Electroconvulsive Therapy Increases Circadian Amplitude and Lowers Core Body Temperature in Depressed Subjects

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Background: *Reduced amplitude of the circadian temperature rhythm and elevated nocturnal body temperature normalize after successful pharmacotherapy of major depression.* **Methods:** *Core body temperature was continually monitored in three groups: a) 6 depressed patients before an electroconvulsive therapy (ECT) course and b) after an ECT course; and c) 6 healthy, sex-matched controls of similar age.* **Results:** *The 24-hour profile of temperature was significantly different in patients pre-ECT than in patients post-ECT or in controls. Post-ECT subjects and controls manifested 24-hour profiles similar to one another. Circadian temperature rhythm amplitude increased after ECT. The mean asleep and mean 24-hour temperatures were significantly higher in patients pre-ECT than post-ECT and controls.* **Conclusions:** *We find that ECT restores a disrupted circadian temperature rhythm in depressed patients.*

Key Words: Circadian rhythms, depressive disorders, electroconvulsive therapy, temperature

BIOL PSYCHIATRY 1997;42:1130–1137

Introduction

Disrupted circadian physiology is a common manifestation of major depressions (Hallonquist et al 1986). Symptoms of altered circadian biology frequently encountered in depression include diurnal mood variation and sleep–wake cycle disturbances. The prevailing complaint of patients with major depression is of sleep disturbance. Reduced REM latency and diminished amplitude of circadian cortisol and thyrotropin (TSH) rhythms are common biological findings that resolve with successful treatment (Hallonquist et al 1986; Souêtre et al 1986, 1988; Wehr et al 1985). Even the regularity of daily social contacts is altered in patients with depression (Szuba et al 1992).

While early studies suggested that depression was associated with a phase shift of the circadian system (Wehr et al 1983), amplitude blunting appears the most consistent circadian change (Sack et al 1988; Souêtre et al 1989). Some have suggested that the blunting of the amplitude of circadian rhythms may reflect either impaired coupling between various rhythms or abnormal entrainment to external zeitgebers (Souêtre et al 1989).

Disturbances in the 24-hour pattern of core body temperature, including reduced amplitude of the circadian

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Received June 5, 1995.

0006-3223/97/$17.00
PII S0006-3223(97)00046-2

Table 1. Demographic and Clinical Variables of Patients Undergoing ECT and Controls

Subject	Age (years)	Sex	Dx	Medications pre-ECT	Medications during ECT	Medications post-ECT
P1	31	F	UP	BZDP, diphenhydramine, neuroleptic, SSRI	Acetaminophen, BZDP, neuroleptic, NSAID	BZDP, HCA, neuroleptic
P2	34	M	UP	BZDP, decadron, diphenhydramine, neuroleptic, prednisone	BZDP, benztropine, decadron, neuroleptic, prednisone	Amantidine, benztropine, decadron, HCA, neuroleptic, prednisone
P3	36	F	BP	BZDP, Li, NSAID, SSRI, T4	Acetaminophen, ASA, BZDP, NSAID, T4	Carbamazepine, T4
P4	40	F	BP	BZDP, diphenhydramine, Li, MAO	Acetaminophen, BZDP	Buspirone, BZDP, benztropine, Li, neuroleptic
P5	42	M	BP	BZDP, captopril, Li, T4, verapamil, valproic acid	Acetaminophen, BZDP, captopril, NSAID, T4, verapamil, valproic acid	BZDP, captopril, Li, T4, verapamil, valproic acid
P6	52	F	UP	HCA, neuroleptic	Neuroleptic	HCA
C1	34	F	—		—	—
C2	31	M	—		—	—
C3	38	F	—		—	—
C4	34	F	—		—	—
C5	27	M	—		—	—
C6	49	F	—		—	—

Dx, diagnosis; UP, unipolar depression; BP, bipolar depression; P, patient; C, control; HCA, heterocyclic antidepressants; SSRI, selective serotonin reuptake inhibitor; MAO, monoamine oxidase inhibitor; Li, lithium; T4, thyroxine; BZDP, benzodiazepine; NSAID, nonsteroidal anti-inflammatory drug; ASA, acetylsalicylic acid, and caffeine.

temperature rhythm and elevated nocturnal temperature, normalize after successful antidepressant treatment (Avery et al 1986; Souêtre et al 1988). The specific temperature abnormalities observed in these studies may reflect impaired thermoregulation, particularly at night, during depressive episodes. To date there have been few studies of the effects of electroconvulsive therapy (ECT) on core temperature (Avery et al 1986; Bicakova-Rocher et al 1989; Cosgrove 1974). Although the previous studies included small subsets of ECT-treated patients and were well-designed studies, the authors did not analyze ECT subjects separate from the medication-treated group (Avery et al 1986, 1992; Bicakova-Rocher et al 1989).

We set out to determine whether ECT, like antidepressant medication, would normalize the 24-hour profile of core body temperature in major depression. We hypothesized that ECT would increase the amplitude of the circadian temperature rhythm and lower asleep temperature in patients with depression.

Methods and Materials

We carried out all procedures in accordance with guidelines set forth by the UCLA Human Subjects Protections Committee.

Subjects

Demographic and clinical information of patients undergoing ECT and the controls can be found in Table 1. Seven inpatients between 27 and 52 years old meeting research diagnostic criteria for major depression, unipolar or bipolar type, who were going to receive ECT at the recommendation of their primary physician were enrolled in the study. Diagnoses were established by agreement of two physicians. We excluded patients from the study if they had an organic mood disorder, rectal hemorrhoids, or medical illnesses known to affect mood or temperature. Due to clinical and ethical issues, we were unable to study patients medication-free. One patient was dropped from the protocol due to the development of an upper respiratory infection with fever just before the post-ECT monitoring.

Six sex-matched subjects, approximately the same age, who had no psychiatric or substance use disorders, who were free of medical illnesses affecting mood, and who were not taking any psychotropic medications were included as a control group. Acetaminophen and aspirin were not allowed for 3 days before, or during, the temperature monitoring for any subjects.

Mood Ratings

The 6 depressed patients included in the final sample (3 unipolar and 3 bipolar) were rated with the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton 1960) and the Global Assessment Scale for current functioning (GAS). We rated patients during the circadian temperature monitoring periods before and after ECT. We

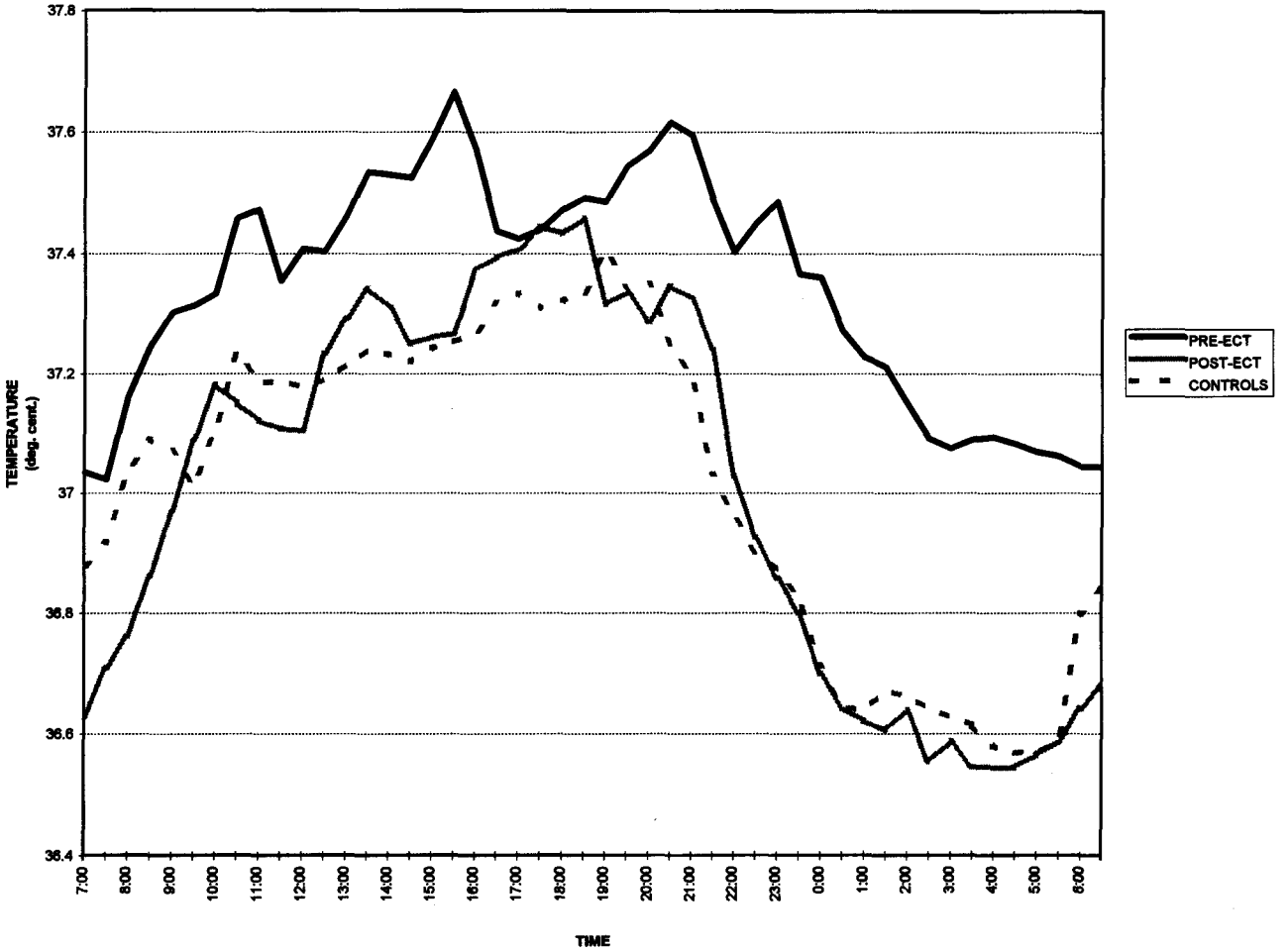

Figure 1. Circadian pattern of core body temperature in 6 depressed patients before and after ECT and in 6 controls.

rated control subjects with the same mood scales during their single temperature monitoring period.

Environment

The protocol was carried out on inpatient units that were maintained at a constant temperature of 68°F and lighting intensity of 50–900 lux at eye level. All subjects followed the regular ward routine, which included a daily 1-hour exposure between 09:00 and 10:00 hours to outdoor sunlight for recreational therapy. Otherwise, patients had no passes off the unit during the trial. Controls were studied in their everyday environment.

Temperature Monitoring

To monitor core body temperature, subjects wore a portable monitor consisting of a small belt-worn, computerized device and a thin rectal or vaginal probe inserted 3–5 inches into the rectum or vagina. The data were stored in solid state memory and subsequently recovered by personal computer. Core body temperature was measured for up to 72 hours at 5-min intervals, and probes were removed only during toileting or bathing. In patients, the temperature monitoring took place before ECT and was restarted within 1–5 days after the completion of the ECT course. Controls were monitored only once.

ECT Parameters

Clinical decisions regarding electrode placement, stimulus intensity, and number of ECT per course were made by the treating physicians and the physician administering ECT based on clinical factors and without regard for the study. ECT was administered between 08:00 and 12:00 hours for all subjects. The subjects underwent 11 ± 1.8 ECT treatments over 17.3 ± 3.1 days. The seizures lasted for a mean of 44.3 ± 8.4 sec. All subjects were medicated with methohexital and succinylcholine during each ECT, while 5 subjects had unilateral and 1 subject had bilateral ECT.

Statistical Analysis

The continually obtained temperature data points within each subject were averaged to produce a 24-hour profile for each individual. Each individual's data were then averaged over 30-min epochs to smooth the data for plotting and statistical analysis.

We calculated the following parameters from the temperature data for each individual as follows:

1. Mean awake (07:00–22:55) and asleep temperatures (23:00–06:55).
2. The difference between the mean awake and asleep temperatures.
3. The ratio of the mean awake to asleep temperatures.
4. A rater blind to all clinical data determined the amplitude, minima, timing of minima, and timing of maxima of the circadian temperature rhythm by visual inspection of the smoothed core temperature curves for each subject.

We attempted to fit the temperature curves to a cosinor function as described previously (Souêtre et al 1988). Data for each condition (pre-ECT, post-ECT, and controls) were then compared as described below.

All data are presented as mean ± standard deviation unless otherwise indicated. We set significance level set at .05. Categorical data were analyzed with Fisher's Exact Test. On continuous variables, paired t tests were used to compare patients pre-ECT to post-ECT. Unpaired t tests were used to compare patients (pre-ECT and post-ECT) to the controls.

The 24 temperature profiles were compared within subjects, pre- vs. post-ECT, by two-way analysis of variance (ANOVA) (mood state × time of day), with time of day as the repeated measure. Separately, pre-ECT subjects and post-ECT subjects were compared to controls by means of a two-way ANOVA (group × time), with time of day as the repeated measure.

Pearson correlation coefficients were calculated to determine the relationship between mood and temperature measures.

Results

Circadian Measures

The circadian variation in core body temperature appears to be diminished in patients before ECT. Figure 1 illustrates the dramatic contrast in the circadian pattern of core body temperature between the patients in the depressed state and in the recovered state [mood state: $F(1,235) = 10.2$, $p = .02$; time of day: $F(47,235) = 10.7$, $p < .000000$; mood state × time of day: $F(47,235) = 1.69$, $p = .006$]. Patients before ECT also manifested 24-hour temperature profiles quite different from controls [group: $F(1,470) = 5.0$, $p = .05$; time of day: $F(47,470) = 13.0$, $p < .000000$; group × time of day: $F(47,470) = 1.8$, $p = .001$]; however, patients after ECT had a circadian profile highly similar to that of controls [group: $F(1,470) = 0.008$, $p > .05$; time of day: $F(47,470) = 25.3$, df = 47, $p < .000000$; group × time of day: $F(47,470) = 0.82$, $p > .05$].

In attempting to fit the temperature profiles to a cosinor function, we found the data of most patients pre-ECT did not fit a cosinor function. We believe the cosinor function is not an accurate model of the profile. Therefore, we did not calculate this function for the other groups. This result

Table 2. Mood and Temperature in Patients before ECT, after ECT, and in Controls

	Pre-ECT[a] (n = 6)	Post-ECT[b] (n = 6)	Controls[c] (n = 6)	Pre- vs. post-ECT (paired t test)		Pre-ECT vs. controls (unpaired t test)		Post-ECT vs. controls (unpaired t test)	
				t (df = 5)	p	t (df = 10)	p	t (df = 10)	p
Illness measures									
HDRS	26 ± 9.3	6.3 ± 2.4	2.3 ± 2.3	5.7	.001	6.1	6×10^{-5}	3.0	.007
GAS current	40.8 ± 7.4	66.7 ± 10.3	91.5 ± 4.2	4.4	.003	14.7	2×10^{-8}	5.5	.0001
Temperature measures (°C)									
Amplitude	0.34 ± 0.19	0.59 ± 0.19	0.43 ± 0.08	2.3	.03	0.99	ns	1.9	ns
Awake–asleep difference	0.26 ± 0.39	0.55 ± 0.28	0.50 ± 0.13	1.7	ns	1.4	ns	0.41	ns
Awake/asleep ratio	1.007 ± 0.011	1.015 ± 0.008	1.014 ± 0.004	1.7	ns	1.5	ns	0.4	ns
Awake	37.43 ± 0.26	37.19 ± 0.21	37.18 ± 0.26	2.2	.04	1.7	ns	0.03	ns
Asleep	37.17 ± 0.36	36.63 ± 0.33	36.68 ± 0.33	3.2	.01	2.5	.02	0.24	ns
Temperature minimum	36.83 ± 0.32	36.3 ± 0.42	36.45 ± 0.31	2.6	.05	2.1	.03	0.7	ns
24-hour[d]	37.34 ± 0.23	36.99 ± 0.22	37.01 ± 0.28	3.4	.01	2.2	.02	0.16	ns

[a]Asleep = awake: $t = 1.6$, df = 5, p = ns.
[b]Asleep < awake: $t = 4.9$, df = 5, $p = .002$.
[c]Asleep < awake: $t = 9.6$, df = 5, $p = .0001$.
[d]24-hour temperature is mean temperature across 24 hours.

has been found by another group in seasonal depressed subjects (Rosenthal et al 1990).

The amplitude of the circadian temperature rhythm increased significantly from pre-ECT to post-ECT (Table 2). The controls' amplitude was not significantly different from either patient group. The awake minus asleep temperatures and awake to asleep temperature ratios as measures of circadian variation were higher in post-ECT subjects and controls than in pre-ECT subjects, but the differences did not reach statistical significance (Table 2). There were no differences between timing of temperature minima or maxima between any groups.

The final measure of circadian variation, the within-subject comparison of awake and asleep temperatures, was not statistically significant in patients pre-ECT; however, patients post-ECT and controls manifested significant differences between awake and asleep temperatures, further suggesting that the circadian variation is diminished in patients during the depressed state (Table 2).

Mean Temperature Measures

Table 2 also illustrates the intergroup and intragroup differences in body temperature over different epochs. Before ECT, patients manifested awake temperatures significantly higher than after ECT. Temperature minima, and asleep and 24-hour temperatures dropped significantly after ECT compared to that of controls. Post-ECT subjects and controls manifested similar temperatures over all epochs ($p > .05$). Likewise, the temperature minima were significantly lower after ECT than in controls.

Demographic and Mood Variables

There were no statistically significant differences in age or gender between patients and controls. We could find no consistent pattern to the medications patients received before, during, or after ECT to explain the mood or temperature results (Table 1). Male subjects did not differ from female subjects on any demographic, clinical, mood, or temperature variable using visual inspection of the circadian curves, and formal statistical analyses.

As seen in Table 2, pre-ECT patients scored significantly worse on the HDRS and the GAS than did patients post-ECT. Controls scored significantly better than patients (both pre- and post-ECT) on these scales.

Correlations

There were significant inverse correlations between the level of depression severity and the diurnal variation in core body temperature as measured by the awake/asleep temperature difference or awake/asleep temperature ratio values (see Table 3). HDRS scores were significantly correlated with asleep and 24-hour temperatures. GAS scores were negatively correlated with asleep and mean 24-hour temperatures.

Table 3. Correlations between Mood and Core Body Temperature in 6 Patients before ECT, 6 Patients after ECT, and 6 Controls

	Pearson's correlation coefficient (p value)	
	HDRS	GAS
Asleep temperature	.63 (.005)	−.54 (.02)
Awake temperature	ns	ns
24-hour mean temperature	.46 (.05)	−.48 (.04)
Awake − asleep	−.63 (.005)	ns
Awake/Asleep	−.63 (.005)	ns
Amplitude	ns	ns

Though we found no correlation between either HDRS or GAS scores with amplitude, amplitude did correlate significantly with awake/asleep difference ($r = .46$, $p = .05$) and with awake/asleep ratios ($r = .47$, $p = .05$).

Because subjects were not perfectly age-matched, we also performed all above analyses with age as a covariate. The group differences were unchanged.

Discussion

We found multiple lines of evidence that the daily variation of core body temperature is reduced in depression in this small study. ECT reestablishes the disrupted circadian temperature rhythm. Especially impressive about the elevation of circadian amplitude is that it occurred in the face of lowering daytime temperatures, since lowering daytime temperature would reduce the amplitude.

In reviewing the literature, we found 11 studies that collected around-the-clock temperature data at regular intervals in depressed subjects and systematically compared their results to recovery temperatures and/or to healthy controls (see Table 4). Despite the heterogeneity of treatments given, all the studies found evidence of temperature dysregulation in depression. Each study showed that depressed patients in remission or controls had greater circadian amplitude (Wehr's study found differences between 07:00–10:00, 16:00–19:00, and 19:00–22:00, but not between 22:00–07:00) and/or lower core body temperatures than patients in the depressed state.

Our study is consistent with the hypothesis that blunted amplitude is the main chronobiological abnormality (Souêtre et al 1989) in nonseasonal depression. Eight of the 11 studies we reviewed showed reduced amplitude during the depressed state. Whether amplitude blunting is due to inadequate input to the pacemaker of zeitgeber informa-

Table 4. Controlled Studies of Circadian Temperature in Depressed Patients (Case Studies Excluded)

Reference	Total *n* (% bipolar)	Main temperature findings in depressives	Comparison group	Treatments
Mellerup et al 1978	35 (100%)	Higher nocturnal temperatures Higher early morning temperatures	Controls	Lithium
Wehr et al 1980	10 (100%)	Mean temperature from 07:00–10:00, 16:00–19:00, and 19:00–22:00 higher No phase difference	Controls	None
von Zerssen et al 1985	16 (n/a)	Amplitude reduced Nocturnal temperature elevated No phase difference	Controls	n/a
Avery et al 1986	9 (22%)	Nocturnal temperature elevated 24-hour temperature elevated[a] Amplitude reduced No phase difference	Recovery Controls	HCA, MAOI, ECT, spontaneous recovery
Goetze and Tölle 1987	32 (19%)	Amplitude reduced[a] Minima phase advanced[b]	Recovery Controls	HCA, sleep deprivation[c]
Souêtre et al 1988	8 (100%)	Nocturnal temperature elevated Minimum temperature increased Peak temperature decreased[b] Amplitude reduced Amplitude correlates negatively with HDRS No phase difference	Recovery Controls	HCA
Bicakova-Rocher et al 1989	10 (n/a)	Amplitude reduced Shorter circadian period	Recovery	HCA, ECT
Tsujimoto et al 1990	38 (24%)	Mesor not different Depression severity correlates with mesor Amplitude reduced[b] Increased phase variability	Recovery Controls	HCA, lithium, spontaneous recovery, 3 unspecified
Rosenthal et al 1990[d]	10 (90%)	Nocturnal temperature elevated Amplitude reduced[a]	Recovery	Phototherapy
Controls				
Levendosky et al 1991[d]	9 (n/a)	24-hour temperature elevated[a]	Recovery Controls	Winter depressed, summer remitted

If comparison is not specified then it applies to controls and recovered patients vs. depressed patients. HCA, heterocyclic antidepressants; n/a, data not available, MAOI, monoamine oxidase inhibitor.

[a]Only depressed vs. recovered patients manifested differences. Patients and controls were not significantly different.

[b]Only depressed vs. controls manifested differences. Depressed vs. recovered patients were not significantly different.

[c]Sleep deprivation led to no change in any temperature parameters.

[d]Depressed seasonal affective disorder patients.

tion, an abnormally sensitive pacemaker, or impaired coupling between the internal pacemaker and the central nervous system (CNS) systems it temporally regulates, remains to be seen (Healy 1987). A disturbed molecular/biochemical/cellular interface between the pacemaker and its temporal influence (i.e., pacemaker coupling) on the cortex and lower neurophysiological systems involving metabolism/thermoregulation, activity, drives, etc., may account for the whole range of data on depression. Bright light, an important circadian zeitgeber, can, if administered at the proper times, either produce the abnormalities in circadian organization described above or normalize circadian rhythms in depressed patients (Czeisler et al 1986, 1989; Lewy et al 1987; Jewett et al 1991). Manipulations of the circadian system through sleep deprivation or bright light therapy can improve some depressive episodes, while antidepressant medications, including lithium, alter the circadian system (Baxter et al 1986; Hallonquist et al 1986; Johnsson et al 1983; Lewy et al 1987; Souêtre et al 1988; Szuba et al 1991, 1994; Wehr et al 1979). Taken together, these facts suggest that circadian dysrhythmias are involved in the pathogenesis of depression. Czeisler et al (1987) predicted that enhanced circadian rhythm amplitude may be responsible for the antidepressant effects of phototherapy. Since we have now seen that antidepressant medications and ECT can enhance amplitude, perhaps amplitude enhancement is necessary for all antidepressant interventions.

Some measures of circadian variation (amplitude, awake–asleep difference, and ratio) were not different between pre-ECT subjects and controls, suggesting that the symptomatic group did not have dampened circadian

amplitude relative to controls but only to themselves in remission; however, the ANOVA and the temperature minima show differences between pre-ECT and controls, suggesting the mean measures are insensitive to the true group differences and that greater disruption occurs in the asleep phase of the circadian cycle than the awake phase.

As hypothesized, ECT significantly lowered nocturnal core body temperature to that of matched control subjects; age cannot account for these results. This drop in asleep temperatures is consistent with findings from eight of the 11 studies in Table 4; however, in contrast to some studies, we found awake temperature and mean 24-hour temperatures also dropped significantly after ECT. Although elevated core body temperature, per se, is neither sufficient nor necessary to cause depression (Monk et al 1994), work by Wehr et al (1990) suggests that temperature lowering might *facilitate* depression recovery.

Animal studies of electroconvulsive shock (ECS) have produced relevant, albeit somewhat conflicting, effects on core body temperature. A single ECS reduces core body temperature in mice, but causes no sustained changes even after a series of ECS (Gleiter et al 1989). Rats and rabbits, contrarily, show *elevations* in temperature after a single ECS (Nowak 1985) and after a series of ECS (Belenky and Holaday 1981; Hoyt and Rosvold 1951). These elevations persist for over 24 hours, suggesting that excessive motor activity is not solely responsible for the temperature elevations.

Adult humans show transient elevation in core body temperature after spontaneous, nonfebrile, generalized seizures, even in the absence of infection (Wachtel et al 1987). Although tonic–clonic motor activity may account for some of this transient elevation, the postictal hyperthermia persists up to 48 hours. Thus, the seizure seems to fundamentally alter thermoregulation. It is then all the more impressive that ECT, while inducing a generalized seizure, actually lowers core body temperature. This further supports the view that core body temperature is pathologically elevated in depression.

Potential sources of bias must be addressed. The sample size is indeed small. We could not control medication administration because of ethical issues. One might predict conflicting effects by examining the medication changes; however, we found such great variability in medications prescribed before, during, and after ECT that it is perhaps surprising we found significant temperature differences at all. Further, the similarity between our results and those of other studies in remitted depressives after various treatments suggests that thermoregulation is indeed impaired in depression.

We could not control for menstrual cycle, which may have confounded our results; however, only 2 of our patients had menstrual cycles. The other 2 women were amenorrheal throughout the study. Thus, we do not believe menstrual factors account for our results. All the women opted for vaginal temperature monitors, and all men of course had rectal monitors. Although this may have introduced bias, we found no difference between our men's and women's temperature results.

Insomnia, commonly experienced by patients with major depression, can produce elevated nocturnal temperature. Since we did not perform nocturnal polysomnography, we cannot rule out the possibility that reversal of insomnia effected the observed nocturnal temperature changes. Likewise, since activity can influence circadian rhythms, these results might be confounded by a lack of a constant routine for subjects.

These results demonstrate that ECT, like antidepressant medications and phototherapy, can correct the circadian (amplitude blunting) and homeostatic (mean temperatures) abnormalities present in depression. The intimate relationship between temperature dysregulation and depressive episodes warrants further study with larger sample sizes.

Supported by National Alliance for Research on Schizophrenia and Depression (NARSAD) Young Investigator Award; U.S. Public Health Service-NIMH Training (#T32-MH-17140); and an NIMH Biomedical Research Support Grant for the UCLA Neuropsychiatric Institute.

Deep gratitude goes to Herbert Weiner, MD for intellectual guidance, to David Dinges, PhD for editorial suggestions, and to Geralyn Groh-Szuba, MD, Bruce Turetsky, MD, and Andrew Cucchiara, PhD for assistance with data analysis.

This work was presented in part at the 1994 Society of Biological Psychiatry Annual Meeting in Philadelphia.

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