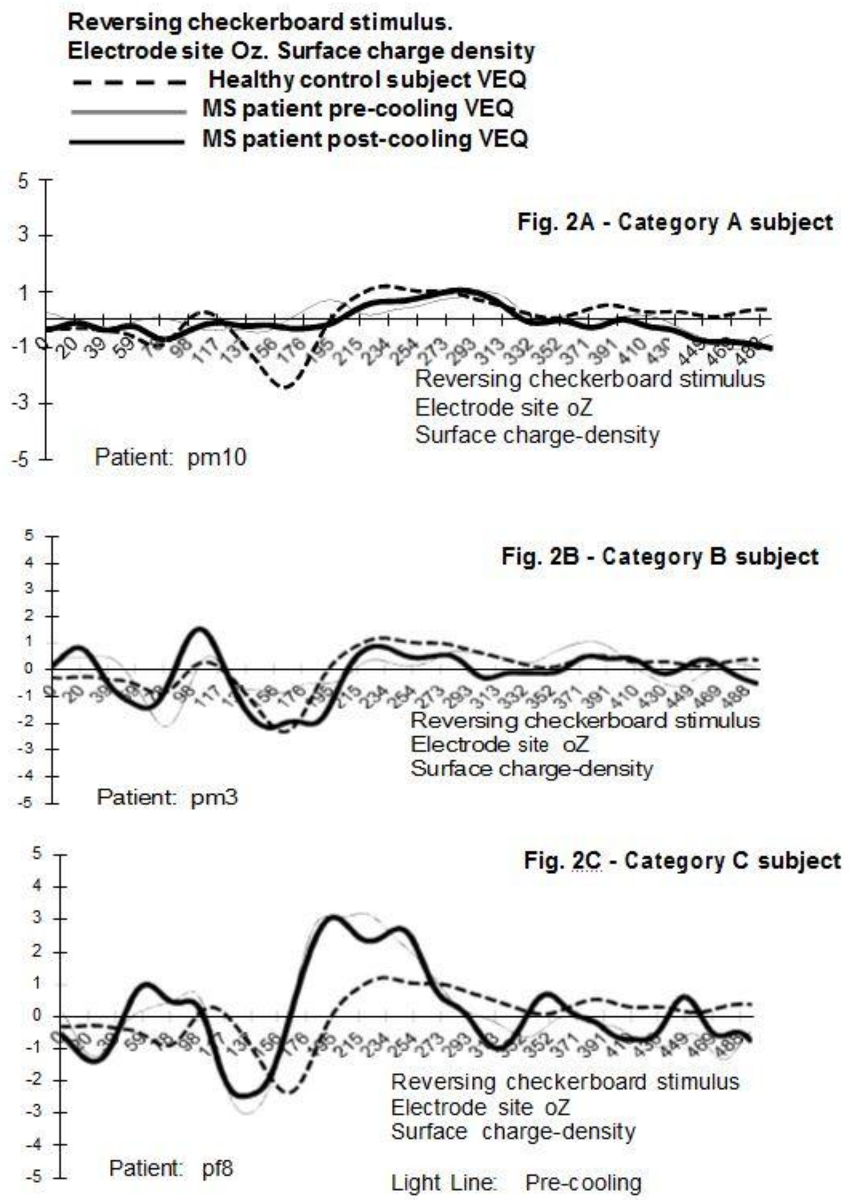

Figure 2: Typical category A, B and C patients' VEQ response before and after cooling.

Group B appears most consistent with the familiar hypotheses that, when cooling strengthens the impulse transmission properties of demyelinated nerve fibers, MS patients improve cognitive performance. Group A may be interpreted as show impaired transmission, and little improvement by cooling. It is Group C that is particularly interesting. Other researchers have discussed the possibility that cooling may have opposing effects on neural conduction, and that the balance may depend upon the state of demyelization. Schauf and Davis (1974) developed a theoretical model of a nerve to examine the combined effects of temperature and myelin loss on conduction. Figure 3 (derived from the Schauf and Davis publication) shows that decreased temperature can have two different effects upon conduction in the nerve fiber.

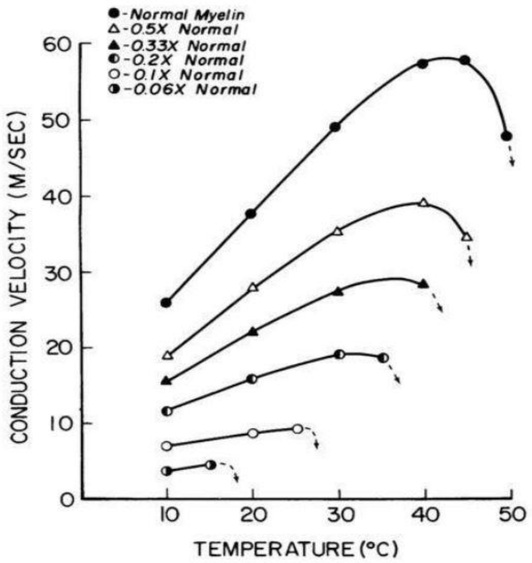

Figure 3. Schauf and Davis theoretical model of axon conduction.

Reproduced from Impulse conduction in multiple sclerosis: A theoretical basis for modification by temperature and pharmacological agents. C.L. Schauf and Floyd A. Davis. 37. 152-161. 1974 with permission for BMJ Publishing Group Ltd.

In general, a decrease in nerve temperature will reduce the conduction velocity in normal nerves or in nerves with a small amount of demyelination. In nerves with moderate demyelination a small reduction in temperature may actually increase conduction velocity, i.e., reverse the effect of blockage and restore conduction. The model predicts that a temperature decrease of 15 to 20 °C is required to restore conduction in the heavily demyelinated nerve fiber.

Schauf and Davis (1974) calculated conduction velocity as a function of temperature for a normal nerve fiber and a series of demyelinated nerves ranging from 0.06 to 0.50 times the normal myelin resistance. Conduction velocity was found to increase linearly with temperature in the normal nerve, reaching a broad maximum at approximately 42 °C. A further increase in temperature caused the conduction velocity to drop sharply and completely fail at 50 °C. In demyelinated fibers the conduction velocity also increases with elevated temperature; however the slope of the curve is reduced with increased nerve damage and becomes almost horizontal with extensive demyelination. In addition, nerve blockage occurs at lower temperatures with increased demyelination.

Blockage takes place at approximately 50 °C in the normal nerve fiber approximately at 46 °C in the fiber with 50% of the normal resistance, and at ~ 40 °C in the fiber with 33% of the normal resistance. Blockage occurs at temperatures lower than 38 °C when the resistance of the myelin sheath falls below 20% of normal. The model predicts that complete conduction blockage will occur at 28 °C when the myelin resistance is 10% of normal and at 16 °C when the myelin resistance is 6% of normal.

Honan *et al* (1987) suggest that these results can be used to explain the seemingly paradoxical effect of temperature upon the increased symptoms of some multiple sclerosis patients with slight elevations of temperature and in others with small decreases in body temperature. Elevation of temperature in the unblocked nerve may increase conduction velocity thereby reducing symptoms of MS or it may cause blockage and greatly increase the symptoms. On one hand a reduction of temperature in the unblocked nerve will reduce conduction velocity and increase MS symptoms. But on the other hand it may restore conduction in a blocked nerve and greatly reduce the symptoms of MS. In nerve tracts that contain individual fibers with different amounts of demyelination, changes of temperature can cause a wide range of effects, which, for the most part, will depend upon the summation of the above effects.

Summarizing, although our data support the expectation that cooling is often beneficial, our results are also consistent with Schauf's and Davis's (1974) theoretical model and the interpretative suggestions set forth by Honan *et al* (1987 that cooling therapy may produce a wide range of responses among MS patients. The nature of their impairment and the extent of their heat sensitivity should be taken into consideration. So should other factors, such as the differences in location of cerebral cognitive function of MS patients vs. that in healthy individuals (Bonnet *et al* 2010).

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