Warmer outdoor temperature is associated with worse cognitive status in multiple sclerosis

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ABSTRACT

Objective: Patients with multiple sclerosis (MS) have more clinical exacerbations and T2 lesion activity during warmer weather. The current study is the first to investigate whether outdoor temperature is related to cognitive status across patients with MS (cross-sectional analysis), and whether cognitive status fluctuates with changes in outdoor temperature within patients with MS (longitudinal analysis).

Methods: For the cross-sectional analysis, 40 patients with MS and 40 healthy control (HC) subjects were recruited throughout the calendar year. Cognitive status (processing speed, memory) and outdoor temperature were recorded for the day of testing. We calculated partial correlations between cognitive status and temperature for patients with MS and HCs, controlling for demographic and disease variables. For the longitudinal analysis, cognitive status and outdoor temperature were recorded at baseline and 6-month follow-up in a separate sample of 45 patients with MS. We calculated the partial correlation between temperature and cognitive status at follow-up, controlling for baseline temperature and cognitive status (i.e., whether temperature changes are related to cognitive changes within patients with MS).

Results: Cross-sectionally, warmer temperature was related to worse cognitive status in patients with MS ($r_p = -0.45$, $p = 0.006$), not in HCs ($r_p = 0.00$, $p = 0.984$). Longitudinally, increased outdoor temperature from baseline to follow-up was related to a decline in cognitive status within patients with MS ($r_p = -0.39$, $p = 0.010$).

Conclusions: Cognitive status in patients with MS is worse on warmer days, consistent with a previously established link between heat and lesion activity. Our findings have implications for clinical trial planning, treatment, and lifestyle decisions. We discuss cognitive status as a potential marker of quiescent exacerbations. *Neurology*® 2012;78:964–968

GLOSSARY

CVLT-II = California Verbal Learning Test–Second Edition; **HC** = healthy control; **MS** = multiple sclerosis; **SDMT** = Symbol Digit Modalities Test; **SRT** = Selective Reminding Test; **TVW** = third ventricle width.

Growing evidence supports the critical role of outdoor temperature in clinical/neurologic symptomology among persons with multiple sclerosis (MS). In particular, warmer seasons are associated with a higher incidence of clinical exacerbations,[1,2] and a recent investigation found a strong association between new T2 lesion activity and warmer daily temperature ($r = 0.50$, $p < 0.0001$).[3] Importantly, in that study, only a small fraction of new T2 lesions were accompanied by a clinical exacerbation. That is, T2 lesion activity frequently occurred in the absence of observable sensorimotor symptomology (e.g., optic neuritis, paresthesias), likely because lesion activity occurred outside of primary sensorimotor pathways. In contrast to sensorimotor functions, the complexity of cognitive functions requires wide recruitment of a more distributed network of white matter tracts. As such, cognitive functions may also be vulnerable to disruption by MS lesion activity, including temperature-related increases in lesion activity. Anecdotally, patients tend to report more cognitive

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problems in warm weather. Despite this, the current study is the first to objectively measure whether warmer daily temperature is associated with worse cognitive performance in persons with MS. The present study examines this association in 2 separate samples using 2 independent analyses: 1) a cross-sectional analysis capturing cognitive status at a single timepoint in a sample of 40 persons with MS and 40 healthy controls (HCs), and 2) a longitudinal analysis of 45 persons with MS tested at 2 timepoints, baseline and 6-month follow-up.

METHODS

Subject enrollment. ***Cross-sectional investigation.*** Subjects were 40 persons with MS[4] (36 women) without an exacerbation in the last 4 weeks, no current corticosteroid use, and no history of serious psychiatric illness, substance abuse, learning disability, or other neurologic condition. Mean age was 45.0 ± 7.2 years, with 16.2 ± 2.3 years of education. Disease duration was 9.9 ± 6.7 years, with MS courses including relapsing-remitting (n = 33) and secondary progressive (n = 7). A group of 40 matched healthy controls (age: 44.2 ± 8.9; education: 16.2 ± 2.0; 36 women) were selected for comparison.

Longitudinal investigation. An independent longitudinal sample of 45 patients with MS (35 women) meeting the aforementioned inclusion criteria was recruited to investigate the impact of temperature change on cognitive status within patients over a 6-month period. Mean age was 43.3 ± 7.2 years, with 15.2 ± 2.4 years of education. Disease duration was 12.1 ± 8.7 years, with MS courses including relapsing-remitting (n = 36) and secondary progressive (n = 9).

Standard protocol approvals, registrations, and patient consents. Institutional review boards responsible for ethical standards at UMDNJ and the Kessler Foundation Research Center approved collection of the data analyzed for both studies. Written informed consent was obtained from all subjects prior to participation.

Daily outdoor temperature. Subjects were enrolled throughout the calendar year, and the mean daily outdoor temperature for the testing site (West Orange, NJ) was recorded. All daily temperatures were acquired from www.weather.org.

Cross-sectional investigation. The mean outdoor temperature on the day of testing was 55.5 ± 18.9°F.

Longitudinal investigation. The mean outdoor temperature was 50.2 ± 16.2°F on the day of baseline testing, and 50.6 ± 16.0 on the day of follow-up testing. Temperature decreased from baseline to follow-up for 53.3% of the sample, and increased for the other 46.7%, with a mean absolute difference in temperature between baseline and follow-up of 18.7 ± 13.4°F across the sample. Temperatures within this study were representative of the climate within the continental United States, as the National Oceanic and Atmospheric Administration's National Climatic Data Center reported a mean annual temperature of 53.8°F across the contiguous United States in 2010 (http://www.ncdc.noaa.gov/sotc/national/2010/13).[5]

Cognitive status. Slowed processing speed and learning/memory problems are the most prevalent cognitive deficits among persons with MS.[5]

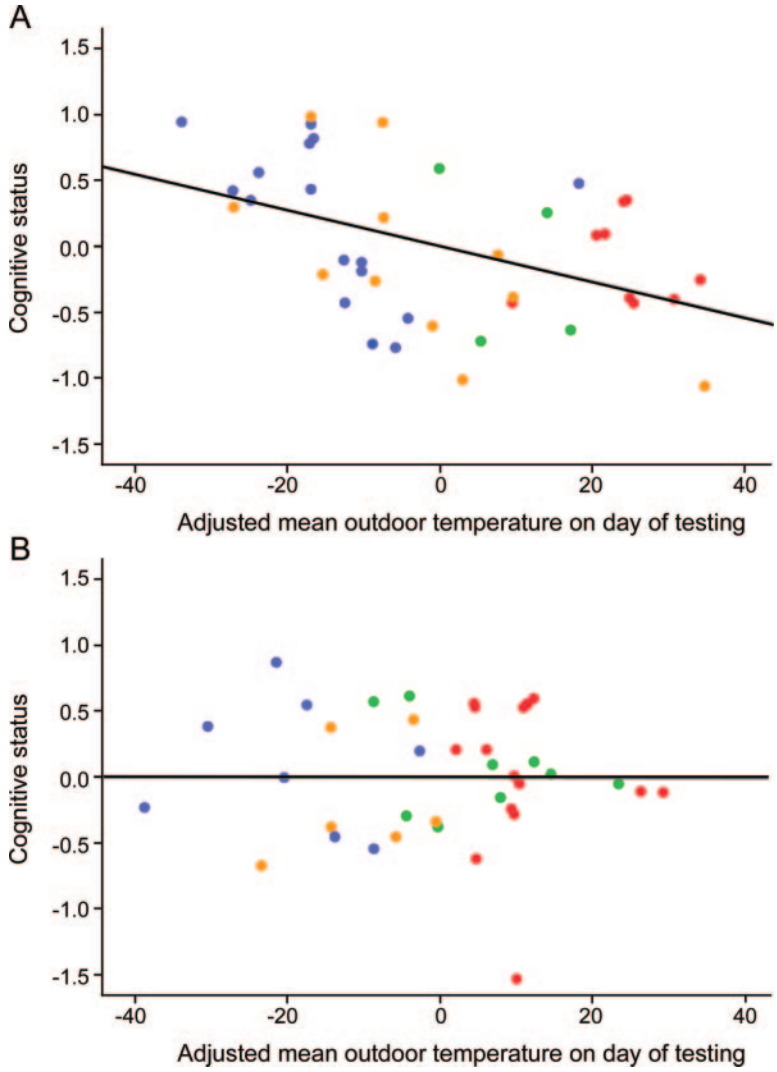
Cross-sectional investigation. We assessed processing speed with the Symbol Digit Modalities Test (SDMT),[6] and learning/memory with trials to criterion on the open-trial Selective Reminding Test (SRT).[7] Consistent with previous research,[5] two-tailed *t* tests showed that patients with MS demonstrated poorer performance than healthy controls on both processing speed (SDMT, HC: 63.9 ± 9.2; MS: 53.8 ± 12.6, $t[78] = 4.10$, $p < 0.001$) and learning/memory (SRT, HC: 6.6 ± 3.2; MS: 9.3 ± 3.7, $t[78] = 3.46$, $p = 0.001$). Scores were converted to sample-based *z* scores, which were then averaged into a single cognitive status score. Positive *z* scores represent better performance. Cognitive status scores were higher among healthy controls (mean $z = 0.39$) than patients with MS (mean $z = -0.39$; $t[78] = 4.66$, $p < 0.001$).

Longitudinal investigation. Neuropsychological testing was conducted for each subject at 2 time points throughout the calendar year: time 1 was baseline and time 2 was 6 months later. We assessed processing speed with the SDMT, and learning/memory with the short-delay free recall and long-delay free recall scores of the California Verbal Learning Test–Second Edition (CVLT-II).[8] Alternate forms of the CVLT-II were used to prevent practice effects. Scores were converted to norm-referenced *z* scores, which were then averaged into a single cognitive status score. Positive *z* scores represent better performance. Cognitive status within this sample of patients with MS was approximately 1 SD below published norms at baseline (mean $z = -1.07 \pm 1.2$).

Brain atrophy. Brain atrophy for patients with MS within the cross-sectional sample was estimated with third ventricle width (TVW), which has been identified as the best neuroanatomic predictor of cognitive performance in patients with MS.[9,10] Consistent with established procedures, TVW was defined as the distance in millimeters between the left and right boundaries of the third ventricle as imaged in the axial plane of high-resolution 3-dimensional images of the brain acquired from magnetization-prepared rapid gradient echo scans performed in a 3.0-T Siemens Allegra scanner. Interrater and intrarater reliabilities were high ($rs > 0.96$). Mean TVW for the MS group was 5.0 ± 2.0 mm.

Statistical analyses. ***Cross-sectional investigation.*** To investigate the relationship between outdoor temperature and cognition among patients with MS, we performed a partial correlation between the mean temperature for the day of testing and cognitive status, controlling for age, education, gender, and brain atrophy. We expected a negative correlation, such that warmer temperatures are associated with worse cognitive performance. To investigate the specificity of this relationship to MS, the partial correlation between mean daily temperature and cognitive status was also tested in healthy controls, controlling for age, education, and gender. If the relationship between temperature and cognitive status is specific to MS, no relationship is expected between temperature and cognitive performance in healthy persons. Note that we controlled for brain atrophy in our analysis of patients with MS, but not healthy persons. Brain atrophy is a marker of MS disease progression.[11] As such, we sought to statistically control for random error produced by interpatient variability in disease progression within our cross-sectional MS sample, especially since brain atrophy was related to our outcome variable (cognitive status, $r = -0.56$, $p < 0.001$), but not our predictor variable (outdoor temperature, $r = -0.04$, $p = 0.812$). Controlling for atrophy allowed us to examine whether temperature is related to cognitive status among

Figure 1 Cross-sectional sample



Partial correlation between daily temperature and cognitive status in (A) patients with multiple sclerosis (MS) ($r_p = -0.46$, $p = 0.006$) and (B) healthy controls ($r_p = 0.00$, $p = 0.984$), controlling for age, education, and gender. Brain atrophy was also controlled within the MS sample. Color coding provides season of testing for each subject: blue = winter, orange = fall, green = spring, red = summer.

patients with MS equated for level of disease progression. Unlike patients with MS, healthy persons show very little variability in brain atrophy,[9] consistent with the absence of a neurologic disease. As such, there was no need to control for brain atrophy within the HC group.

Longitudinal investigation. To investigate whether changes in outdoor temperature are related to fluctuations in cognitive status within patients with MS, we performed a partial correlation between mean daily temperature and cognitive status during the 6-month follow-up, controlling for baseline temperature and baseline cognitive status. If warmer weather negatively impacts cognitive status within patients with MS, then we expect a negative partial correlation.

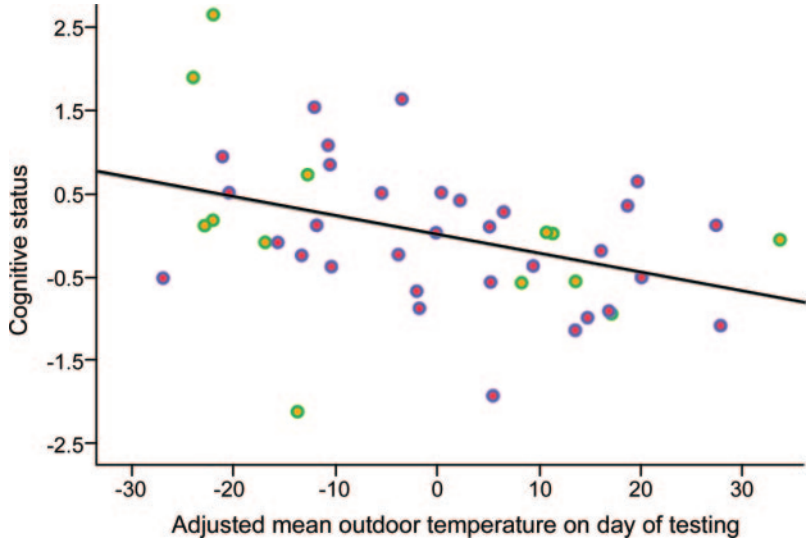
RESULTS **Cross-sectional investigation.** Intercorrelations were calculated among all variables within each group. For patients with MS, the only reliable correlation was a negative association between brain atrophy and cognitive status ($r = -0.56$, $p < 0.001$). Within the HC group, age was negatively associated with cognitive status ($r = -0.59$, $p < 0.001$), and education was weakly correlated with outdoor temperature ($r = -0.36$, $p = 0.021$). No other correlations were reliable.

Regarding our primary analysis, there was a negative partial correlation between outdoor temperature and cognitive status in patients with MS ($r_p = -0.45$, $p = 0.006$), indicating worse cognitive performance on warmer days (figure 1A). In contrast to these results in patients with MS, there was no relationship between outdoor temperature and cognitive status among healthy controls ($r_p = 0.00$, $p = 0.984$; figure 1B). As discussed, there is no variability in atrophy within healthy control populations.[9] However, to be thorough, atrophy (TVW) was entered as a covariate for a subset of 10 healthy controls and did not change the nonsignificant result ($r_p = -0.03$, $p = 0.95$). As such, the negative relationship between temperature and cognitive status appears specific to persons with MS.

Longitudinal investigation. Regarding our primary correlation of interest, there was a negative partial correlation between outdoor temperature and cognitive status during the 6-month follow-up, controlling for baseline temperature and baseline cognitive status ($r_p = -0.39$, $p = 0.010$; figure 2). That is, consistent with expectations, cognitive status within individual patients with MS declined more when temperatures were warmer at follow-up relative to baseline. Correlational analyses of other variables resulted in the following: significantly correlated variables were age and follow-up cognitive status ($r = 0.37$, $p = 0.013$), education and cognitive status at baseline ($r = 0.32$, $p = 0.032$), and follow-up ($r = 0.34$, $p = 0.023$).

DISCUSSION Warmer outdoor temperature has been linked to clinical exacerbations[1,2] and T2 lesion activity[3] in patients with MS. Although approximately 65% of patients with MS experience cognitive deficits,[5] the current study is the first to formally investigate the relationship between outdoor temperature and cognition in patients with MS. We found that warmer temperatures are associated with worse cognitive performance across 2 independent samples of patients with MS. Our cross-sectional analysis demonstrated that cognitive status is worse on warmer days in patients with MS equated for level of disease severity (i.e., brain atrophy). This relationship was specific to MS, as cognitive status was unrelated to temperature among matched healthy controls. The longitudinal/within-subjects analysis showed that changes in outdoor temperature are as-

Figure 2 **Longitudinal sample**



Partial correlation between follow-up cognitive status and temperature ($r_p = -0.39$, $p = 0.010$) in persons with multiple sclerosis, controlling for baseline cognitive status and temperature. Color-coding depicts the 2-season pairing of baseline and 6-month follow-up: spring/fall = green/orange, winter/summer = blue/red. Note that the majority of baseline/follow-up pairings were winter–summer (70.1%).

sociated with cognitive fluctuations within individual patients with MS. Importantly, results of the longitudinal/within-subjects analysis demonstrate that individual patients have a measurable decline in cognitive status when the outdoor temperature is warmer.

Clinicians frequently rely on sensorimotor symptoms (e.g., optic neuritis, muscle weakness) as clinical indicators of MS disease activity. Such symptoms are most likely to result from a focal disruption of critical white matter tracts underlying these primary functions; as such, sensorimotor symptoms likely underestimate the true extent of MS disease activity throughout cerebral white matter. Indeed, a recent study showed that MS disease activity frequently occurs in the absence of sensorimotor symptoms,[3] suggesting that subclinical disease activity is common. The need for more sensitive markers of disease-related activity is therefore critical. Cognition relies on diffusely distributed white matter tracts throughout the brain, making changes in cognitive status uniquely suited to detect otherwise "quiescent" exacerbations.

The association of warmer outdoor temperatures and worse cognitive function in persons with MS holds important implications for treatment. Clinicians should carefully monitor patients with MS for heat-related cognitive exacerbations, which may occur even in the absence of sensorimotor symptomology. Additionally, awareness of heat-related cognitive decline may inform lifestyle decisions by patients with MS, especially when demands for optimal cognitive functioning are high (e.g., taking summer-session courses in college). Researchers investigating cognition in MS must consider/control for temperature, especially in clinical trials where seasonal temperature can differ greatly at baseline and follow-up. (Indeed, the 6-month follow-up within our longitudinal analysis approximates a typical clinical trial.) More generally, the effects of temperature should be considered as a possible confound for any clinical trial using cognition as an outcome of interest, including drug trials; follow-up at warmer temperature may obfuscate the beneficial effects of experimental treatments.

A limitation of the present study is that it does not elucidate the underlying mechanisms for the association of outdoor temperature and cognition. In addition, while the recently reported finding of increased T2 lesion activity during warmer temperatures[3] provided the impetus for the present investigation, we did not look at lesion activity in our samples and can therefore draw no conclusions as to whether increased lesion activity occurred. However, future studies examining the neuropathologic changes associated with worse cognition in warmer temperatures are warranted. In addition, putative mechanisms underlying the effect of temperature on cognition remain to be explored in future research. That is, separate lines of research have shown that increased temperature is associated with increased lesion activity[3] and slowed or blocked conduction within demyelinated axons (for review, see[12]), but it remains unclear whether these mechanisms or an as-yet unidentified mechanism is responsible for the heat-related decrements in cognitive status observed among patients with MS in the current study. It may also be useful to examine individuals with secondary progressive MS, as we may expect to see exaggerated effects of slowed/blocked conduction as a result of demyelination in this more advanced disease subtype.

AUTHOR CONTRIBUTIONS

Dr. Leavitt: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Sumowski: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis. Dr. Chiaravalloti: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, study supervision, obtaining funding. Dr. DeLuca: drafting/revising the manuscript, analysis or interpretation of data, statistical analysis, study supervision, obtaining funding.

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