OBJECTIVES: 1.) To characterize the disruption of sleep and circadian rhythmicity in patients with dementing illnesses and examine the physiological and structural basis for these disturbances. 2.) To elucidate the nature of the circadian timing system in humans by examining disease-specific structural deterioration in elements of the system and by matching the information derived from this examination to previously recorded behavioral measurements.

RESEARCH PLAN: We propose to test four hypotheses over the next five years. 1) Polysomnographic sleep in Alzheimer's disease (AD) will be more disturbed in patients with large phase-delays of their circadian core-body temperature rhythm characterized by reduced sleep efficiency and longer sleep latency. Sleep will be more fragmented in patients with frontotemporal degenerative dementia (FTD) compared to AD patients with an increased number of awakenings. 2) Female patients with probable AD will have similarly delayed phase of temperature and activity as male patients and normal controls; 3) Nocturnal agitation and restlessness, seen in AD, results from loss of serotonergic innervation of the suprachiasmatic nuclei (SCN) and will be detectable as lower RIA serotonin transporter protein (5-HTT) in SCN compared to FTD patients and controls. In addition, measurements of nocturnal agitation will be higher in AD patients with lower 5HTT; and 4) Patients with FTD will have lowered levels of orexin/hypocretin in target tissue of perifoncal area of the hypothalamus, locus coeruleus, midline thalamus and/or dorsal raphe nuclei compared to AD and controls. The extent of dissociation of activity and temperature will be related to the loss of orexin/hypocretin in patients carrying the same dementia diagnoses.

METHODOLOGY: To accomplish these objectives we will study 91 patients with progressive dementing illnesses collecting core-body temperature, polysomnographic and locomotor activity data every 6 months and followed by post-mortem neuropathological studies. We will also perform postmortem, diagnosis-based neuropathological studies without antemortem data collection.

CLINICAL RELEVANCE: Sleep disturbance is a disruptive symptom shared by the spectrum of progressive dementing illnesses, and its presence often precipitates decisions by families and others to seek institutional care for patients. Normal sleep-wake regulation is characterized by an oscillatory, circadian, alerting process and a sleep-inducing process that builds need to sleep as a function of the duration of prior wakefulness. In our previous studies in these populations we have found diagnosis-specific circadian abnormalities in men which implicate central, circadian dysfunction in the etiology of sleep-wake disturbances in AD, FTD, and Lewy body disease. In addition, we have found abnormalities in SCN cellular populations in men associated with specific circadian and behavioral changes in AD. We now wish to build upon these initial findings and expand some of our studies to the extra-SCN circadian system as well as the SCN itself.