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Measuring sociogenic, behavioral, and environmental impacts on circadian and rest-activity rhythms in healthy and pathological populations using actigraphy

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MEASURING SOCIOGENIC, BEHAVIORAL, AND ENVIRONMENTAL IMPACTS ON CIRCADIAN AND REST-ACTIVITY RHYTHMS IN HEALTHY AND PATHOLOGICAL POPULATIONS USING ACTIGRAPHY

by

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EPIGRAPH

"With only a slight touch of levity one may say that rhythms are one of the few constants in the biological regime."

– Wanliss et al., 2018

DEDICATION

I would like to dedicate this work to humanity: those who are, those who have been, and those to come. We're all in this together.

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This work is, first and foremost, a product of the human endeavor. While it may have been written by my hand, it was our combined efforts that brought its existence from a potentiality to a reality. There are too many to name – in truth, all of humanity has contributed to this work in one way or another – but there are a few whose contributions were so timely, significant, and essential to this work's existence that I feel obligated – and honored – to acknowledge them. These words may be flat and sterile, but know they come from a depth of emotion and gratitude impossible to fully convey through writing.

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MEASURING SOCIOGENIC, BEHAVIORAL, AND ENVIRONMENTAL IMPACTS ON CIRCADIAN AND REST-ACTIVITY RHYTHMS IN HEALTHY AND PATHOLOGICAL POPULATIONS USING ACTIGRAPHY

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ABSTRACT

Few biological systems are as ubiquitous as the circadian rhythm, a distributed yet interconnected "system of systems" that coordinates the timing of physiological processes via a self-regulating, flexible network present at every level of biological organization, from cells to cities. Its functional role as the interface between time-dependent internal processes and external environmental cues exposes the circadian rhythm to disruption if these drift out of synchrony. This is especially common in industrialized human societies, where the abundance of resources – in combination with the fact that anthropogenic calendars have largely supplanted the sun as the primary determinant of our daily cycles of rest, activity, and sleep – disrupts the circadian rhythm's ability to synchronize biological processes with each other and the geophysical solar day. Humans are now beholden to two increasingly disconnected clocks, and the ever-accelerating curve of human progress suggests our biological and social times will only grow more disconnected.

Longitudinal "out-of-clinic" monitoring is an ecologically valid alternative to well-controlled laboratory studies that can provide insight into how human circadian and behavioral rhythms exist in day-to-day life, and so has great potential to provide contextual data

for translating chronobiological science into clinical intervention. However, methodological diversity, inconsistent terminology, insufficient reporting, and the sheer number of potential factors has slowed progress. Herein is presented scientific work focused on detecting and quantifying some of these factors, particularly "sociogenic" determinants such as the seven-day week. Through rhythmometric analysis of longitudinal in-home actigraphy, weekly behavioral patterns were observed in both young adult males (n = 24, mean age = 23.46 years) and older adults with Parkinson's disease (n = 13 [7 male], mean age = 60.62 years, mean Hoehn & Yahr Stage = 2.31) that evince a seven-day "circaseptan" rhythm of circadian and sleep disruption. This is hypothesized to be dependent upon the seven-day calendar week, particularly the regular and abrupt shifts in timing between work and rest days. These perturbations vary by chronotype in young adults, and by disease severity in Parkinson's disease. Collectively, these results contribute to the growing evidence that our daily rhythms are shaped by sociogenic factors in addition to well-documented environmental and biological mechanisms. Moreover, the study of these subtle infradian patterns presents serious – yet surmountable – methodological challenges that must be overcome in order to accurately monitor, quantify, analyze, report, and apply findings from observational studies of naturalistic human behavior to scientific and clinical problems.

PREFACE

There is so much to see in this world, so much to learn and study, to interpret and communicate, to build and protect. No single lifetime is enough to do it all; the best one can do is experience as much as possible, and this is what led me to the study of rhythms. Oscillatory patterns are ubiquitous in nature, from the vibrations of an atomic nucleus to the life cycle of a star. Rhythms are a function of information and time; they are emergent patterns from natural systems that give insight into their organization; they are a common language for mapping the imperceptible connections between seemingly unrelated phenomena; and yet they are also mundane and familiar, underpinning nearly every aspect of our lives, and so common and fundamental that rarely do we consciously acknowledge their existence. We move through invisible cycles, guided by natural forces we are only just beginning to understand, and we must be thorough in our examination because we do not know what we do not know. As we continue to push the limits of our technology and expand the scope of our perspective, we must acknowledge how far we've come and how far we have left to go. Humanity's fate lies starside, and we as a species have only just begun to appreciate the magnitude and implications of this blunt reality. It is my earnest hope that our work on biological rhythms may contribute to our species' ability to safely explore, study, and colonize extraterrestrial space. Through a better understanding the material nature of our biological rhythms, their organization and origins, their role in health and disease, and the major factors that influence them, I hope to deepen our knowledge of ourselves and our environment so that we may apply it to our imperative goals of exploring, studying, and ultimately understanding our place in the universe.

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LIST OF ABBREVIATIONS

χ^2	chi-square
κ	Cohen's kappa statistic
%	percent
Φ	phi ("acrophase")
±	plus-minus
AASM	American Academy of Sleep Medicine
AB	Amyloid Beta
AC	Activity Counts
AC Max	peak Activity Counts over 15-seconds during sleep
ACm	average Activity Counts per minute during sleep
Acro	Acrophase
ADL	Activities of Daily Living
AKA	Also Known As
AM	*ante meridiem* (Latin: "before midday")
Amp	Amplitude
ANOVA	ANalysis Of VAriance
ARNTL	Aryl hydrocarbon Receptor Nuclear Translocator-Like
ASN	Alpha-SyNuclein
ASP	Average Sleep Propensity
ATP	Adenosine Tri-Phosphate
AVP	Arginine VasoPressin

BMAL1	Brain and Muscle Aryl hydrocarbon Receptor Nuclear Translocator-Like protein 1 (ARNTL) Like 1
BMI	Body Mass Index
BS	Bachelor of Science
BU	Boston University
BUSM	Boston University School of Medicine
CCG	Clock Controlled Genes
CI	Confidence Interval
CLOCK	Circadian Locomotor Output Cycles Kaput
CN	Cranial Nerve
CNS	Central Nervous System
Coef.	Coefficient
CoM	Center of Mass
COVID-19	COronaVIrus Disease 2019
CRY1	CRYptochrome 1
CRY2	CRYptochrome 2
CS	Coding Scheme
CSM	Composite Scale of Morningness
DA	DopAmine (DA)
DAT	DopAmine Transporter
DBS	Deep Brain Stimulation
df	degrees of freedom

DLMO	Dim Light Melatonin Onset
DNA	DeoxyriboNucleic Acid
DRN	Dorsal Raphe Nucleus
e.g.	*exempli gratia* (Latin: “for example”)
EDS	Excessive Daytime Sleepiness
EEG	ElectroEncephaloGraphy
ENMO	Euclidean Norm Minus One
EQ-5D	EuroQol 5-Dimension
EQ-5D-VAS	EuroQol 5-Dimension Visual Analogue Scale
ESS	Epworth Sleepiness Scale
EST	Eastern Standard Time
F	Fisher’s statistic
FI	Fragmentation Index
FPS	Frames Per Second
g	standard acceleration due to gravity
GABA	Gamma AminoButyric Acid
GDP	Gross Domestic Product
GHT	GeniculoHypothalamic Tract
GRP	Gastrin Releasing Peptide
HRQOL	Health-Related Quality Of Life
H&Y	Hoehn and Yahr stage
Hz	Hertz

i.e.	*id est* (Latin: “that is” or “in other words”)
ICSD-3	International Circadian and Sleep Disorder, Third Edition
ID	IDentification number
IGL	InterGeniculate Leaflet
IgY	Immunoglobulin Y
IMU	Inertial Measurement Unit
Inc.	Incorporated
ipRGC	intrinsically photosensitive Retinal Ganglion Cells
iPS	instrumented Postural Sway
IQR	InterQuartile Range
IRA	InterRater Agreement
IRB	Institutional Review Board
iTUG	instrumented Timed Up-and-Go
iTW	instrumented Timed Walk
kAR	activity fragmentation
kg	kilogram
kRA	rest fragmentation
LLC	Limited Liability Company
LLE	Left Lower Extremity
LUE	Left Upper Extremity
m	meter
MA	Massachusetts

MAD	Mean Amplitude Deviation
MCTQ	Munich ChronoType Questionnaire
MDS	Movement Disorders Society
MDS-UPDRS	Movement Disorders Society's Unified Parkinson's Disease Rating Scale
MEQ	Morningness-Eveningness Questionnaire
MESOR	Midline Estimating Statistic of Rhythm
mg	milligram
MI	Myocardial Infarction
MINOCA	Myocardial Infarction with Non-Obstructive Coronary Arteries
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRN	Median Raphe Nucleus
n	number of samples
N1	Non-Rapid Eye Movement (NREM) 1
N2	Non-Rapid Eye Movement (NREM) 2
N3	Non-Rapid Eye Movement (NREM) 3
N4	Non-Rapid Eye Movement (NREM) 4
NMS	Non-Motor Symptoms
NPY	NeuroPeptide Y
NREM	Non-Rapid Eye Movement
NREM1	Non-Rapid Eye Movement 1

NREM2	Non-Rapid Eye Movement 2
NREM3	Non-Rapid Eye Movement 3
NREM4	Non-Rapid Eye Movement 4
NTP	Network Time Protocol
OSA	Obstructive Sleep Apnea
p	p-value
p-tau	phosphorylated tau181
p-value	calculated probability value
PARS	Parkinson Associated Risk Study
PD	Parkinson's Disease
PDQ	Parkinson's Disease Questionnaire
PDQ8	Parkinson's Disease Questionnaire, 8-point
PDQ8SI	Parkinson's Disease Questionnaire, 8-point Summary Index
PDQ39	Parkinson's Disease Questionnaire, 39-point
PDQ39SI	Parkinson's Disease Questionnaire, 39-point Summary Index
PER1	PERiod 1
PER2	PERiod 2
PER3	PERiod 3
PFK	PhosphoFructoKinase
PGN	PreGeniculate Nucleus
PGT	Posture, Gait, and/or Transition
PIGD	Postural Instability and Gait Disturbances

PIM	Proportional Integration Mode
PM	*post meridiem* (Latin: “after midday”)
POA	PreOptic Area
PPN	PedunculoPontine Nucleus
PSG	PolySomnoGraphy
PSQI	Pittsburgh Sleep Quality Index
PST	Percent Sleep Time
pTau	phosphorylated-Tau_{181}
PTO	Post-Translational Oscillator
PVN	ParaVentricular Nucleus
QOL	Quality of Life
RAR	Rest-Activity Rhythm
RBD	Rapid Eye Movement (REM) Behavioral Disorder
REM	Rapid Eye Movement
RHT	RetinoHypothalamic Tract
RLE	Right Lower Extremity
RLS	Restless Leg Syndrome
Rm.	Room
rMEQ	reduced Morningness-Eveningness Questionnaire
RNA	RiboNucleic Acid
RUE	Right Upper Extremity
SCN	SupraChiasmatic Nucleus

SD	Standard Deviation
SE	Sleep Efficiency
SI	Summary Index
SitS	Sit-to-Stand
SJL	Social Jet Lag
SMID	Sleep Mid-Time
SNpc	Substantia Nigra pars compacta
SOFF	Sleep Offset time
SOFFL	Sleep Offset Latency
SON	Sleep Onset time
SONL	Sleep Onset Latency
SP	Sleep Period
sPVZ	subParaVentricular Zone
Stata/SE	Stata Special Edition
STN	SubThalamic Nucleus
SWS	Slow-Wave Sleep
t	t-value
t-value	hypothesis test statistic
TAT	Time Above Threshold
TiB	Time in Bed
TOM	Technology-based Objective Measure
TST	Total Sleep Time

TTFL	Translational-Transcriptional Feedback Loop
TUG	Timed Up-and-Go
TX	Texas
UCSD	University of California San Diego
UK	United Kingdom
UPDRS	Unified Parkinson's Disease Rating Scale
USA	United States of America
v	version
VAS	Visual Analogue Scale
VIP	Vasoactive Intestinal Peptide
VM	Vector Magnitude
VPAC2	Vasoactive Intestinal Peptide (VIP) Receptor 2
w/	with
w/o	without
WA	Washington
WAIS	Wechsler Adult Intelligence Scale
WASO	Wake After Sleep Onset
z	z-score
z-score	calculated standard (distribution) score
ZCM	Zero Crossing Mode

CHAPTER ONE: BACKGROUND

Introduction

Amongst the fundamental emergent properties of our universe is *rhythmicity*, or the tendency for some *thing* to regularly and repeatedly alternate between multiple states. Rhythmicity is agnostic to field and scale, and has been observed at every level of nature, from the infinitesimal fluctuations in an atom's potential energy, to the revolution of our planet and its orbit around the Sun, to the stellar life cycle that produced the "starstuff" currently reading this manuscript. Biological systems - at all scales, both spatially and temporally - exhibit rhythmicity, including cellular division, neuronal firing, temperature homeostasis, social behavior, prey-predator population dynamics, and the life cycle itself. Many of these are emergent from interactions between more fundamental factors such as chemical diffusion and electrical conductance; they therefor contain information about the system they arose from, information which can inform and optimize other biological systems that interact with the rhythmic process. For example, the metabolic enzyme phosphofructokinase (PFK) is inhibited by the Adenosine Tri-Phosphate (ATP) it produces, which creates a rhythmic negative feedback loop that inhibits ATP production when it is abundant within the cell and increases when ATP is scarce; this helps maintain cellular energy homeostasis and conveys information (through the concentration of ATP) about the cell's energy availability to other cellular systems (e.g. deoxyribonucleic acid [DNA] replication)[1] (Fall, 2002).

[1] ATP is not produced by PFK, but is produced downstream of the glycolytic pathway PFK is a part of

Fascinatingly, the process of natural selection has led to the evolution of centralized systems that sustain, amplify, adapt, and coordinate these emergent biological rhythms to exploit their latent information and synergistically maximize their efficiency in response to cues from endogenous (i.e. biological) and exogenous (i.e. environmental) cycles. Collectively, these biological rhythms serve to synchronize an organism's physiology to itself and its habitat to maintain homeostasis, regulate its behavior (e.g. eating and sleeping), and optimize its ability to exploit its environment. Disruption of these rhythmic regulators therefore reduces overall fitness through the accumulation of myriad minor inefficiencies, analogous to how accelerating a spacecraft before it reaches periapsis will use more fuel than if it accelerated at periapsis itself. Biologically, this means the disrupted organism will have to expend more energy to maintain certain rhythmic processes (e.g. thermoregulation) to overcome sub-optimal internal and external environments. For example, human body temperature and therefore muscular contraction velocity (Bell & Ferguson, 2009) are at their lowest point in the early morning when physical movement is least needed due to sleep; physical movement during this time will less efficiently convert stored energy into biomechanical force, reducing fitness. In humans, pathological and environmental factors (e.g. Parkinson's disease [PD] and jet lag, respectively) interfere with biological rhythms, leading to negative outcomes such as fatigue, sleep disruption, and misalignment of biological rhythms.

This chapter will discuss how biological rhythms emerge from and are maintained by biochemical and anatomical systems, their functional systemic role in and with healthy

and pathological biological systems, how these biological rhythms are quantified and modelled, and the causes and consequences of their disruption - particularly in the uniquely human context of technologically advanced societies that no longer depend on biological or astronomical rhythms to organize themselves.

The Circadian Rhythm

Amongst the biological rhythms, the most well known and most intensely studied is the *circadian rhythm*. While any rhythm with a period of 24 hours may be accurately called a circadian (*circa*- "about", -*dian* "day") rhythm, the term "circadian rhythm" usually refers to the systemic, self-sustaining, and entrainable oscillation of biological processes - and their myriad controllers and drivers - observed in virtually all eukaryotic life on Earth (M. Bailey & Silver, 2014)[2]. For example, the daily oscillation in human core body temperature, our daily cycle of restful sleep and active wakefulness, the excretion of hormones such as cortisol at regular daily intervals, and the neuropsychological phenomenon of "sleep pressure" are all facets of our circadian rhythm. In other words, the circadian rhythm is a "system of systems", a distributed yet coordinated network of independent biological rhythms that collectively harmonize vital functions at all levels of organization, from cellular to behavioral.

[2] Unless otherwise noted, "circadian rhythm" refers to the biological circadian rhythm throughout this manuscript

Functionally, this prepares an organism for certain expected events and/or behavioral states, such as eating, physical activity, or sleeping. For example, the contraction velocity of a muscle is partially dependent on its temperature (Bell & Ferguson, 2009); in humans, body temperature oscillates by approximately half a degree Fahrenheit across a 24-hour day (Harding et al., 2019), reaching its nadir in the early morning, when humans are usually asleep and sedentary, and peaking in the early evening when we are most likely to be active and most in need of optimal muscle contraction time. Similarly, melatonin - a hormone involved in sleep regulation, especially sleep induction - increases in concentration several hours before an individual's normal bed-time (Vetter, 2018). In these and other ways, the circadian rhythm enables an organism to anticipate and prepare for expected future conditions and is thus an essential systemic regulator that conveys a potent evolutionary advantage.

Natural History

An organism's ability to exploit their environment has been the central driver of the evolution of life on Earth. In order to reproduce, life requires energy and raw material; extracting more energy and resources from their surroundings therefore improves the odds that a given organism will survive, reproduce, and pass on its genetic information. As life grew increasingly complex and diverse, random mutations enabled new ways of exploiting the environment. For example, the evolution of photosynthesis - the transformation of solar radiation into storable chemical energy - allowed access to a vast source of untapped energy. Those organisms which could most efficiently exploit solar radiation therefore gained

an immense evolutionary advantage, and photosynthesis now represents the single largest source of biological energy in Earth's biosphere. Of course, the sun is not a permanent fixture in the sky. Due to Earth's rotation, photosynthetic organisms were only exposed to sunlight during certain times of day. Moreover, the relative stability of Earths rotation [3] meant that daylight availability was periodic - i.e. occurred at consistent, regular intervals - and thus represented a natural and consistent clock.

The consistency of the geophysical light-dark cycle made sunlight a potent *zeit-geber* (German: "time giver") - a temporal reference point for biological rhythms (Daan & Gwinner, 1998). Biological systems sensitive to this cue (through photosynthesis, temperature change, radiation sensitivity, vision, etc.) now had access to temporal information about the current state of their environment and were subsequently subjected to tremendous evolutionary pressure. This is because organisms that can accurately monitor the current time have an innate advantage over their temporally agnostic peers, as it allows them to *anticipate* future conditions (e.g. cyanobacteria and sunlight) and apply this information to *proactively optimize* themselves for those conditions. In doing so they increase their ability to exploit their environment compared to those organisms which can only react to changes in the environment. The evolution of more efficient photosynthetic proteins and larger photosynthetic substrates would help to capture more energy, but "learning" only needed to

[3] The Earth constantly experiences minute variations in rotational period due to terrestrial and astronomical cycles. Overall, the rotational period is thought to be gradually slowing across geological timescales due to tidal forces; e.g. a recent study estimated that the Earths rotational period was ~5.5 hours shorter 1.4 billion years ago (Meyers & Malinverno, 2018). It is assumed that these gradual changes are imperceptible to biological systems day-to-day (and thus don't interfere with circadian entrainment), and that their influence only manifests across evolutionary timescales.

expend energy on photosynthesis or mitigating heat shock during part of the day allowed organisms to *conserve* energy, energy which could then be spent on resource gathering, reproduction, etc. This evolutionary pressure is likely the source of the circadian rhythm (Bhadra et al., 2017).

To continue using the example of photosynthesizers (e.g. cyanobacteria), this temporal information would manifest as a periodic fluctuation in energy production directly tied to Earth's rotation - a circadian rhythm. Downstream biochemical processes dependent on energy production would likewise exhibit this circadian rhythm. For example, nitrogen fixation is essential to cyanobacteria, but the oxygen byproduct of photosynthesis directly inhibits nitrogen fixation. Since cyanobacteria are unicellular prokaryoates, they cannot spatially sequester these reactions as eukaryotes do via membrane-bound organelles such as mitochondria (or as heterocystous filamentary cyanobacteria do via specialized nitrogen-fixing cells). Instead, ancient cyanobacteria developed the means to sequester these incompatible biochemical reactions temporally: photosynthesis occurs during the day when sunlight is available, and nitrogen fixation occurs at night once photosynthetic byproducts are cleared (Bhadra et al., 2017).

A System of Systems

The biological substrates of circadian rhythms found in cyanobacteria and those found in complex life (e.g. mammals) are vastly different in their scale and complexity, yet exhibit the same three, basic properties: an "innate" biological oscillation that maintains a 24-hour

period across a range of temperatures, sensitivity to and ability to be entrained by endogenous temporal cues (i.e. zeitgebers, especially sunlight), and the ability to independently maintain circadian rhythmicity in the absence of said zeitgebers (Brown et al., 2019).

The circadian rhythm in cyanobacteria is maintained by a Post-Translational Oscillator (PTO) (S. E. Cohen & Golden, 2015), a stereotyped sequence of protein phosphorylation and dephosphorylation events that gate access to physiological signaling pathways by selectively binding signaling molecules dependent on the current phosphorylation state. The phosphorylation-dephosphorylation cycle takes ~24 hours to complete across a wide range of temperatures, and can be "reset" (i.e. entrained) by the presence of byproducts of photosynthetic redox reactions. DNA replication, chromosome configuration, and many other critical cellular processes are downstream from – and so regulated by – the PTO. In summary, the prokaryotic PTO exhibits all three circadian properties: it continuously and autonomously undergoes an about daily phosphorylation cycle resistant to temperature-dependent changes in reaction velocity, which can be modified by temporal cues from the environment, and which persists in their absence.

Note that the PTO is not just a central clock that can synchronize to its environment; while the PTO itself can be defined by a relatively small number of proteins and their phosphorylation events, it is more accurately described in the context of the cellular milieu. To wit, the PTO lies at the physiological nexus of a distributed network of cellular systems and pathways, where the flow of temporal information, its biochemical computation, and its translation into physiological application is a continuous dynamic process orchestrated by the PTO. By facilitating the efficient transfer of information between a cell's myriad

systems, the PTO enables the organism to flexibly integrate environmental and physiological information to temporally coordinate and optimize biological processes downstream of the PTO. Much like how the development of standardized clocks allowed the nascent transcontinental railroad network to efficiently coordinate its widely distributed arrivals and departures, or how a conductor synchronizes the individual musicians in an orchestra to create cohesive music, the PTO enables the cell's distributed systems to communicate temporal information and coordinate systemic physiological processes like photosynthesis and nitrogen fixation to create a "system of systems" greater than the sum of its part (Bhadra et al., 2017; S. E. Cohen & Golden, 2015).

Unlike cyanobacteria, eukaryotic circadian oscillators involve transcriptional and translational processes - respectively, the production of Ribonucleic Acid (RNA) from DNA and the production of proteins from RNA. Although there are many notable differences between the cyanobacterial PTO and the eukaryotic Translational-Transcriptional Feedback Loop (TTFL), the basic premise of both systems is strikingly similar - a stereotyped series of proteomic events whose current state gates access to downstream cellular signaling pathways that control critical biological processes (Buhr & Takahashi, 2013; Dibner et al., 2010; M. H. Hastings et al., 2014). Like the PTO, the TTFL is a proteomic pacemaker that coordinates a distributed system of systems facilitating the maintenance and dissemination of temporal information to physiological systems. In mammals, cellular TTFLs are found in every nucleated cell[4] and represent the finest, smallest "tier" of the

[4] Erythrocytes exhibit molecular, rather than genetic, feedback loops that resemble cyanobacterial PTOs (Bhadra et al., 2017; O'Neill & Reddy, 2011)

circadian rhythm's distributed network. While TTFLs coordinate biological processes at the cellular level, the cells themselves are synchronized at the tissue level and share tissue-specific modifications to their TTFL and its downstream pathways tailored to the specific physiological systems they support (Michael H. Hastings et al., 2003). This is accomplished through the TTFL-dependent expression of Clock Controlled Genes (CCGs) and their downstream pathways; expression of CCGs varies by tissue and is selectively up- or down-regulated during specific points in the TTFL (i.e. time of day).

Collectively, these "peripheral oscillators" - and their constituent cellular TTFL's - are synchronized to each other and the environment through endocrine, neurological, and/or metabolic cues that ultimately stem from the Suprachiasmatic Nucleus (SCN), the "central oscillator" or "central pacemaker" of the mammalian circadian rhythm that receives mono-synaptic photic input via the Retinohypothalamic Tract (RHT). Although peripheral oscillators are incapable of detecting photic cues from their environment[5], and thus are reliant on the SCN for this information, many are capable of reacting and synchronizing to physiological cues, such as food intake or body temperature (Michael H. Hastings et al., 2003; Heyde & Oster, 2019). In addition, peripheral oscillators reinforce their mutual synchrony via interactions between their physiological processes; e.g. the diurnal cycle in blood pressure emerges from the interaction between vasodilation/vasoconstriction and heart rate, which are independently regulated (in part) by TTFL-controlled CCG's in vascular and cardiac tissue TTFL's, respectively (Michael H. Hastings et al., 2003). These

[5] Peripheral oscillators in "lower" species such as *Drosophila melanogaster* are light-sensitive, but this property is absent in mammals (Michael H. Hastings et al., 2003)

emergent systemic rhythms provide yet another tier in the circadian hierarchy that can be fine-tuned by top-down regulators like the SCN, or bottom-up via local physiological signals. This is analogous to how an individual (i.e. cells) may set their clock to the time shown on their local news station (i.e. tissues and organs), who in turn set that time based on the United States' National Institute of Standards and Technology's atomic clock (i.e. SCN), which measures time by observing the natural resonance of cesium atoms (i.e. sunlight).

This model of circadian organization can be likened to an orchestra: each individual musician plays off the same sheet music, yet they struggle to play in harmony when they only have themselves (and perhaps their neighbors) to synchronize with. The individual can keep their own rhythm and play their assigned notes, but without a central timekeeper the orchestra as a whole will rapidly drift out of sync as the growing discordance interferes with the ability to hear and align with the other musicians. Eventually the intended music will be indiscernible from random noise. This is why the conductor is so essential to the orchestra: they provide a rhythmic reference point each musician can see and synchronize to, and from their harmony emerges music[6]. Where each musician is an individual component in the larger system of the orchestra, each peripheral oscillator is likewise an individual constituent of an organism's circadian rhythm; and while a single musician can maintain a rhythm and make music (i.e. PTO in cyanobacteria), an orchestra composed of many

[6] It's not a coincidence that both the circadian rhythm and music benefit from synchrony. Destructive and constructive interference are natural properties of all rhythmic processes: misalignment deteriorates ("cancels out") their signal and synchrony reinforces it.

different individuals (i.e. cellular TTFL's) with unique functions and instruments (i.e. tissue-specific CCG's) require a central conductor (i.e. SCN) to achieve harmony and create music (i.e. maintain optimal homeostasis).

In summary, the circadian rhythm is a distributed system of systems, a network of interconnected rhythms (ranging in scale from cellular to systemic, and from central to peripheral) that individually regulate biological processes within their respective domains, reinforce each other through harmonious physiological processes, and which are collectively coordinated at the organismal level by a central pacemaker synchronized with the environmental day-night cycle (top-down regulation) while retaining some degree of self-sustaining autonomy and sensitivity to local physiological signals (bottom-up regulation). The circadian rhythm is an emergent property of the self-optimization of our biological processes, the product of an integrated, dynamic, adaptable, centrally coordinated, and peripherally distributed system of systems.

Circadian Anatomy in Mammals

The SCN is the central oscillator – often colloquially referred to as the "central pacemaker" or "master clock" - of the mammalian circadian rhythm. The SCN receives direct photic inputs from photosensitive retinal ganglion cells via the RHT and physiological information from the Median Raphe Nucleus (MRN) and Intergeniculate Leaflet (IGL) of the thalamus, integrates these signals to maintain an autonomous and intrinsic physiological oscillation at a constant phase relative to the day-night cycle, and distributes this information to the myriad peripheral circadian rhythms throughout the body via extensive direct

and indirect projections (Dibner et al., 2010; Lawrence P Morin, 1999; Lawrence P. Morin, 2013; D. K. Welsh et al., 2010).

As its name implies, the SCN is located immediately superior to the optic chiasm - the merging and decussation (crossing the midline) of optic fibers as they course caudally from the retina - and consists of two symmetrical nuclei that flank the third ventricle in the inferior hypothalamus. The SCN is relatively small, with each nucleus containing ~8,000 - 10,000 neurons in mice, ~20,000 in rats, and ~50,000 in humans (M. Bailey & Silver, 2014). It is conspicuously cell-dense compared to the adjacent diffuse grey matter of the anterior hypothalamus, and is readily visualized with a Nissl stain; due to its paucity of internal and crossing axonal fibers, it is also easily visualized with Golgi impregnation or a myelin stain (Van den Pol, 1980). Its gross shape is roughly oblong or "tear shaped", with a swollen ventral portion and a tapering dorsal tail (Lawrence P. Morin, 2013). As with many aspects of the SCN, this varies by species; for example, rats have a more oblate SCN.

The SCN has been organized according to neurochemical, functional, and anatomical criteria. Two main sub-divisions are generally recognized: a compact ventrolateral *core* that is encapsulated within a somewhat diffuse dorsomedial *shell* (M. Bailey & Silver, 2014; M. H. Hastings et al., 2014; Lawrence P. Morin, 2013). Additional and/or different sub-divisions have been identified in species with uniquely specialized circadian systems, such as desert-dwelling mammals. For example, the camel SCN is unusually large and differentiated[7], and has been divided into three partitions along the rostral-caudal axis based on immunohistochemical analysis (El Allali et al., 2017). In addition to differences

[7] Potentially due to finer control of water retention and thermoregulation needed in hot, arid desert

in cell density, these regions are distinguishable by their distinct neurochemical makeups: the core contains neurons that express Vasoactive Intestinal Peptide (VIP) and/or Gastrin Releasing Peptide (GRP), where-as shell neurons express Arginine Vasopressin (AVP) (Dibner et al., 2010). The SCN is rich in inhibitory Gamma Aminobutyric Acid (GABA), and the core and shell are commonly visualized through the colocalization of GABA and VIP/GRP or GABA and AVP, respectively; calbindin is also a popular alternative, as it is found only in part of the core (Lawrence P. Morin, 2013). This neurochemically defined model has been supported by observed differences in the physiology – shell neurons possess robust diurnal rhythms in their spontaneous firing rate and PER gene expression, where-as core neurons have weak rhythms easily reset by light (Jobst & Allen, 2002) – and through study of afferent/efferent projections of the core and shell, most notably the observation that RHT neurons synapse almost exclusively on core neurons (El Allali et al., 2017; Lawrence P. Morin, 2013). Functionally, the retinorecipient cells (i.e. those which receive direct projections from retinal ganglion cells) in the core are capable of resetting the phase of neuronal oscillations in the shell through VIP-mediated paracrine signaling, which conveys temporal information to other regions through direct and indirect projections (Kriegsfeld et al., 2004); in other words, the shell is the "clock" that encodes time, and the Core is the "synchronizer" that keeps it in phase with the environment.

The SCN receives diverse inputs from numerous brain regions: ~35 brain regions directly (monosynaptically) innervate the SCN, and this number increases to 85 if indirect (multisynaptic) projections are included (Lawrence P. Morin, 2013). Although the SCN is

widely innervated, the bulk of its afferents are found in three major pathways: photic stimulus from the retina via the RHT, thalamic input from the IGL, and serotonergic innervation from the MRN. These inputs convey circadian information from both the environment (photic RHT) and the body (non-photic IGL and MRN) capable of influencing SCN's latent circadian oscillation, effectively creating a central "master clock" sensitive to both endogenous and exogenous zeitgebers (Dibner et al., 2010). Mapping the terminal fields of these pathways has been a major objective of neuroanatomical research on the SCN (Lawrence P. Morin, 2013).

Photic input from the retina via the RHT forms the largest and most influential afferent to the SCN, as evinced by its large terminal field in the SCN core and the sensitivity of the SCN's latent oscillation to environmental light (Lawrence P. Morin, 2013). RHT afferents consist of melanopsin-positive intrinsically photosensitive Retinal Ganglion Cells (ipRGC) that directly synapse on VIP+ retinorecipient cells in the SCN core (Dibner et al., 2010). Although the RHT is the dominant photic input in virtually all mammals, the extent and concentration of retinorecipient cells varies between species (Karatsoreos, 2004). For example, interspecies differences in RHT terminal fields have been identified in the ventrolateral SCN in both hamsters (Johnson et al., 1988) and mice (Abrahamson & Moore, 2001), with the latter being significantly more dense and containing additional sparse dorsomedial RHT inputs, where-as retinorecipient cells are found only in the ventral SCN in the rat (R. Y. Moore, 1996). ipRGC's project to at least 30 other brain regions in addition to the SCN (Lawrence P. Morin, 2013), including adjacent hypothalamic structures that are reciprocally connected with the SCN, notably the IGL and subparaventricular Zone (sPVZ)

(Dibner et al., 2010; Kriegsfeld et al., 2004; Major et al., 2003). Interestingly, individual ipRGC axons have been observed to bifurcate and project to both SCNs, or to one SCN and either the IGL, Olivary Pretectal nucleus (OPT), the superior colliculus, or the contralateral SCN (L.P. Morin et al., 2006).

Fibers characterized by the presence of Neuropeptide Y (NPY) and GABA project from the IGL to the SCN via the Geniculohypothalamic Tract (GHT) (Dibner et al., 2010). These NPY+ cells synapse on retinorecipient neurons in the SCN core, and are particularly dense in rodents (Abrahamson & Moore, 2001) and dromedaries (El Allali et al., 2017). The IGL is bilaterally connected with over a hundred brain regions in addition to the retina and SCN (Lawrence P. Morin, 2013), and is believed to be an important source of integrated multimodal circadian information for the SCN in non-primate mammals (L.P. Morin & Allen, 2006). The Pregeniculate Nucleus (PGN) is believed to be the functional analog of the IGL in primates as it contains NPY+ positive cells that receive overlapping photic and serotonergic projections from the retina and Dorsal Raphe Nucleus (DRN), respectively. Moreover, their concentration and volume vary between nocturnal and diurnal primates, which would be expected of a multimodal circadian integration system (Pinato et al., 2009). However, there is no primate homologue of the GHT, and NPY+ fibers are scarce and diffuse in the human, indicating an altered functional role of the PGN in circadian processing in primates (Lima et al., 2012).

The SCN receives strong serotonergic input from the MRN and, to a lesser extent, the DRN via the serotonergic pathway (Dibner et al., 2010; Lawrence P Morin, 1999). In

rodents, serotonergic fibers synapse on ventromedial neurons in the SCN, partially overlapping with the core's VIP+ RHT terminal fields (Lawrence P. Morin, 2013). Much like the IGL, serotonergic projections from the MRN and DRN are believed to convey integrated photic and non-photic information. For example, desert-dwelling mammals such as the camel (El Allali et al., 2017) and jerboa (Lakhdar-Ghazal et al., 1995), possess a remarkably large and dense serotonergic projection to the dorsomedial SCN. This implies that the MRN feeds the SCN extensive integrated information – primarily non-photic – to fine-tune the circadian rhythm and maintain tight synchrony between their peripheral oscillators and their harsh and dynamic environment.

The SCN's extrinsic efferents consist predominantly of short-distance monosynaptic hypothalamic projections, especially to Paraventricular Nucleus (PVN), Preoptic Area (POA), IGL, and sPVZ (Kriegsfeld et al., 2004), which in turn project to numerous autonomic and endocrine neural controllers (Lawrence P. Morin, 2013). This hierarchal network processes and distributes the temporal information encoded in the SCN throughout the nervous and endocrine systems, enabling the SCN to synchronize hundreds of physiological processes with distinct phases (e.g. melatonin secretion and body temperature) through a relatively small number of projections (Dibner et al., 2010). Anatomical studies have provided the evidence showing that these hypothalamic projections are essential for circadian function, as their destruction – either through direct transection or the ablation of intermediate nuclei (e.g. the PVN) – suppresses diurnal rhythms such as melatonin concentration and abolishes the regular period of sleep-wake cycle (Abrahamson & Moore, 2006; Vrang et al., 1995). Beyond the hypothalamus, the SCN projects inhibitory GABA-

ergic fibers to the melatonin-producing pineal gland; it is through this pathway that environmental light inhibits the production of melatonin, a critical component of normal circadian behavior (Dibner et al., 2010; Kriegsfeld et al., 2004). In total, the SCN monosynaptically projects to ~15 distinct brain regions (Lawrence P. Morin, 2013).

Lastly, the SCN contains extensive intrinsic efferents, both to the contralateral nucleus and ipsilaterally between the core and shell of a single nucleus (Lawrence P. Morin, 2013). The majority of intrinsic efferents project from the core to the ipsilateral and, to a lesser extent, the contralateral shell, with sparse shell-to-core reciprocal connections. Although the function of the contralateral projections are poorly understood, core efferents to the ipsilateral shell are believed to supplement the photic information conveyed through VIP-mediated paracrine signaling (Hamnett et al., 2019; Kriegsfeld et al., 2004).

Circadian Physiology in Mammals

The SCN regulates our circadian rhythm through three distinct components: (1) intrinsic oscillators in the SCN shell that autonomously maintain a 24-hour rhythm, (2) photic stimuli via the RHT capable of synchronizing the phase of shell oscillations to the environment via the core, and (3) numerous direct and indirect projections that convey temporal information to central neurological controllers (M. Bailey & Silver, 2014; Dibner et al., 2010).

Synchrony between SCN neurons and sub-divisions is maintained through VIP-mediated paracrine signaling (Buhr & Takahashi, 2013; Hamnett et al., 2019). This process, referred to as ‘photic entrainment’, maintains the synchronicity of the SCN’s latent

TTFLs to environmental light and consequently ensures the SCN as a whole is synchronized to a common phase (Hamnett et al., 2019; D. K. Welsh et al., 2010). VIP is released by SCN retinorecipient cells (primarily in SCN's core) in response to photic stimuli via the RHT. The released VIP then binds to adjacent, non-retinorecipient cells in the SCN's shell containing VIP Receptor 2 (VPAC2). This triggers a molecular cascade that induces membrane depolarization and increased intracellular calcium retention, priming the cell for activity; note that the highest spontaneous SCN activity is generally observed during the day, when photic input is strongest (M. H. Hastings et al., 2014). This paracrine cascade also directly upregulates the expression of *period* (PER) and *cryptochrome* (CRY), two genes at the center of the TTFL, effectively resetting the neurons "clock" and synchronizing the VPAC2 neuron's TTFL to environmental light (D. K. Welsh et al., 2010). Note that shell neurons are not perfectly in sync; paracrine signaling and is restricted by diffusion and distance, so VPAC2 neurons exhibit staggered TTFLs that are spatiotemporally encoded based on their distance from the retinorecipient core, a wave of phasic synchronization that spreads across the SCN (Hamnett et al., 2019).

The TTFL is ubiquitous in mammalian nucleated cells, and is the fundamental driver of both the central pacemaker (i.e. the SCN) and the peripheral oscillators (Dibner et al., 2010; M. H. Hastings et al., 2014). Although there are tissue- and species-specific exceptions, the generic mammalian TTFL consists of two protein heterodimers: the CLOCK/BMAL1 heterodimer consisting of Circadian Locomotor Output Cycles Kaput (CLOCK) and Brain and Muscle Aryl hydrocarbon Receptor Nuclear Translocator-Like protein 1 (ARNTL) Like 1 (BMAL1), and the PER/CRY heterodimer formed from Period

1/2/3 (PER1/PER2/PER3) and Cryptochrome 1/2 (CRY1/CRY2) proteins (Buhr & Takahashi, 2013; Dibner et al., 2010; M. H. Hastings et al., 2014). Both heterodimers are transcriptional regulators that together form a continuous feedback loop: CLOCK/BMAL1 increases expression of PER, CRY, and numerous CCGs, and PER/CRY inhibit CLOCK/BMAL1 transcriptional activity. Numerous cellular and metabolic functions are closely tied to the TTFL via CCGs that are up-regulated by CLOCK/BMAL1. As their expression is dependent on the central TTFL oscillator, CCGs enable the propagation of temporal information to downstream processes and, ultimately, the synchronization of physiological functions (e.g. cell division, protein expression) to optimize efficiency (Korenčič et al., 2015).

The same basic molecular machinery used by SCN is also found throughout the various peripheral oscillators, although the exact protein composition of the cellular TTFLs and the specific CCGs they activate varies widely between tissues according to their functional role and physiology; on average, ~10% of the transcriptome in a given tissue is under circadian regulation via TTFL/CCG (Michael H. Hastings et al., 2003). While peripheral TTFLs are usually out of phase with the SCN by ~4-8 hours, their timings relative to each other are maintained and stabilized by temporal information via intermediate neurological (e.g. PVN), endocrine (e.g. pineal gland and melatonin), and homeostatic (e.g. hypothalamic control of body temperature) relays that receive mono- and multi-synaptic SCN efferents. Once thought to be functionally dependent on the SCN, peripheral oscillators have since been shown to be self-sustaining (Yoo et al., 2004), resilient to large differences in temperature (Dibner et al., 2009), and persistent through cell division (Nagoshi

et al., 2004). Note that while peripheral TTFLs can sustain themselves in SCN-lesioned animals for several weeks, their individual phases will gradually desynchronize from each other (Guo et al., 2006). This suggests that the SCN is required to maintain phase coherence within a tissue (Dibner et al., 2010), analogous to a conductor maintaining harmony in an orchestra.

In addition to direct (e.g. hormone secretion) and intermediate (e.g. RAR and body temperature) pathways, the SCN entrains the billions of autonomous cellular TTFLs indirect pathways as well. Consider food intake, which prompts numerous physiological and homeostatic changes through the production of metabolites (e.g. glucose), secretion of hormones (e.g. leptin), and alteration of cellular metabolism (e.g. redox ratio) to prepare the body for digestion (Dibner et al., 2010). The SCN indirectly entrains food-seeking behavior by restricting the times when animals are mobile and able to feed, which is determined by their circadian rest-activity rhythms (RAR) - the daily cycle of waking activity and somnolescent torpor, itself reinforced by the circadian fluctuation in body temperature and cellular metabolism. However, this can lead to peripheral TTFLs receiving conflicting temporal information. As shown by artificial disruptions of the phase of RAR, temperature, sleep, and other "indirect pathways", these are capable of decoupling peripheral oscillators from the SCN; e.g. limiting feeding opportunities to the day in nocturnal animals - effectively inverting their RAR by forcing them to seek food when they would normally be asleep - desynchronizes peripheral oscillators in cardiac, pancreatic, hepatic, and renal tissues from the SCN (Damiola, 2000; Stokkan, 2001). Although the liver primarily synchronizes to the central pacemaker - and thus can optimally coordinate its processes with other

biological rhythms like body temperature - this coupling can be overwritten by acute physiological changes that occur outside their anticipated time; writ large, this property allows an organism to flexibly adapt to dynamic environments at the cost of short-term decohesion of its circadian rhythm and the subsequent stresses and inefficiencies.

In light of these examples, the circadian rhythm may once again be appreciated as a distributed yet coordinated network of semi-autonomous systems who regulate and stabilize each other via top-down and bottom-up integration of exogenous and endogenous zeitgebers in order to optimally adapt to their environmental and physiological conditions.

Circadian Biomarkers and Assessment

As a distributed system of systems, the circadian rhythm is detectable in some form or another in almost all biological measures. This includes the aforementioned diurnal fluctuations in body temperature, cortisol, and melatonin, as well as hormonal regulators of appetite such as ghrelin and leptin (Challet, 2015; P. C. Smith & Mong, 2019), metabolic processes such as glucose uptake and insulin concentration (Panda, 2016), neurotransmitters like dopamine (Poceta et al., 2009) and serotonin (Matheson et al., 2015), biological responses such as inflammation and the immune response (Bellet et al., 2013), homeostatic regulators such as heart rate (Morris et al., 2012) and cutaneous blood flow (Vaughn et al., 2018), biochemical reactions such as mitochondrial respiration and gene expression (de Goede et al., 2018), and even anatomically as demonstrated by diurnal fluctuations in the amount of fluid in the thorax (Kirchner et al., 2015). Although any biomarker with a diurnal

fluctuation may be used as a measure of the circadian rhythm, melatonin and body temperature have been the most popular due to their relative ease of measurement, robust amplitude of oscillation, and their "centrality" to the circadian rhythm *vis-à-vis* the large role the SCN plays in their regulation (Benloucif et al., 2005). In addition to specific biomarkers and biological processes, an individual's circadian rhythm may be assessed through their behavior; specifically, both the sleep-wake cycle and RARs exhibit a strong circadian pattern (Ancoli-Israel et al., 2003; Pollak et al., 2001). In other words, humans regularly and periodically shift between gross behavioral states in synchrony with the solar day, a circadian rhythm which can be measured through self-report (e.g. sleep diaries) and/or objective monitoring (e.g. wearable accelerometers).

The circadian rhythm has been assessed in numerous models using a multitude of measures since antiquity (McClung, 2019). The first written record of a circadian process was made by Androsthenes, a 4th century Greek explorer who accompanied Alexander the Great, when he noted that certain tree leaves moved in a predictable pattern throughout the day (Androsthenes, n.d.; Bretzl, 1903, p. 412). Over 2,000 years after Androsthenes penned "The Navigation of the Indian sea", French biologist Jean-Jacques d'Ortous de Mairan produced the first experimental evidence of an intrinsic circadian rhythm when he observed that the diurnal movement of plants continued even in complete darkness (de Mairan, 1729). A century later, Swiss botanist Augustin Pyramus de Candolle showed that shifting the light-dark cycle subsequently shifted the daily rhythm of movement, the first evidence of exogenous entrainment (de Candolle, 1832).

Throughout the mid-1900's, German physician Jurgen Aschoff contributed to several fundamental findings about human chronobiology, including the first description of circadian fluctuations in body temperature; he is also credited with coining zeitgeber to describe environmental cues capable of entraining the circadian rhythm (Daan & Gwinner, 1998; Foster & Roenneberg, 2008). Together with Rütger Wever, Aschoff pioneered novel methods such as an isolation "bunker" for human subjects where zeitgebers could be rigorously controlled, an experimental paradigm that has since become fundamental to the field of chronobiology.

Much of our understanding of circadian biology has been derived from in-laboratory experiments built upon the foundation of Wever's and Aschoff's methodology. This approach allows for careful experimental design and precise measurement with which subtle effects may be detected and distinguished (Vetter, 2018). However, controlled laboratory settings cannot replicate the circadian rhythm's *in situ* function for several reasons. Consider sleep studies, normally conducted in-clinic with polysomnography (PSG); clearly the unfamiliar technicians, myriad instruments attached to the subject, and the dramatically different clinical setting each have poorly understood effects on sleep biology (Roenneberg et al., 2015). Moreover, while controlled sleep studies have advanced our knowledge of sleep's structure and neurological substrates, they have given relatively little insight into the functional interactions between an individual's sleep and circadian rhythm, and their behavior and normal environment. Said another way, in-laboratory studies lack *ecological validity*: they offer unparalleled resolution and specificity, yet this narrow scope inherently

limits their generalizability and therefore our ability to translate their findings into clinical and functional applications (Andrade, 2018; Roenneberg et al., 2015; Vetter, 2018).

In contrast, field and observational studies – which monitor an individual's "natural" behavior outside of the laboratory – offer ecologically valid data at the cost of reduced precision and control (Andrade, 2018; Bei et al., 2016; Vetter, 2018). By measuring the cumulative effect of the interactions between an individual's biology, environment, and behavior through a systemic circadian marker (e.g. sleep timing), one can measure that individual's authentic[8] circadian rhythm as it exists in their day-to-day life. More practically, the reduced cost of out-of-laboratory methods allows for larger cohorts to be assessed over longer periods of time, but this also increases the variance of the sample. This is both a benefit and a drawback: while the data may be ecologically valid and clinically relevant, one cannot easily distinguish between the numerous effects that may have influenced the measured rhythm from each other, or from normal inter- and intra-individual variance. For example, Jane may have disrupted sleep, but is it attributable to a sleep disorder, a restless bed partner, binge drinking, a stressful work-week, or just an artifact of normal intra-individual variance in the measurement?

[8] Observation bias and the white-coat effect undeniably exist even in observational and field studies, though the use of subject diaries, wearable sensors, and lengthy out-of-clinic recording periods with minimal contact with research staff reduces the magnitude of these confounding effects.

Chronotype

Much like personality, there is considerable variability in the precise phase of an individual's circadian rhythm relative to the light-dark cycle. One's "circadian phenotype" is referred to as their chronotype, defined as "the individual phase of entrainment, i.e. the phase at which an individual synchronizes to the 24 hr day" (Roenneberg et al., 2012; Vetter, 2018). More generally, chronotype refers to one's preference for "morningness" or "eveningness", embodied by the colloquial idioms "morning lark" and "night owl"[9].

Although chronotypes vary widely in humans, there are predictable population-level trends related to age and sex; in general, women and older people are more likely to have a morningness chronotype. A cross-sectional analysis of self-reported chronotype showed that children tend toward morningness, then progress toward eveningness with increasing age throughout adolescence and peaking at ~20 years old (19.5 for females, 21 for males), and thenceforth gradually shifting back toward morningness with increasing age (Foster & Roenneberg, 2008; Roenneberg, 2004). The sex difference in peak eveningness - specifically the 1-2 year delay in males - may explain why men are typically observed to have later chronotypes then women, especially in age-controlled studies. However this sex difference diminishes as age increases beyond the early 20's and disappears (i.e. men and women's average chronotype is the same) at ~52 years of age, which is also the typical age for menopause (Foster & Roenneberg, 2008). Beyond 52, interpretation becomes difficult

[9] "Robin" has been proposed as a moniker for intermediate chronotypes with neither a strong morningness nor eveningness preference (Hancock & Szalma, 2008, p. 234)

due to high variance in the data and the possibility of statistical confounders (i.e. survivor bias, limited sample size, unrelated age-dependent factors, etc.).

Infradian Rhythms

Although the circadian rhythm is by far the most well-known and documented, rhythms with longer and shorter periods have also been observed in biological systems. For example, ~4-hour rhythms in dopamine concentration in the brain and in locomotor activity have been observed in mice (Blum et al., 2014), and the human menstrual cycle has a regular period of ~28 days. Rhythms with periods shorter than 20 hours or longer than 28 hours are referred to as ultradian and infradian rhythms, respectively (F. Halberg, 1960; Reinberg et al., 2017)[10]. This mirrors the nomenclature used for classifying wavelengths of electromagnetic radiation; i.e. *ultra*violet light has a longer wavelength than visible light, and *infra*red light likewise has a shorter wavelength than visible light.

Just as the circadian rhythm ultimately derives from the light-dark cycle caused by earth's rotation, most infradian rhythms are likewise tied to periodic macroscopic changes in the environment attributable to the earth's astronomical properties; i.e. seasons and years. A well-known example is hibernation, a behavioral state characterized by reduced metabolic demand, lowered body temperature, and decreased locomotor activity that typically occurs in the winter. Hibernation is induced through several endogenous circannual

[10] Rhythms with periods between 20 and 28 hours are considered circadian, as these represent the approximate range of periods that the SCN can adapt to

(*circa*- "about", -*annual* "year") rhythms, such as changes in sleep duration (with the maxima occurring in winter), thermogenesis, and vasoconstriction that persist even when environmental conditions are kept constant (Frare et al., 2019; Walker et al., 1980). Hibernation is considered a systemic behavioral outcome that emerges from physiological circannual rhythms, analogous to how sleep is a systemic behavioral outcome produced by a confluence of physiological circadian rhythms. Interestingly, hibernation and sleep are both induced through similar rhythmic physiological changes - decreased body temperature, vasoconstriction, and increased sensitivity of adenosine A1 receptors (Frare et al., 2019) – albeit on dramatically different temporal scales.

Seasonal variations in behavior, physiology, and pathology have also been observed in humans. Stothard and colleagues (2017) demonstrated that the length of the *biological night* - i.e. when melatonin secretion is elevated, usually co-occurring with sleep and night-time - adapts to seasonal differences in the light-dark cycle, growing longer in the winter as nights also grow longer. As light is the primary zeitgeber in humans, the presence of artificial lighting confounds and largely abolishes the circannual rhythm in melatonin secretion, instead inducing a relatively constant duration of biological night that resembles those observed in the natural summer photoperiod. Cortisol exhibits a strong circannual rhythm (Morgan et al., 2017), as does body temperature, although it's been argued that the increases/decreases in temperature observed in the summer/winter (respectively) are attributable to ambient temperature and fall within a constant homeostatic range (Harding et al., 2019). Behaviorally, human reproduction exhibited a profound circannual rhythm in pre-industrial societies and varied by as much 60% across the year, although the

amplitude has since fallen to ~0-5% in modern industrialized populations (Foster & Roenneberg, 2008)[11]. Similar trends and their diminishment have been observed in other population-level statistics: seasonality is observed in the frequencies of births, deaths, and diseases, but the amplitude of these fluctuations is lower in more industrialized countries. While lunar cycles are essential for certain ecosystems (e.g. tidal zones), and although they have been fundamental in shaping human cultures and calendars, there is little evidence that lunar cycles directly influenced our biological evolution (Foster & Roenneberg, 2008).

Circaseptan Rhythms

Of special interest to this dissertation are *circaseptan rhythms* (*circa*- "about", -*septan* "seven"), a class of infradian rhythms with a period of ~7 days (Franz Halberg et al., 1965; Levi & Halberg, 1982). The extent to which circaseptan rhythms arise from innate biological processes, as opposed to emerging from non-biological circaseptan cycles such as the seven-day week, is a topic of much study and controversy.

Unlike days (earth's rotation), months (lunar cycle), and years (earth's revolution), the week has no clear astronomical or geophysical correlate (Franz Halberg, 1984; Levi & Halberg, 1982; Reinberg et al., 2017). In other words, there is no apparent natural zeitgeber capable of entraining circaseptan rhythms *à la* the 24-hour light-dark cycle that entrains

[11] Unlike most animals who reproduce and rear offspring during specific periods of the year, humans reproduce year-round and care for their young for several years after birth; this precludes strong, centrally controlled circannual rhythms tied to reproduction, and thus human birth-rates are much more sensitive to exogenous changes in resource availability, temperature, and other environmental circannual rhythms, as well as sociocultural factors like the summer migration of Inuit families resulting in more opportunities for intimacy (Condon' & Scaglion, 1982), and historical events like famines and wars.

circadian rhythms or the seasonal changes that entrain circannual rhythms. This naturally leads to the hypothesis that all circaseptan rhythms are artificial or emergent from interactions between artificial constructs and biological processes. For example, the habit of sleeping in on the weekend creates a circaseptan rhythm in the timing of sleep and activity that oscillates between later on the weekends and earlier during the work week (Beauvalet et al., 2017; Hulsegge et al., 2019; Vetter, 2018).

Numerous endogenous circaseptan rhythms have nevertheless been documented in spite the lack of a natural circaseptan zeitgeber (Reinberg et al., 2017), including water uptake in pole bean (*Phaseolus vulgaris*) seeds (Spruyt et al., 1987), melatonin production in the pike fish (*Esox lucius*) SCN (Cornélissen et al., 1995), physical activity in the beach beetle (*Chaerodes trachyscelides*) (Meyer-Rochow & Brown, 1998), Immunoglobulin Y (IgY) antibody concentration in chicken (*Gallus gallus domesticus*) egg yolk (He et al., 2014), and myriad physiological biomarkers in rodents: melatonin content of the pineal gland (Sánchez de la Peña et al., 1986), urinary sodium content while on high-sodium diets (Uezono et al., 1987), and systemic responses to therapeutic interventions like vaccines (DeLisi et al., 1983) and toxic conditions such as irradiation (Reinberg et al., 2017).

Sleep

Essential for health yet poorly understood, sleep is "an active, repetitive and reversible brain process of reduced perception and responsiveness to environmental stimuli" (Dahl & Lewin, 2002; Krueger et al., 2016). Being diurnal, humans are normally active during the day and sleep during the night, a behavioral rhythm promoted by our circadian biology and

thus entrained by the geophysical light-dark cycle. Specifically, photic input to our retinas (which is greatest during daylight hours) is received by specialized retinal ganglion cells and relayed to the SCN via the RHT, effectively "resetting" the SCN's intrinsic oscillators and ultimately causing a shift in the timing of the SCN's, and thenceforth the body's, circadian rhythm (M. H. Hastings et al., 2014). Physiologically, peak "sleepiness" usually occurs between 03:00 and 04:00 when the rate of melatonin excretion is greatest and body temperature is lowest, two systems closely regulated by the circadian rhythm (Lack & Wright, 2007). Although sleep and wakefulness are promoted by the circadian rhythm at certain times of day, humans can (and often do) consciously delay sleep for myriad reason, and sleep itself is homeostatically regulated through "sleep pressure" independently of the circadian rhythm. Sleep may therefore be seen as a systemic behavioral output partially regulated by the circadian rhythm: sleep timing is entrainable via diurnal rhythms in body temperature and melatonin, yet sensitive to other factors such as conscious control and homeostatic sleep pressure (Vetter, 2018).

Architecture and Classification

Sleep is heterogeneous in terms of its physiological and neurological markers, which have been used to divide sleep into distinct stages. At the grossest level, sleep is part of a spectrum of behavioral states that reflect different levels of *arousal*. Colloquially defined as an evoked response especially in the context of waking up from sleep, arousal in scientific contexts generally refers to the overall activity of the central nervous system (CNS) in

relation to the sleep-wake cycle (Oken et al., 2006). Arousal's functional meaning is dependent on the field: for example in the context of behavior arousal refers to the sensitivity of an organism to stimuli (Beri & Reddy K, 2019), and in neurophysiology it refers to the overall activity and capacity of a neurological system (Schiff, 2008). In this manuscript, these definitions are combined, with arousal referring to generalized behavioral states characterized by differences in responsiveness to stimuli and cortical activity (Goldfine & Schiff, 2011).

While arousal is typically conceptualized as a spectrum of behavioral states, this continuity is often divided into two broad categories - sleep and wake - with sleep being further divided into two distinct states. In descending order of sensitivity to stimuli and neurological activity, these three broad arousal states are: wakefulness, Rapid Eye Movement (REM) sleep, and non-REM (NREM) sleep (Goldfine & Schiff, 2011). As these are systemic states that affect the entire organism, they can be differentiated using a broad variety of biomarkers (e.g. heart rate, muscle activity, response to stimuli, metabolic rate, etc.). In sleep and circadian research, polsysomnography (PSG) is considered the most accurate and reliable method (the "gold standard") for identifying the level of arousal, as sleep entails major changes to neurological function readily visualized via electroencephalography (EEG) (Ancoli-Israel et al., 2015; Colten & Altevogt, 2006). PSG also frequently incorporates physiological and biomechanical measures in addition to EEG, such as heart rate, blood oxygenation (aids in screening obstructive sleep apnea), electromyography of lower limbs (aids in screening restless leg syndrome), electrooculography (to detect eye-blinks and associated EEG artifacts), and respiration rate.

Sleep has historically been divided into five stages - NREM1, NREM2, NREM3, NREM4,[12] and REM - based on Rechtschaffen and Kales' (1968) criteria for scoring sleep off of cortical EEG data[13]. These criteria have been reviewed several times since, with the most recent standards being set by the American Academy of Sleep Medicine's (AASM) official guidelines (Moser et al., 2009). In addition to changes in scoring and reporting, these new standards define only four sleep stages (N1, N2, N3, and REM) with N4 and N3 being merged together; N3 is often referred to as slow-wave sleep (SWS).

Humans normally progress through the sleep stages in a regular, stereotyped cycle with an approximate duration of 90 minutes: starting from wakefulness, an individual will enter N1 upon falling asleep and progress to the "deeper"[14] stages of N2, N3, and finally to REM, before returning to N1 and repeating the cycle (Atkin et al., 2018). The time spent in each stage varies predictably throughout the night, with REM growing longer and N3 shorter with each successive cycle. The cycle is also significantly affected by age, with older individuals experiencing longer N1 and N2 stages, a shorter N3 stage, and fewer full sleep cycles on a given night (Mander et al., 2017). Older age is also associated with advanced (i.e. earlier) sleep timing, greater sleep onset latency, higher sensitivity to arousing

[12] Often abbreviated as N1, N2, N3, and N4, respectively

[13] Two additional stages were included in these criteria: *Wake* for periods of wakefulness, and *Movement Time* for periods where movement artifacts prevented accurate scoring. Movement Time has since been removed from the official AASM standards, and such periods are now scored based on data from proximal epochs.

[14] Colloquially, it is more difficult to rouse someone from a "deeper" sleep than from a "lighter" sleep. Sleep stages also follow this paradigm: an individual would be less responsive to stimuli in N3 than they would be in N1.

stimuli, and a corresponding increase in sleep fragmentation and Wake After Sleep Onset (WASO).

Each stage has distinct resting and transient waveforms created by differences in neural activity, which are used to identify sleep stages in cortical EEG recordings. Briefly, N1 is the transition from wakefulness to sleep and is marked by a pronounced theta oscillation (~4 - 7 Hz) and the absence of the waking alpha rhythm (~8 - 15 Hz). N2 is characterized by a greater amplitude in the theta rhythm and the appearance of low-frequency K-complexes and high-frequency sleep spindles, the latter of which is produced by thalamocortical interactions (Atkin et al., 2018). N3 is the deepest stage of NREM and is frequently referred to as SWS due to the presence of relatively low frequency delta waves (~0.1 - 3 Hz). Collectively, NREM stages (especially N3) are characterized by reductions in body temperature, breathing rate, blood pressure, muscle tone, and diminished activity in cognitive, memory, and emotional systems. Note that, although muscle tone decreases in NREM, it is still present and the individual can unconsciously respond to potentially dangerous stimuli, suggesting that motor and somatosensory systems are less dampened (Atkin et al., 2018; Koella, 1982; Schulz, 2008).

Aside from its titular rapid eye movements, REM sleep is distinguished from NREM by arousal of the CNS, the appearance of low-amplitude high-frequency theta waves in EEG, the abolition of muscle tone throughout the body, and a relaxation of homeostatic regulation resulting in fluctuating body temperature, heart rate, blood pressure, and so on (Atkin et al., 2018; Parmeggiani, 2011). REM is also referred to as “paradoxical sleep” due to the observation that the increased cortical activity resembles that seen in an

awake brain - despite the fact they're asleep. Dreaming occurs primarily in REM sleep - likely facilitated by the sudden arousal of cognitive and memory systems - whereas parasomnias such as sleepwalking usually occur in N3 (Atkin et al., 2018). Since NREM is characterized by the depression of higher order brain functions and maintenance of motor systems, NREM parasomnias usually involve motor acts (e.g. sleepwalking) without conscious awareness; in contrast, dreams in REM sleep can be recalled and narratively described due to arousal of cognitive systems, but the physical actions occurring in those dreams are suppressed by the loss of muscle tonicity (Koella, 1982; Schulz, 2008).

Homeostatic and Circadian Regulation of Sleep

Sleep timing is believed to be regulated through the interplay of two circadian rhythms (Landolt & Dijk, 2019): a centrally controlled oscillation in melatonin secretion, and a physiological "sleep pressure" that increases while awake due to the accumulation of certain neuromodulators (referred to as somnogens) in the central nervous system (CNS). These systems and their interactions are collectively known as the "two process model" of sleep regulation.

Melatonin is secreted from the pineal gland in response to indirect innervation from the SCN via the hypothalamic Paraventricular Nucleus (PVN). Melatonin is a *chronobiotic* - i.e. a modulator of the timing of biological rhythms - that is primarily secreted during periods of darkness and which is associated with decreased physical activity and increased sleep proposensity (Arendt & Skene, 2005; Silva et al., 2019). The duration of melatonin secretion proportionally reflects seasonal changes in environmental light, allowing it to

entrain *photoperiodic* processes dependent on the length of the night (e.g. sleep timing, body temperature), and feeds back on the SCN via G-protein coupled receptors to adjust the phase of its TTFLs (Pévet, 2016). The sudden increase in melatonin secretion before sleep is referred to "dim light melatonin onset" (DLMO), occurring around dusk and followed by a marked increase in sleepiness and decrease in body temperature. The proximity of the pineal gland to the SCN in terms of synaptic intermediaries and latency, as well as the relative ease by which melatonin can be measured and the high amplitude of its crepuscular secretion, has made DLMO a popular and robust indicator of circadian phase (Pévet, 2016).

In contrast to the centrally regulated DLMO, the accumulation of somnogens is thought to be a byproduct of normal neurometabolic processes during wakefulness – e.g. extracellular adenosine, a classic somnogen, is produced from ATP catabolism (Lazarus et al., 2019). Numerous somnogenic molecules have been identified, including the aforementioned adenosine, prostoglandin-2, and several cytokines. Although the production, neurological targets, and anatomical localization of several somnogens have been well characterized, the complexity and broad distribution of the neurological sleep propensity system has slowed the consolidation of a unified theory of sleep-wake regulation (Landolt & Dijk, 2019). Where-as DLMO prepares the body for sleep based on environmental conditions (time of day), sleep pressure does so based on neurobiological conditions (time spent awake). Their interaction through sleep regulation at a systemic level allows for the integration of exogenous and endogenous cues into a cohesive behavioral output.

Sleep and Circadian Disruption

In previous sub-chapters, the anatomical, physiological, and functional aspects of the circadian rhythm have been discussed in the context of an idealized organism that is effectively synchronized with its environment. As with any other biological system, however, the circadian rhythm can be disrupted by intrinsic and extrinsic factors. The impacts of circadian disruption are myriad and generalized, manifesting as impairments to systemic processes like cognition, sleep, metabolic efficiency, and disease risk. Although the causes of circadian disruption (e.g. misalignment between biological and environmental phases) are well understood and in fact a core element of chronobiological experimental design, the precise biological mechanisms that translate misalignment into systemic impairments are poorly understood (Vetter, 2018). Circadian disruption is becoming increasingly common in humans for myriad reasons: artificial zeitgebers created by technological (e.g. artificial lighting) and sociological (e.g. food availability) factors can interfere with the circadian rhythm's ability to synchronize to the geophysical day/night cycle, individuals can and often do choose to shift their sleep timing out of phase with their circadian rhythm in response to personal, professional, and social pressures, and activities unique to modern society – such as long distance travel and daylight savings time – can abruptly decouple one's circadian rhythm from the environment with deleterious consequences (Chattu et al., 2018; Colten & Altevogt, 2006). Certain populations (e.g. shift workers) are disproportionately vulnerable to circadian disruption, and the circadian rhythm can be further disrupted directly and/or indirectly by numerous pathologies, such as Parkinson's Disease (PD).

Definition and Scope

Any discussion of circadian disruption must account for the fact that the circadian rhythm is innately *adaptive*. The circadian rhythm constantly receives and integrates internal and external zeitgebers to optimize the timing and coordination of biological processes. Consider the fact that the TTFL - the fundamental oscillator in the mammalian circadian rhythm - has an innate period of ~24.2 hours (Burgess & Eastman, 2005; Czeisler et al., 1999). Without constant entrainment to environmental cues (i.e. light), the circadian TTFL (and it's downstream processes such as CCGs) would gradually drift out of sync with the environment even in ideal conditions. In other words, the circadian rhythm is constantly "disrupted" because it is a dynamic system of systems that is constantly adapting to changes in exogenous and endogenous zeitgebers. Small changes in timing are easily tolerated; for example, the gradual day-to-day change in sunrise time is a constant challenge, but the shift of several dozen seconds per day is easily and quickly accommodated with minimal systemic effects (i.e. we are not jet lagged every morning). In other words, humans can tolerate some degree of variance in the relative timing and amplitude of our myriad circadian rhythms and their zeitgebers/regulators. Therefore any discussion of circadian disruption must distinguish between normal *adaptations*, tolerable *variation*, and abnormal *disruptions* in the circadian system/endpoint of interest (Vetter, 2018).

In this context, *circadian disruption* refers to a significant challenge to the circadian rhythm (i.e. an unexpected or out-of-phase stimulus) and the adverse negative outcomes it incurs. The circadian rhythm's distributed and multifaceted nature means it cannot "turn on a dime" - human circadian rhythms can adapt by ~1 hour/day on average (Vetter, 2018)

- meaning larger deviations are proportionally more difficult to adapt to. For example, flying from New York to Los Angeles phase advances environmental (i.e. solar) time by three hours relative to biological time within a single day, a shift several orders of magnitude larger than the normal day-to-day change in daylight. Such a dramatic shift results in a multitude of negative symptoms as the circadian rhythm "lags behind" and slowly resynchronizes with the environment; colloquially referred to as *jet lag*, these symptoms include daytime sleepiness, mood shifts, and difficulty sleeping.

Building upon the seminal example of jet lag, consider the different zeitgebers and their interaction with the circadian rhythm in this hypothetical New York to Los Angeles flight. The retinorecipient SCN core quickly detects the abnormal environmental shift via signals from retinal ganglion cells and begins resetting its non-retinorecipient shell TTFLs to align with the new Los Angeles time. As this information slowly propagates throughout the SCN via paracrine signaling, the body's peripheral oscillators (which are largely insensitive to environmental conditions) continue unaware of the shift. As the sun begins to set in New York (yet is still high in the Los Angeles sky), the peripheral oscillators enter "biological night" as melatonin is secreted, heart rate slows, temperature decreases, and so on. Some are influenced by conflicting temporal information conveyed by non-photic behavioral and physiological zeitgebers. For example, the individual is awake past their usual bedtime, resulting in greater buildup of somnogens and reduced cognitive performance. Meals are suddenly taken at a later time, forcing the liver and other digestive organs to work at a reduced efficiency as the body is homeostatically prepared for fasting, causing indigestion and nausea. They wake up too early after their first night in Los Angeles, a

consequence of their body temperature and peripheral blood flow increasing with the rising sun in New York, and they experience daytime sleepiness due to their "sleep debt"; i.e. residual somnogens that were not cleared due to an incomplete night of sleep. Meanwhile, the SCN and its neurological relays, now well on their way to synchronizing with the Los Angeles day, are entraining the peripheral oscillators at varying rates depending on their scale, functional "distance" from the SCN, and the influence of non-photic zeitgebers like feeding. The symptoms of jet lag emerge from these conflicting stimuli and misaligned biological processes, and it takes several days before the combination of top-down (i.e. SCN and light) and bottom-up (i.e. digestive organs and feeding) signals fully adapt to the new environment and each other. Of course, the individual then returns to New York and once again decouples the phase of their circadian rhythm from the environmental phase. Despite the common perception of jet lag as a minor annoyance that causes drowsiness, headaches, and nausea, its symptoms demonstrate the fundamental importance and systemic influence the circadian rhythm has on our biology (Evans & Davidson, 2013): a relatively minor misalignment of biological and environmental times is enough to cause circadian disruption, resulting in myriad minor inefficiencies from unoptimized biological processes that cumulatively manifest as generalized systemic symptoms.

As mentioned earlier, circadian disruption has been used as a general term to describe the adverse effects that manifest as the circadian rhythm resynchronizes itself to environmental zeitgebers and its constituent rhythms to each other (Vetter, 2018). More discretely, the study of circadian disruption refers to its myriad potential disruptions (e.g.

jet lag, neurodegenerative disease, unique photoperiods such as polar latitudes, genetic predisposition) acting through a range of mechanisms (e.g. misalignment, sleep disruption, behavioral interference, etc.) at different levels of biological organization (e.g. cellular, tissue, systemic, behavioral) (Potter et al., 2016). Furthermore, behavioral and environmental factors may only disrupt specific aspects of the circadian rhythm; e.g. by shifting meal times while keeping environmental zeitgebers unchanged, the diurnal fluctuation in blood glucose concentration can be discretely decoupled from the circadian rhythm (Vetter, 2018; Wehrens et al., 2017). Circadian disruption is often treated as an umbrella term that takes on different meanings and scopes in different scientific and clinical contexts, in much the same way that "mental illness" may refer to a broad spectrum of pathologies, or to specific symptoms and etiologies. This manuscript will use the definition provided by Qian and Scheer (2016, p. 4): "*circadian disruption* is a disturbance of biological timing, which can occur at different organizational levels and/or between different organizational levels, ranging from molecular rhythms in individual cells to misalignment of behavioral cycles with environmental changes."

Sleep disruption is closely related to and is often used as a proxy for circadian disruption - e.g. jet lag can be quantified by changes in sleep timing relative to the local environment (Vetter, 2018). There is considerable overlap in terms of their causes, mechanisms, and symptomology (Potter et al., 2016): one can be caused by the other (e.g. shift work disorder), both can be the consequence of a common insult (e.g. jet lag), and both can synergistically contribute to a common symptom. For example, both sleep and circadian disruption contribute to obesity: the former through reduced metabolic function, the latter

through dysregulation of the gut microbiome, and both interfere with normal endocrine function (Potter et al., 2016). Obese individuals are more likely to develop sleep disorders such as Obstructive Sleep Apnea (OSA), which in turn can further disrupt sleep (and thus circadian rhythms related to it) via sleep fragmentation. Conversely, sleep fragmentation can occur as a result of the misalignment between circadian and somnogenic rhythms caused by jet lag, and the abrupt change in sleep timing can decouple elements of the circadian rhythm from each other and/or the environment (Vetter, 2018). Circadian disruption can also directly cause sleep disruption. For example, a study evaluating different combinations of on/off duty shifts on United States Naval vessels found that a 5-hour ON / 10-hour OFF shift had the greatest reduction in performance despite spending more hours asleep than any other shift. The authors attributed this seemingly paradoxical finding to the fact that the timing of 5/10 sleep periods was highly irregular and misaligned with both their natural environment and their circadian rhythm; i.e. they induced chronic circadian disruption, which subsequently disrupted their sleep and thus their performance (Shattuck & Matsangas, 2016). Lastly, sleep disruption (as with circadian disruption) can be caused by behavioral and social factors that restrict sleep duration and timing, such as staying up late for a social event, waking up early to go to work, etc. Put simply, sleep disruption can be considered a specific type of circadian disruption.

In summary, the circadian rhythm is a distributed yet coordinated system of systems that dynamically adapts to constantly changing internal and external conditions. Dysregulating, misaligning, or otherwise disrupting one system inevitably impacts the adjacent systems it's integrated with. While this interconnectedness increases the susceptibility of the

circadian rhythm to disruption, it is also protective in the sense that the effects of an isolated insult will be attenuated and dissipated by the unaffected systems, analogous to a trampoline distending to absorb kinetic energy, or an out-of-time musician falling back in measure with their orchestra. The circadian rhythm is innately adaptive; following acute disruption it will, over time, resynchronize its constituent biological rhythms to each other and (via the SCN) the environment (Vetter, 2018). Ultimately, circadian disruption describes this period of dynamic adaptation, its functional and biological etiologies, and the adverse effects that emerge during it.

Epidemiology and Consequences

Sleep and circadian disruption are widespread in modern industrialized societies (Colten & Altevogt, 2006; D. R. Hillman & Lack, 2013), and have been found to be associated with numerous health issues, including but not limited to obesity and metabolic diseases (Potter et al., 2016), cardiovascular disease (Portaluppi et al., 2012), neuropsychiatric disorders (Musiek & Holtzman, 2016), neurodegenerative diseases (Colten & Altevogt, 2006; Videnovic, Lazar, et al., 2014), and disruption of the endocrine system (Bedrosian et al., 2016; Vetter, 2018). Acute symptoms of circadian disruption (e.g. fatigue and impaired attention) have contributed to the occurrence of fatal accidents (Gottlieb et al., 2018) - the rate of which has increased in the United States of America (USA) over the past decade (Murphy et al., 2018) - and has been implicated as a contributing factor in numerous high profile accidents and catastrophes such as the Three Mile Island disaster, the Chernobyl disaster, the Exxon Valdez oil tanker spill, the Space Shuttle Challenger disaster, and the

Union Carbide disaster in Bhopal, India (Colten & Altevogt, 2006; RAND Corporation, 2016). Insufficient sleep, which is both a cause and consequence of circadian disruption, has been linked with seven of the fifteen most common causes of death in the USA[15] (RAND Corporation, 2016) and is associated with worse academic performance in school-children and undergraduates (Okano et al., 2019).

Epidemiological studies quantifying the full extent of circadian disruption are scarce due its multifaceted and indistinctly defined nature (D. R. Hillman & Lack, 2013); however, epidemiological studies of sleep disruption have estimated that over a third of Americans experienced insufficient sleep (Liu et al., 2016) and a similar proportion of Australians reported sleep disorders (D. R. Hillman & Lack, 2013). Another study estimated that young and middle aged French adults slept ~1.5 hours less than recommended (Léger et al., 2011). Sleep disruption is not limited to western countries and is as or even more common in Asian countries, including China, Taiwan, Thailand, and Singapore (Lin et al., 2017). An international survey (National Sleep Foundation, 2013) estimated that over half of Japanese adults achieved less than seven hours a sleep a night; by comparison, the proportion of insufficient sleep amongst American, British, German, and Canadian adults ranged from 26% to 45% (RAND Corporation, 2016). Moreover, the problem appears to be worsening over time: retrospective analyses of Swedish and Finnish cohort studies suggest that sleep duration has declined by as much as 18 minutes/night over a period of ~30 years (Kronholm et al., 2008; Rowshan Ravan et al., 2010), and the prevalence of sleep

[15] Cardiovascular disease, malignant neoplasm, cerebrovascular disease, accidents, diabetes, septicemia, and hypertension

disruption is expected to continue rising, particularly in at-risk populations (Ferrie et al., 2011).

A recurring[16] theme in the study of the circadian and sleep regulation is the sheer breadth and interconnectedness of their constituent elements, including the complex systemic properties that arise from their dynamic interactions. This is well demonstrated by the myriad risks associated with increased sleep disruption, which run the gamut from biological to artificial and include behavioral, genetic, and social factors. To wit, lower sleep duration has been associated with higher Body Mass Index (BMI), habitual cigarette smoking, habitual consumption of sugary drinks, low physical activity, being at high risk of experiencing mental health problems, experiencing financial stress, having children, being male, being divorced, never having been married, experiencing workplace stress, inconsistent work schedules (i.e. shift workers), having long commute times, and having limited workplace autonomy (RAND Corporation, 2016). Determining the causal relationship of these risk factors with respect to sleep and circadian disruption – i.e. the degree to which disruption gives rise to and/or is caused by, e.g., obesity – is a major objective of current chronobiological research. Furthermore, multiple populations have been identified as having an elevated risk and/or incidence of sleep disruption. For example, the demanding schedule of United States Military Academy cadets leaves them severely sleep deprived throughout their education (Miller et al., 2010) and into their military service (Miller et al., 2011), and medical residents on intensive care units often work lengthy hours and consequently suffer from sleep disruption during their residency, leading to increased rates of

[16] No pun intended.

serious medical errors compared to residents working less demanding schedules (Colten & Altevogt, 2006; Landrigan et al., 2004; Lockley et al., 2004). Night-time shift workers, employees with unusual schedules (e.g. off-shore oil workers), and those with unpredictable shifts (e.g. emergency first responders) risk decoupling their circadian rhythm from natural zeitgebers via behavioral disruption, with the resultant circadian maladjustment leading to sleep disruption; in other words, their daily schedule changes independently of the day-night cycle, depriving biological circadian regulators access to a consistent zeitgeber schedule (Colten & Altevogt, 2006).

Analogous to how desynchrony between different zeitgebers gives rise to biological inefficiencies that manifest as systemic symptoms, circadian disruption impairs the efficiency of employees with significant economic implications. Increased rates of fatigue, absenteeism, presenteeism, and accidents undoubtedly reduce productivity, and the endemic nature of circadian disruption in modern industrialized societies has made these inefficiencies increasingly common. While it is difficult to unambiguously separate out productivity lost due to sleep and circadian disruption from other causes, the use of symptomatic proxies such as fatigue and behavioral outcomes like tardiness has allowed for estimation. In 2002, the total economic cost of lost productive time at work was estimated at $226 billion per year in the USA alone, of which 70% was attributable to reduced performance at work caused by personal health reasons (Stewart et al., 2003). 14 years later, one international model (RAND Corporation, 2016) estimated that this cost had increased to ~$350 billion, making up over half of the $680 billion estimated yearly economic burden across the combined American, German, British, Japanese, and Canadian economies, and

ranging from ~0.85% to 2.92% of their national Gross Domestic Products (GDP). In Australia, the estimated economic burden roughly doubled between 2004 and 2017, reaching ~$45 billion per year (D. Hillman et al., 2018; Koritala & Çakmaklı, 2018).

The increasing prevalence of sleep disruption, accumulating evidence of its numerous deleterious health outcomes, identification of numerous risk factors and susceptible populations, and a growing burden on the global economy has led to its recognition as a public health crisis, a modern day (Bonnet & Arand, 1995; Chattu et al., 2018; Colten & Altevogt, 2006; D. R. Hillman & Lack, 2013; Wittmann et al., 2006).

The Seven-Day Week and Sociogenic Circaseptan Rhythms

The social construct of a "week" was likely borne from a confluence of utilitarian, sociological, and potentially biological factors (Meyer-Rochow & Brown, 1998; Zerubavel, 1989). The seven-day week serves an important utilitarian function as an intermediary unit of time between the natural circadian (daily) periodicity of Earth's rotation and the larger circatrigintan (monthly) and circannual (yearly) periodicity of the Moon's revolution about the Earth and Earth's revolution about the Sun, respectively. In the same way that it is easier to carry $0.55 as two quarters and a nickel than as 55 pennies, it is easier to define the sabbath as "the last day of the week" than as "the 7th, 14th, 21st, and 28th days of the lunar cycle". In other words, tiered units of proportional magnitude (i.e. day, week, month, year) can convey information more efficiently than the absolute number of the smallest unit (i.e. day) and so entail a utilitarian benefit. Sociologically, the week acts as a "temporal scaffold" around which societies can order themselves: the week's utilitarian function as

an intermediary unit of time provides a tractable means to establish, organize, and maintain societal customs and activities that cannot be accomplished within a single day but which would be inefficient or inappropriate to extend over the course of a month (e.g. work and rest days). Biologically, circaseptan (i.e. weekly) periodicity has been documented in humans in biological phenomena – e.g. 17-ketosteroid concentration in urine (Franz Halberg et al., 1965) – as well as secondary biological outcomes – e.g. sudden cardiac death (Rabkin, 1980).

Whether these effects are attributable to an intrinsically circaseptan biological process, are the consequence of our biology conforming to an exogenous socially-mandated 7-day week, or a mixture of both remains an open question. Even if one assumes that there are no natural phenomena with an intrinsically circaseptan period, it is still a reasonable assertion that the first societies to employ a seven-day week did so by quartering the ~29 day lunar cycle into four seven-day periods (Levi & Halberg, 1982) - or perhaps derived it from the circaseptan harmonic of the circadiseptan rhythm in spring and neap tides driven by the lunar cycle (Meyer-Rochow & Brown, 1998). In other words, if the observed circaseptan periodicities in our biology did not emerge from natural circaseptan pressures in human evolution, then they did so as a consequence of how modern humans organized their society.

Notwithstanding the biological, sociological, and/or utilitarian origins of the 7-day week, it has now become fundamental to the organization of our society and therefore has quantifiable implications on our behavior and health (Levi & Halberg, 1982). The common interest in the periodicity and long-term trends of variation in biological processes was first

quantitatively realized by Santorio Sanctorios who, in the 17th century, accumulated nearly thirty years of longitudinal metabolic data. Although Sanctorios' data was lost, a more recent and similarly inspired longitudinal collection of metabolic data – specifically urinary volume and 17-ketosteroid secretion – was found to contain a significant circaseptan component (Franz Halberg et al., 1965). More recently, an increased incidence of sudden cardiac events on Mondays has been documented for nearly half a century using cohorts dating back to the second World War (Rogot et al., 1976). Interestingly, this may be associated with an intrinsic circaseptan rhythm in the secretion of neurohypophyseal hormonal secretions (Rabkin, 1980), and exacerbated by the psychological (e.g. anxiety), environmental (e.g. pollutants), and physical (e.g. activity) stressors that accompany the return to societal and professional obligations at the beginning of the work week. It is conceivable that these same stressors, regularly experienced on a seven-day cycle, would also impact other aspects of health such as sleep and rest-activity cycles (Rabkin, 1980). In other words, our social calendar, societal organization, and their influence on our behavioral, emotional, and psychological states may disrupt biological rhythms independently of intrinsic biological and extrinsic environmental challenges, a phenomenon referred to a *sociogenic* (*socio*-: social, -*genic*: origin) disruption in this manuscript.

Sociogenic Disruption

Humans are innately social creatures who self-organize into complex cooperative systems - i.e. societies. Amongst the myriad benefits of communal organization is the logistical ability to synchronize activities to optimize efficiency and minimize energy consumption,

analogous to how the circadian rhythm synchronizes biological processes to maximize the organism's fitness. Much in the same way the evolution of photosynthesis opened up a new source of energy in the form of solar radiation, humanity's development of technology, language, and science has given us access to vast new sources of energy - fire, wood fuel, animal husbandry, hydropower, steam, fossil fuels, electricity, nuclear fission, and even artificial photosynthesis *vis-à-vis* solar power - and led to our dominance of Earth's biosphere. Industrialized human society embodies the epitome of biological evolution, concerned primarily with optimizing the efficient and widespread exploitation of our environment to improve our fitness and resiliency. Ironically, this has increasingly divested us from the biological systems we evolved to exploit. The unique capacity of humans to gather, infer, integrate, record, communicate, and apply information has enabled us to exploit our environment in ways never before seen on Earth, but it has also made us dependent upon the artificial systems and technologies we use to do so. Moreover, our technological development has rapidly outpaced our biological evolution. Consider the fact that most modern *Homo sapiens* in industrialized regions live independently of the geophysical solar day; i.e. a doctor in Chicago need not look outside to know if she should eat, sleep, or leave work, only at her watch and her calendar. She no longer sleeps in synchrony with the sun, but with her shift schedule.

This is not unique to medicine, as many industries function autonomously from the geophysical day based on their practical needs: a cargo ship will dock when it's cheapest and safest to do so, not because the sun is at a certain point in the sky. This independence from the geophysical day is enabled by technology; before sonar, the aforementioned cargo

ship may have only been able to safely dock during the day when the offshore reefs were visible and could be navigated around. Such restrictions imposed on human behavior and social time by the day-night cycle have been gradually alleviated by technology, allowing the artificial pressures of economics, logistics, and convenience to grow in influence. Globalism, international trade, electronic media, air travel, and the internet have increased the interconnectedness (and interdependence) of human societies around the globe, contributed to the modern phenomenon of "24/7" industry, and exacerbated the growing irrelevance of local solar time to human society. These are reminders that modern society keeps its own time; one might note that our modern calendar is to our society what our circadian rhythm is to our body. While the calendar does not have a circadian rhythm, we do. Fundamentally, it is this disconnect between our social calendar and our biological circadian rhythm that leads to sociogenic circadian disruption (Foster & Roenneberg, 2008; Roenneberg et al., 2015; Vetter, 2018).

Perhaps one of the most well-studied sociogenic disruptions is *Social Jet Lag* (SJL), the habitual discrepancy in behavioral chronotype between days of the week, especially work days and rest days (Roenneberg et al., 2012; Vetter, 2018; Wittmann et al., 2006). SJL arises from the difference in internal (i.e. biological) and external (i.e. social) timing systems; put simply, people do not always get to choose when they wake up. Much of the population is forced by social and professional obligations to adapt to a social schedule too early or too late for their natural chronotype during work days, and then revert back to their natural preference once these social constraints are removed on rest days. This is analogous to jet lag: crossing time zones imposes an immediate artificial shift in time and behavior

(e.g. sleep), and waking up early to go to work likewise abruptly decouples the behavioral rest-activity rhythm from the biological circadian clock. People who experience SJL may therefore be described as living in two separate time zones: a social time during the work week, and a biological time during the rest week (Roenneberg et al., 2015). Looking across multiple weeks, this periodic transition between social and biological "time zones" may be described as a circaseptan rhythm of chronic circadian disruption, where-as jet lag is acute, non-rhythmic, and relatively infrequent by comparison.

SJL is usually assessed subjectively through self-reported sleep times and standardized instruments like the Munich Chronotype Questionnaire (MCTQ) or Morningness-Eveningness Questionnaire (MEQ), and/or objectively with actigraphy collected by wearable accelerometers (Roenneberg et al., 2019). The low cost, ease of use, and good scalability of these methods have led to SJL being widely assessed in numerous studies; however, the rapid proliferation of SJL as an endpoint has led to considerable methodological inconsistencies in its application, calculation, and interpretation (Beauvalet et al., 2017; Roenneberg et al., 2019). Nonetheless, there is a growing consensus that SJL (like other forms of sleep disruption) is widespread in modern populations and associated with similar negative health outcomes: greater SJL has been linked with decreased academic performance (Díaz-Morales & Escribano, 2015; Haraszti et al., 2014), a higher chance of smoking cigarettes (Wittmann et al., 2006), developing metabolic disorders (Koopman et al., 2017; Wong et al., 2015), including obesity (Alves et al., 2017; Malone et al., 2016; Parsons et al., 2015; Roenneberg et al., 2012; Rutters et al., 2014), poor diet (Almoosawi et al., 2018), and may be a risk factor and/or side effect of depression (Cespedes Feliciano et

al., 2019; Malone et al., 2016; West & Bechtold, 2015; Wittmann et al., 2006), although this is debated (Knapen et al., 2018; Roenneberg et al., 2019).

Epidemiologically, SJL is widespread in the general population (Islam et al., 2020; McMahon et al., 2019; Sűdy et al., 2019), with over 30% of European adults reporting two or more hours of SJL (Roenneberg et al., 2012). Those living in latitudes further from the equator may have increased SJL, potentially due to latitudinal changes in exposure to and intensity of sunlight (Leocadio-Miguel et al., 2018). This effect was observed to be more pronounced in persons with the 4-repeat PER3-(4/4) allele, itself associated with a preference for evening chronotype (Hida et al., 2018). Secondary evidence, such as the delayed timing in power grid consumption on weekends versus weekdays (Stowie et al., 2015) and in peak social media usage (Leypunskiy et al., 2018), further supports the notion of a regular delay in sleep timing on weekends in a large portion of the general population.

Certain cohorts, especially those already known to be susceptible to circadian disruption (e.g. shift workers, students, first responders, etc.), are more susceptible to developing SJL (Parsons et al., 2015). Moreover, the severity of SJL is closely related to chronotype, with evening chronotypes being disproportionately more likely to have SJL (Roenneberg et al., 2019; Takahashi et al., 2018; Wittmann et al., 2006; Zerbini et al., 2020). While the distribution of chronotypes in the general population is broad, ranging from extreme eveningness to extreme morningness, the distribution of work schedules is far more compact and constrained by nonbiological factors such as economics, logistics, law, and culture; chronotypes whose natural sleep timing preference overlaps with social

and professional obligations therefore are more likely to have SJL. Other factors such as commute time, can further impinge upon one's chronotypical sleep time and induce SJL.

Closely related to SJL is *Sleep Debt*, the cumulative effect of sleep deprivation over time (Saghir et al., 2018). Where-as SJL is the difference in sleep *timing* between work and rest days, Sleep Debt is calculated as the difference in sleep *duration* between work and rest days (Wong et al., 2015). On average, human adults require 6 – 9 hours of sleep a night to feel rested and to avoid Excessive Daytime Sleepiness (EDS), as recommended by the American Centers for Disease Control (Hirshkowitz et al., 2015). Although the body may be able to adapt to minor changes in sleep timing (J. Horne, 2011), chronic sleep deprivation will lead to increased sleep pressure and tiredness, and the body will homeostatically compensate by extending sleep duration (unless otherwise interrupted, e.g., by waking up early for work) until the "debt is paid". These variations in sleep duration also extend to its quality, and vary by age and chronotype; e.g. both adults and schoolchildren tend to sleep longer, later, and poorer on weekend nights, reflecting increased Sleep Debt, SJL, and sleep disruption, respectively (Bei et al., 2016; Crowley & Carskadon, 2010; Taylor et al., 2008). As with SJL, these effects are more pronounced in those with chronotypes (usually eveningness) whose preferred sleep time conflicts with their social obligations (i.e. work). When this obligation is removed on rest days, they "sleep in" to make up the sleep debt accumulated during the workweek (Vitale et al., 2015). In this way Sleep Debt and SJL can compound each other: those with high SJL are likely to have high Sleep Debt, so not only will they sleep and wake later on weekends, their wake time will be further delayed

as they recoup their Sleep Debt, which in turn delays their rest-activity rhythm, light exposure, meal times, social interactions, and other important influential zeitgebers.

In summary, humans, as social creatures, are beholden to two times: solar time (which entrains our circadian rhythm and maintains synchrony between our body and our environment) and social time (which constrains our behaviors, responsibilities, and our interactions with others). For most of human history, social time has been defined by solar time. With the advent of industrialization and the ensuing growth in population and production - further accelerated by the exponential increase in producing and harnessing energy - social time needed to expand beyond daylight hours to maintain social order and cohesion. The proliferation of standard calendars and clocks and artificial lighting has further detached social time from solar time. However, our biology - when we feel tired, when we eat, when we seek out shelter - is still entrained solar time. As a result, our behavior is increasingly disconnected from our biology. This manifests as chronic circadian disruption, a growing 'sleeping crisis' in modern industrialized societies (Chattu et al., 2018; Colten & Altevogt, 2006; D. R. Hillman & Lack, 2013).

Parkinson's Disease

Idiopathic Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting 1% of the population over 60 (de Lau & Breteler, 2006). The onset of PD's characteristic motor symptoms – bradykinesia, tremor, rigidity, and postural instability and gait disturbances (PIGD) (Kalia & Lang, 2015) – occurs years or even decades after the

initial appearance of neuropathology in the CNS. There are numerous non-motor symptoms associated with PD as well, including cognitive impairment, autonomic dysfunction, and disruption of sleep and the circadian rhythm (Jellinger, 2015). These features have been clinically defined and the initial diagnosis of PD is based on their observation in a neurological exam (Postuma et al., 2015). However, in the absence of validated biomarkers – i.e. measures sensitive to a biological or pathological process (Lana M. Chahine & Stern, 2017; Espay et al., 2017; Horak & Mancini, 2013) – the gold standard diagnostic criteria remains post-mortem confirmation of PD neuropathology in the substantia nigra pars compacta (SNpc) (Kalia & Lang, 2015).

PD is markedly heterogeneous, with significant variability in its clinical presentation, rate of progression, response to treatment, and underlying neuropathology (Kalia & Lang, 2015). This is compounded by the fact that its clinical features and pathological mechanisms often overlap with other neurodegenerative diseases, movement disorders, and a growing continuum of "parkinsonisms" (Dickson, 2012; Espay et al., 2017), which has contributed to a diagnostic false positive rate of 10%-20% (Hughes et al., 2001, 2002). This is considered unacceptably high given the deleterious side effects of levodopa/carbidopa dopamine replacement therapy, the primary means of ameliorating PD's motor symptoms (Kalia & Lang, 2015). As a result, the development of asymptomatic disease-modifying treatments, the identification of valid biomarkers sensitive to disease progression, and the translation of these to clinical practice are considered the highest priorities in PD research (Espay et al., 2016, 2017; Goedert et al., 2013).

Neuropathological Progression and Evaluation

Neurodegeneration and clinical progression in PD are closely associated with the appearance and gradual spread of intraneuronal protein aggregates throughout the central, peripheral, and enteric nervous systems (Braak et al., 2003; Lana M. Chahine & Stern, 2017; Goedert et al., 2013). These are commonly referred to as Lewy bodies (aggregates, usually in cell body) and Lewy neurites (strands, usually in neurites) after Fritz Heinrich Lewy, the pathologist who first described them in PD in 1912 (Goedert et al., 2013).

In 1997, the presynaptic protein alpha-synuclein (ASN) was identified as the bulk component of Lewy aggregates (Spillantini et al., 1997) and an ASN mutant was identified in familial PD (Polymeropoulos, 1997), findings that ultimately led to PD's classification as a synucleinopathy (Goedert et al., 2013). While there has been substantial progress in uncovering the mechanisms underlying the formation of Lewy pathology, notably the prion-like spread of ASN between neurons (Visanji et al., 2013), the relationship between the pathological aggregation of ASN and neurodegeneration remains unknown (Goedert et al., 2013). Similar to amyloid beta in Alzheimer's disease, a decrease in the concentration of ASN in cerebrospinal fluid is believed to reflect an uptake of ASN into Lewy aggregates, and therefore may be able to predict the onset of clinical features associated with Lewy pathology prior to motor symptom onset. This is supported by the lower concentration of cerebrospinal fluid ASN in PD patients compared to healthy controls (Lana M. Chahine & Stern, 2017), and is considered a promising potential biomarker of PD's pathological progression (Visanji et al., 2017).

Potential biomarkers like ASN are validated against changes in clinical features assessed using semi-quantitative clinical scales. The most widely used scale, the Unified Parkinson's Disease Rating Scale (UPDRS), is considered the gold standard for assessing PD's clinical features. Originally published in the 1980's, the scale was extensively revised by the Movement Disorder Society (MDS) in 2008 (Goetz et al., 2008). The updated "MDS-UPDRS" consists of a structured interview and motor examination, during which 50 items are scored on a rating scale from 0 ("no symptoms") to 4 ("severe"). Due to its comprehensive nature, compatibility with clinical practice, and clinimetric validation, the MDS-UPDRS has seen widespread use as a measure of disease severity and progression in clinical research (Espay et al., 2017). However, attempts to validate ASN against the MDS-UPDRS have produced inconsistent results, as have other biomarkers (Espay et al., 2017; Kalia & Lang, 2015). Methodological concerns, such as inconsistent assay methods, have been cited as possible explanations (Lana M. Chahine & Stern, 2017). In addition, there is a growing body of evidence implicating amyloid beta (AB) and phosphorylated-tau$_{181}$ (pTau) in PD's neuropathology. For example, amyloid beta plaques and neurofibrillary tangles have been found in the brains of PD patients at levels similar to those seen in Alzheimer's; moreover, their presence predicts a quicker onset of dementia (Irwin et al., 2012; Kalia & Lang, 2015). These neuropathological markers may have a synergistic effect with ASN as they are associated with increased Lewy pathology, and it is hypothesized that subtle differences in their relative concentrations may contribute to the heterogeneity of clinical features in PD (Goldman et al., 2018; Kalia & Lang, 2015; Kang et al., 2013).

Nearly two decades ago, Braak and colleagues (2003) proposed a six-stage neuro-anatomical model for the stereotypical spread of Lewy pathology throughout the peripheral and central nervous systems. Although vigorous debate continues regarding the validity of Braak's staging scheme, it has been found to be consistent with roughly 80% - 90% of neuropathological specimens (Goedert et al., 2013; Hawkes et al., 2010). Additionally, the spread of Lewy pathology predicted by Braak's model correlates with the appearance and progression of PD's symptoms (Peterson & Horak, 2016). Braak Stages I and II are defined by the initial appearance of Lewy pathology in autonomic and sensory systems – notably the olfactory bulb, enteric nervous system, reticular formation, and the nuclei of several Cranial Nerves (CN) including the glossopharyngeal (CN IX) and vagus (CN X) nerves – which comports with the early appearance of autonomic and sensory deficits (e.g. anosmia, sleep disorders, constipation, circadian disruption, etc.) in prodromal PD (Goedert et al., 2013; Jankovic, 2008). The first clinical symptom - in the form of bradykinesia and often accompanied by tremor and rigidity – appear in Braak Stage III, which is defined by the appearance of Lewy pathology in the substantia nigra pars compacta (SNpc) and the basal forebrain. The appearance of bradykinetic motor symptoms is likely due to extensive dopaminergic cell death in the SNpc and the subsequent degeneration of the nigrostriatal pathway (Goedert et al., 2013; Hawkes et al., 2010; Jankovic, 2008; Kalia & Lang, 2015). The resulting depletion of dopamine in the basal ganglia leads to systemic dysfunction in the form of increased inhibitory output to thalamocortical and brainstem motor networks, impairing their ability to recruit and scale descending motor output, and resulting in the

under-recruitment of muscles and decreased force generation and amplitude (Kalia & Lang, 2015; Obeso et al., 2008; Peterson & Horak, 2016).

Postural instability and gait disturbances (PIGD) typically appear in more advanced PD, and have been linked with the appearance of Lewy pathology in the pedunculopontine nucleus (PPN) of the mesencephalic locomotor region in Braak Stages III and IV, and in premotor and then motor cortices in Stages V and VI (Hawkes et al., 2010; Kalia & Lang, 2015). Extensive animal research has established the PPN's role in the initiation and maintenance of gait through the integration of ascending sensory and proprioceptive feed-back and top-down control over spinal central pattern generators (Takakusaki, 2013). This has been supported by evidence in humans using deep brain stimulation (DBS), a common surgical intervention that provides rhythmic stimulation to the basal ganglia, usually via the Subthalamic Nucleus (STN), using an implanted electrode, and which can ameliorate motor symptoms. In studies where the PPN in persons with PD was targeted with DBS - both directly (Stefani et al., 2007) and indirectly via the STN (Weiss et al., 2015) – PIGD decreased. The delayed progression of PIGD symptoms may be due to increased volitional control of locomotion as a compensatory mechanism to circumvent the impaired sub-cor-tical motor networks (Bohnen & Jahn, 2013; Peterson & Horak, 2016). This hypothesis is supported by the vulnerability of gait to dual-task cost and cognitive loading (Kelly et al., 2012), an abnormal increase in cortical activity when performing tasks that normally rely on sub-cortical motor programs (Wu & Hallett, 2005), the impaired ability to sequence motor tasks (such as turning while walking), and the general variability in gait metrics (e.g. step length) in PD compared to controls (Peterson & Horak, 2016).

Neuroanatomical Substrates underlying Clinical Heterogeneity

The heterogeneity of PD's presentation and progression complicates the assessment of the clinical features against which potential biomarkers are validated (Espay et al., 2017). Motor symptoms are evoked through the performance of motor tasks and the degree of impairment is observed by the clinician, who then assigns an ordinal score as defined by the MDS-UPDRS' criteria. However, these task ratings may not account for the differential effects individual clinical features have on task performance. Consider the Gait assessment (MDS-UPDRS, Item 3.10), which requires the patient to walk away from the clinician, turn, and walk back. The MDS-UPDRS instructs the clinician to assess multiple aspects of the patient's gait – e.g. step length, arm swing amplitude, etc. – and to assign a single rating representing the overall severity of impairment. However, walking and turning are complex behaviors that are dependent on multiple neural control systems which are not fully understood, and whose impairment may differentially affect performance on the Gait task (Curtze et al., 2015; S. Lord et al., 2013; Sue Lord et al., 2013; Peterson & Horak, 2016). For example, decreased step length may be caused by decreased force generation attributable to bradykinesia, an increase in double stance time to compensate for general postural instability, cognitive effects such as fear of falling leading to shorter and quicker steps, or some combination of these factors.

There is growing evidence to suggest that these differential impairments result from the dysfunction of distinct motor systems (Nonnekes et al., 2016; Peterson & Horak, 2016). As mentioned above, bradykinesia is likely produced by the depletion of striatal dopamine

resulting in over-inhibition of descending motor output, where-as disruption of the brainstem motor nuclei responsible for gait maintenance is the likely cause of PIGD (Peterson & Horak, 2016). While these systems are by no means isolated from each other – the PPN is extensively connected with both the basal ganglia and the SNpc, for example – their impairment is differentially affected by dopamine replacement therapy (Peterson & Horak, 2016). Levodopa ameliorates bradykinetic symptoms and improves speed and amplitude, where-as PIGD has a variable response: gait speed and asymmetry are generally improved (Galna et al., 2015), while balance and fall risk are insensitive to dopaminergic replacement (Nonnekes et al., 2016; Smulders et al., 2016). Moreover, the integration of wearable sensors and gait analysis systems into walking assessments have revealed that certain discretely measurable properties of gait (e.g. step length) are differentially sensitive to levodopa therapy (Curtze et al., 2015; Nonnekes et al., 2016; Rochester et al., 2017; Smulders et al., 2016). For example, mean step length is significantly greater ON levodopa compared to OFF, where-as the variability of step length is unchanged (Peterson & Horak, 2016). In addition, a factor analysis (S. Lord et al., 2013) identified multiple "domains" of gait properties that closely correlate with each other and are thought to reflect similar aspects of gait performance (e.g. measures of variability). These domains were identified in healthy older adults, replicated in PD (Sue Lord et al., 2013), and were found to have differential responses to levodopa therapy over 18 months (Galna et al., 2015).

These observations may be explained by considering the neuroanatomy of these networks. Levodopa increases the concentration of dopamine in the striatum, reducing inhibitory output from the basal ganglia and thus bradykinetic symptoms (Peterson & Horak,

2016). Unlike the dopaminergic nigrostriatal pathway, the projections of the PPN are predominantly cholinergic and GABA-ergic, which may explain the limited effect levodopa therapy has on postural instability (e.g. variability of step length) despite the PPN's connections to dopaminergic centers (Peterson & Horak, 2016). This is further supported by the therapeutic effect cholinergic agents and cholinesterase inhibitors have on postural instability (Smulders et al., 2016). Together, these data suggest that multiple neural systems underlie the clinical features of PIGD (Peterson & Horak, 2016; Smulders et al., 2016; Zuo et al., 2017).

These systems are differentially affected by PD's neuropathological progression. For example, bradykinetic symptoms appear after the death of approximately 50% of the dopaminergic cells in SNpc (Fearnley & Lees, 1991; Hawkes et al., 2010) and post-mortem pathological studies have identified that approximately 40% of PPN cholinergic cells have died in Hoehn and Yahr stages (H&Y) IV and V (Hepp et al., 2013). This suggests that the SNpc degenerates quicker and may be able to tolerate more cell death than the PPN before bradykinesia and PIGD symptoms manifest. In addition, their impairment is likely mitigated by different compensatory mechanisms, e.g. increased reliance on volitional control of gait (Hawkes et al., 2010; Peterson & Horak, 2016). Together, this evidence suggests that clinical evaluations of PIGD (and possibly other clinical features) may be simultaneously assessing the dysfunction of multiple, differentially impaired motor systems, and thus may be insensitive to their individual impairment and contribution to overall clinical presentation (Espay et al., 2017). This may contribute to the inconsistent findings of biomarker validation studies, which rely on clinical scales like the MDS-UPDRS to define

disease state and severity; small changes in ASN (indicative of Lewy pathology) or in amyloid beta or pTau (which have poorly understood interactions with Lewy pathology) may reflect a change in the severity of some symptoms more than others. In other words, studies attempting to validate a potential biomarker by its correlation with a clinical feature may instead be measuring its correlation with the sum of a wide range of impairments (Espay et al., 2017), each with an unknown severity and, due to their distinct neuropathological substrates, a different relationship to the biomarker.

Objective Measures of Task Performance

Certain properties of task performance may reflect discrete impairments that are sensitive to a single neural control system (Curtze et al., 2015; Horak & Mancini, 2013; Peterson & Horak, 2016; Smulders et al., 2016). As a result, objective measures of task performance are increasingly applied in conjunction with clinical evaluation to improve the precision and sensitivity with which we can monitor disease state in scientific research (Espay et al., 2017; Horak & Mancini, 2013). Body-mounted accelerometers are well positioned to objectively measure these sub-components (Espay et al., 2016; Horak & Mancini, 2013). These "wearable sensors" are capable of continuously recording actigraphy throughout a patient's daily life, often producing data with a temporal resolution < 10 milliseconds, and have been integrated into a wide variety of standard posture and gait tasks over the last decade, such as the instrumented Timed Up-and-Go (iTUG) (Podsiadlo & Richardson, 1991; Salarian et al., 2010; Zampieri et al., 2010), instrumented Timed Walk (iTW) (Horak and Mancini, 2013), and instrumented Postural Sway (iPS) (Dewey et al., 2014). However,

the methodological challenges of wearable accelerometers remain a significant obstacle to their translation into routine clinical practice (Espay et al., 2016; Horak & Mancini, 2013). Specifically, their high resolution and sensitivity leaves them susceptible to noisy interference, complicated and time-consuming analytical techniques are required to derive clinically meaningful endpoints from the large amounts of data they produce, and the lack of standardized methods for their construction, application, and interpretation has created isolated "islands of expertise" that struggle to integrate their different methods (Lana M. Chahine & Stern, 2017; Espay et al., 2016, 2017; Horak & Mancini, 2013; Rabuffetti et al., 2011). These challenges are amplified in the MDS-UPDRS, as the scale's semi-standardized motor tasks (i.e. compared to the iTUG) introduce significant noise into the signal, and its loosely structured format (e.g. patient interview, passive assessments, etc.) further complicates interpretation and crosswalk between studies.

If sensor-derived endpoints and potential biomarkers are indeed sensitive to discrete impairments beyond the resolution of the MDS-UPDRS, and if the MDS-UPDRS is the gold standard means of determining the clinical validity of these impairments, then how should these promising endpoints be validated? This problem has been approached in three main ways. The first approach, a macroscopic "paradigm shift" where-by biomarkers are used as the new gold standard for defining clinical features, was proposed by Espay and colleagues (2017). A second approach is to "cut out the middleman" and relate sensor-derived endpoints directly to the potential biomarkers; e.g. Rochester and colleagues (2017) directly compared changes in levodopa-resistant gait properties to changes in the

cerebrospinal fluid concentration of ASN, AB, and pTau over three years. The third approach argues that sensors integrated directly into the MDS-UPDRS itself may be able to provide objective measures of task performance in parallel with clinical ratings, but this approach has only seen scant exploratory work (Criss & McNames, 2011).

Sleep and Circadian Disruption

Although PD's hallmark motor symptoms are its most conspicuous and studied feature, there are numerous non-motor symptoms (NMS) that manifest throughout the course of the disease (Fifel & Videnovic, 2019). In fact, NMS such as anosmia, autonomic dysfunction, and constipation appear up to 10 years before the onset of motor symptoms and progressively worsen over time (Jankovic, 2008). Two NMS - sleep disruption and circadian disruption - are closely interconnected and of particular interest to this manuscript.

As a systemic disease that affects the entire nervous system, it is no surprise that the circadian rhythm is impacted in PD. Generally speaking, circadian rhythms in persons with PD are more fragmented, lower amplitude, and more resistant to entrainability, and often have altered phases relative to the light-dark cycle. This "dampening" is perhaps most visible in the diminished amplitude of daily rest-activity rhythms (RARs) caused by disrupted sleep and restricted movement due to motor symptoms and fatigue. Similar dampening has been observed in numerous circadian biomarkers (Videnovic, Lazar, et al., 2014), including melatonin secretion (Videnovic, Noble, et al., 2014), CLOCK gene expression (Breen et al., 2014; Cai et al., 2010), retinal dopamine (Wirz-Justice et al., 1984), cortisol secretion (Hartmann, 1997), visual acuity (Struck et al., 1990), and body temperature (K.

Suzuki et al., 2007). Other circadian biomarkers undergo pronounced phase shifts; e.g. a phase reversal of the diurnal blood pressure rhythm (Kallio et al., 2000; Senard et al., 1992). Circadian rhythms have also been observed in PD's symptomology: motor symptoms are most responsive to dopaminergic medication early in the morning (Bonuccelli et al., 2000) and most severe late in the day (Piccini et al., 1991). Intriguingly, chronotherapeutic interventions using light exposure at specific times of day has reduced both motor and non-motor symptoms, including sleep disruption (Videnovic, Lazar, et al., 2014).

CHAPTER TWO: METHODS

Introduction

This chapter will review the historical background, theoretical basis, scientific context, and practical application of the various methods used in subsequent chapters, which include subjective assessments, quantitative scales, qualitative questionnaires, and objective sensors, among others. While each method was developed and optimized for a specific purpose (and are thus individually discussed herein), they are rarely used in isolation. As navigators use multiple reference points to triangulate a location, multiple methods can be synergistically integrated to better understand, characterize, and "triangulate" the true nature of a variable of interest.

Actigraphy

Wearable accelerometers[17] allow for the continuous, longitudinal, and objective monitoring of physical activity; i.e. actigraphy. The applications of actigraphy are diverse (Meyer-Rochow & Brown, 1998), but in humans it is primarily used to quantify rest-activity rhythms (RARs), characterize sleep, assess motor impairment, and infer metabolic activity via physical movement (Ancoli-Israel et al., 2015). Actigraphy has been in use for over half a century (Ancoli-Israel et al., 2015; J. L. Martin & Hakim, 2011; Tryon, 2013) and the first battery-powered wrist-worn actigraphy device was developed nearly four decades

[17] Also referred to as Inertial Measurement Units (IMU), actigraphs, wearable sensors, and on-body accelerometers. "Accelerometer", "actigraph", and "sensor" are often used interchangeably, as are "on-body" and "wearable".

ago (Aubert-Tulkens et al., 1987), though technological developments and sensor miniaturization have greatly increased the quality of actigraphic data through higher accelerometer resolution, greater memory capacity, reduced weight, and increased battery life. As with consumer health monitoring devices (e.g. the FitBit), this has fostered the proliferation of commercially available actigraphy devices and, likewise, research studies employing them. Most actigraphy devices are wrist-worn - most often intended for the non-dominant wrist - though others are designed to be worn around the ankle or strapped to the torso (Ancoli-Israel et al., 2015).

Actigraphy has been applied to the clinical evaluation and monitoring of sleep and circadian disorders, such as shift work disorder and insomnia (Ancoli-Israel et al., 2015; Fekedulegn et al., 2020; Morgenthaler et al., 2007; M. T. Smith et al., 2018). It is considered a useful supplement to standard sleep assessment methods (e.g. sleep diaries and polysomnography [PSG]) and is included in the International Circadian and Sleep Disorder, Third Edition (ICSD-3) diagnostic criteria for several sleep disorders (Ibáñez et al., 2018; Sateia, 2014). In clinical trials of movement disorders such as Parkinson's disease (PD), actigraphy improves the accuracy of clinical endpoints quantifying motor and non-motor symptoms and thus has the capacity to hasten the evaluation of critically needed symptom- and disease-modifying interventions (Merola et al., 2018). Despite growing support from medical directors in industry, actigraphy was included in less than 3% of clinical trials as of 2018 (Artusi et al., 2018).

Actigraphy is quantitative, applicable in a wide variety of populations and environments, produces large amounts of data, and minimizes human error and bias by directly

measuring a physical signal (i.e. movement/acceleration), but also has notable drawbacks: the large data-sets it produces can be logistically challenging to store and manage, the raw data itself requires significant processing to produce useful endpoints, actigraphy infers complex behaviors such as sleep through measures of movement, and there is no standardized method for collecting, processing, or analyzing the data, creating "islands of expertise" (Espay et al., 2016) that hinder replicability and complicate meta-analysis (Ancoli-Israel et al., 2015; Chow et al., 2016; Goldstone et al., 2018; Ibáñez et al., 2018; M. T. Smith et al., 2018). These drawbacks can be mitigated through synergistic use of other methods; for example, sleep diaries provide subjective sleep information that can be cross-referenced with actigraphic estimates to detect sleep detection errors (Schwartz, 2012), and gyroscopes embedded in actigraphy devices allows the sensor's orientation to be easily determined, greatly simplifying analysis (van Hees et al., 2013). Ultimately, actigraphy's accessibility, reduced cost, and ability to continuously monitor behavior in naturalistic environments (e.g. in-home) makes it easily scalable and an appealing option for studies with large sample sizes, long monitoring periods, and/or a desire in capturing ecologically valid data (Andrade, 2018; Fekedulegn et al., 2020). However, there is a strong need for methodological transparency and harmonization, and a growing acknowledgment that future scientific reports should provide detailed technical, scoring, and analytical information to facilitate replication, iterative research, and meta-analysis (M. T. Smith et al., 2018).

Data Quality and Pre-Processing

Before they can record data, actigraphy devices must be configured according to the scientific and/or clinical specifications of their application. Generally, this entails defining a sampling rate for recording accelerometry, a duration of recording, which sensors to record from (e.g. gyroscope, accelerometer, light sensor), and a recording period[18]. The intended location for the device to be worn on the body should also carefully considered, both to maintain consistency with previous studies and to preserve data integrity; i.e. the location should not irritate the subject to avoid unintentionally encouraging noncompliance, and should minimize the effect of confounding movement (e.g. lateralized resting tremor in PD) (Maglione et al., 2013). The intended use of the actigraphy device (i.e. period to be worn, location, etc.) and instructions on how to care for it (e.g. charging, remove when swimming, etc.) should be clearly conveyed to the subject to maximize compliance (Ancoli-Israel et al., 2015). Last, but certainly not least, the processing and analysis of actigraphy should follow a consistent and predetermined protocol that includes criteria for data filtering, artifact identification, statistical analysis, and other study-specific requirements such as sleep detection algorithms and missing data tolerance for RAR modelling and physical activity computations (J. L. Martin & Hakim, 2011).

Actigraphy produces large data-sets that must be exported, cleaned, filtered, condensed, and visualized using computer software. This processing is often handled by proprietary software bundled with actigraphy devices (e.g. Philips ActiWare), though this can

[18] By default devices will begin recording as soon as configuration is finished, though some actigraphy devices, such as the GeneActiv, allow a predetermined recording time to be selected during configuration

also be done using publicly available scripts (e.g. GGIR). Processing begins when the recorded data is exported off the used device; depending on the device used, the exported data may consist of raw accelerometry or endpoints derived using a proprietary algorithm (e.g. activity counts). Actigraphy devices with an onboard clock will usually provide timestamps for the data; otherwise, timestamps will have to be manually derived from the recording start time. If there are any other data-sets of interest that were collected in parallel (e.g. a second actigraphy device, concomitant PSG recording, etc.), these should be synchronized once all data is properly timestamped. Temporal drift is a ubiquitous temporal confound that must be accounted for during synchronization, especially in multimodal data[19]. Although the rate of drift is often quite small, it can accumulate to a considerable magnitude in longitudinal studies with long recording periods. This drift can be accounted for in synchronization using common references at the beginning and end of a recording; this can be as simple as noting the times when the recording(s) began and ended, or involve more complex strategies such as having the device(s) record a known acceleration signal (e.g. shaking for 10 seconds) at known times throughout the recording[20]. Regardless, once the

[19] It is possible to avoid drift by continually synchronizing the device's clock to an absolute reference, such as Network Time Protocol (NTP) servers, though this consumes extra power and is not feasible in most monitoring studies

[20] As internal clocks can be affected by environmental conditions such as temperature and mechanical stress, the rate of drift can also vary over time within the same device; i.e. inter-sample latency is not constant. Therefore adjusting all timestamps to match the true duration would correct for the cumulative net drift, but individual samples may still have incorrect timestamps due to acute variability in drift rate. By using multiple known signals scattered throughout the recording at known times, the drift rate can be more precisely resolved; however, this introduces obvious methodological and logistical challenges, so researchers must weigh the increased temporal resolution of more frequent synchronizing signals with the burden of generating these signals

true duration of recording is known its internal timestamps can be corrected and allow the accelerometry to be aligned with other data.

Invalid data should be identified and judiciously removed (Ancoli-Israel et al., 2015). This includes "off-body time" when the sensor was not being worn by the subject, abnormal data indicative of device malfunction or that contradicts parallel measures (e.g. persistently high night-time activity during the sleep period recorded on a sleep diary), and confounds and artifacts (Ancoli-Israel et al., 2015; Evenson & Terry, 2009; Fekedulegn et al., 2020). Times when the device can be confirmed to be off-body - such as the beginning/ending of a recording before/after the subject has donned/removed the device - are easily removed, but inferring potential off-body times without a ground truth reference is considerably more difficult. Off-body time can be visually identified by plotting the data and looking for the absence of movement; i.e. a "flatlined" signal means the device is perfectly still and thus almost certainly not on the subject. Actigraphy logs, where-in subjects record when and why they removed actigraphy devices (among other contextual information), can also help identify off-body times; some devices also have a binary "marker" button that can be pressed to indicate specific events, such as donning or removing a device. Although there are algorithms for automatically detecting off-body time, these should be considered in addition to - not in place of - manual review (Ancoli-Israel et al., 2015). Differentiating "abnormal" accelerometry from normal data is much more ambiguous; without a ground truth confirmation of the subject's actual behavior, such as via a video recording, it can be difficult to determine whether the fault lies with the actigraphy device or elsewhere - and thus whether the data should be expunged or retained. For example,

high activity during a time the subject indicated they were asleep could be attributable to an erroneous sleep diary entry, restlessness during sleep the subject failed to notice or report, or device failure. In such situations, it is useful to determine if the device is still malfunctioning and if the error can be recreated, which might indicate the data should be expunged. Artifacts and confounding signals can also be ambiguous, both in their identification and in defining what signals should be considered artifacts. However, very consistent signals such as footsteps (Czech & Patel, 2019) can be identified using feature detection algorithms *a la* eyeblink artifact filtering in PSG, and detailed annotation of involuntary activity such as a parent recording when they were rocking their child to sleep in child actigraphy studies (Ancoli-Israel et al., 2015). Missing data is, nonetheless, common in actigraphy due to subject noncompliance and the aforementioned data quality issues (Fuster-García et al., 2013).

Epoching and Epoch-Level Endpoints

Raw accelerometry is rarely directly used in analysis, but is instead condensed into epochs ranging from seconds to minutes in length (Ancoli-Israel et al., 2015), a process colloquially referred to as “data condensation”, “epoching”, or “binning”. This may be done automatically by the device or its accompanying software, by using freeware scripts, or manually via spreadsheet software. Epoching greatly simplifies analysis by reducing the overall volume of data and condensing the raw high-frequency tri-axial accelerometry into epoch-level summary statistics; e.g. a 1-minute 100 Hertz (Hz) recording would contain 60 seconds * 100 samples/second * 3 axes = 18,000 individual data, and epoching reduces this

to a single variable representing the entire minute of recording. This aids statistical analysis by reducing the dimensions of the time-series data and binning key features (e.g. overall activity) into discrete spans of time; this latter aspect also facilitates categorical analysis, such as determining whether an epoch should be classified as asleep or awake. Epochs were borne of necessity due to technological limitations in data storage and epoch lengths of 1-hour were used in the 1990's (van Someren et al., 1996); as the resolution and capacity of wearable accelerometers continues to improve, epoching lengths have become more flexible and capable of shorter durations.

Currently, epoch lengths are usually measured in seconds and are cleanly divisible into a minute; e.g. 60-second, 30-second, 15-second, and 1-second epochs. As is often the case in science , selecting epoch length requires determining the optimal trade-off of benefits and drawbacks . Longer epochs reduce data volume, ease processing, and emphasize long-duration trends in the data (e.g. diurnal RAR), but lose most information related to events shorter than itself (e.g. a 3-second sneezing fit may account for most of the recorded activity in a 60-second epoch). However, this coarse resolution "smooths out" and reduces the confounding effects that random noise and irrelevant transient signals have on gross actigraphy data. Shorter epochs have higher temporal resolution and so can more easily capture briefer signals, distinguish temporally proximal events, and more accurately detect sleep (Ancoli-Israel et al., 2015), but this comes at the cost of increased data volume and thus more processing, as well as greater sensitivity to noise. If the goal is to assess large-scale trends (e.g. diurnal RAR) or if a dataset is particularly large, then the costs of using shorter epochs may outweigh the benefits. Likewise, studies interested in discrete, brief,

and/or high-frequency behaviors (e.g. postural transitions, tremor) would benefit from the increased resolution of shorter epochs.

The activity content of a given epoch can be summarized using a variety of end-points, both proprietary and public. An example of the former are Activity Counts (AC), which are automatically computed by Actiware software using a private algorithm when exporting accelerometry data from an Actiwatch. However, one can infer the principles of this algorithm by considering how other devices, such as the Motionlogger Sleep Watch (Ambulatory Monitoring, Incorporated, NY), collect and process their raw signals (Fekedulegn et al., 2020). Each axial accelerometer[21] continually produces a voltage via an analog transducer that changes in response to movement and which is sampled at the device's sampling frequency; these measured voltage data from the transducer are then processed in one of three ways to produce epoch-level endpoints. Zero Crossing Mode (ZCM) defines some reference voltage (usually near 0) and outputs the number of times the measured voltage crosses the predetermined reference threshold; ZCM is often interpreted as measuring the frequency of movement. Time Above Threshold (TAT) is similar in that it also defines a reference threshold, but instead of yielding how many times it was crossed by the transducer's measured voltage, it outputs the duration of time the measured voltage was higher than the reference; TAT is therefore interpreted as the duration of movement. Proportional Integration Mode (PIM) quantifies the area-under-the-curve of the measured voltage; because it integrates both duration and amplitude, PIM is interpreted as the inten-

[21] Also referred to as an Inertial Measurement Unit (IMU)

sity of movement (Fekedulegn et al., 2020). Of these, ZCM is likely the basis for Actiwatch's AC algorithm because its high accuracy of sleep detection has made it the most commonly used method in sleep research (Fekedulegn et al., 2020); however, it is susceptible to inflation from high-frequency artifacts (e.g. rapid vibration) and is the least sensitive to movement amplitude (Ancoli-Israel et al., 2003). Moreover, the AC produced by ZCM, TAT, and PIM algorithms significantly diverge from each other even when applied to the same data; in combination with the tendency for studies to omit the algorithm they used and report actigraphy as just AC, this creates confusion and undermines the validity of between-study comparisons (Ancoli-Israel et al., 2003). Fortunately, there are publicly available methods that compute epoch-level endpoints directly from raw accelerometry using simple vector equations[22]. Vector Magnitude (VM) is the square root of the summed squares of the x-, y-, and z-axis voltages in a given sample: $VM = sqrt(x^2 + y^2 + z^2)$. VM thus represents the magnitude of acceleration. The VM is usually calculated sample-by-sample, then either summed or averaged across an epoch.

One significant drawback of all methods described so far is their inability to account for the constant acceleration of earth's gravity (Bakrania et al., 2016). Since the three axial accelerometers are at fixed, orthogonal orientations to each other, the directions of their vectors are known and their magnitudes easily integrated into VM using the above mentioned equation. However, the direction of the gravitational vector with respect to the accelerometer can change without restraint by simply reorienting the device. Accelerometers

[22] Some devices, such as the Actiwatch, only allow for proprietary algorithms; the raw accelerometry cannot be directly accessed, only the outputs of the proprietary algorithm

with built-in gyroscopes can easily monitor the device's orientation; this information can be used to calculate the gravitational vector's direction for each sample, and allowing it's magnitude to be removed from the VM. without a gyroscope, the crudest method of accounting for gravity is to uniformly subtract the standard acceleration due to gravity (g; i.e. 9.8 meters/second^2) from the VM; negative values are imputed as 0 since a vector cannot have a negative magnitude. This converts VM into an endpoint called Euclidean Norm Minus One (ENMO) which can similarly be summed or averaged across an epoch. Another derivation of VM is Mean Amplitude Deviation (MAD), which is calculated by subtracting each VM in a given epoch from the average of VMs for all *i* samples in that epoch, summing the differences, and multiplying the sum by the inverse of the number of samples (n) in the epoch (Bakrania et al., 2016): $MAD = (1 / n) * \Sigma(VM_i + (\Sigma(VM_i) / n))$.

Sleep Scoring Algorithms in Actigraphy

Regardless of the epoch-level endpoint used, a time-series of actigraphy epochs can be algorithmically segmented into different behavioral periods via analysis of activity levels. At the most basic level, *sleep scoring algorithms* - also known as (AKA) *sleep scoring functions* - dichotomously categorize epochs as either *asleep* or *awake* (Fekedulegn et al., 2020). Although existing sleep scoring algorithms are tailored to the specific actigraph used, activity endpoints generated (e.g. ZCM), the selected epoch length, and – to a lesser extent – the age and clinical status of the subject, most work off the same general principles with relatively minor variations (Ancoli-Israel et al., 2015; Fekedulegn et al., 2020). Generally, sleep scoring algorithms calculate a moving average (or sum) of activity levels,

which includes the current epoch and those immediately preceding and following it, by multiplying each epoch's activity level by a unique constant or "weight". These weighted activity levels are then either averaged or summed, depending on the specific algorithm, and are sometimes further scaled by some constant. Other descriptive statistics derived from epoch-level activity levels (e.g. variance) may be incorporated in some sleep scoring algorithms. Regardless, the final output of a sleep scoring algorithm for a given epoch - i.e. its *sleep score* - is then compared against some predetermined threshold - i.e. the *wake threshold value* - representing the theoretical upper limit of activity observable during sleep. If the sleep score exceeds the wake threshold value, then the activity level is considered too high for sleep and the epoch is scored as *awake*; otherwise it is scored as *asleep* (Fekedulegn et al., 2020). Note that "invalid" epochs determined to have missing data or some other issue preclusive to analysis are typically removed prior to application of a sleep scoring algorithm.

While there are several sleep scoring algorithms currently in use, the most relevant to this manuscript is the Actiware sleep scoring algorithm for 1-minute epochs (Fekedulegn et al., 2020; Mini Mitter Company, Inc., 2006). As described above, the Actiware algorithm samples a moving average, weighting the activity levels of individual epochs based on their temporal position relative to the current epoch being scored. The specific formula is:

$$T = (w_{-2} * A_{-2}) + (w_{-1} * A_{-1}) + (w_{0} * A_{0}) + (w_{+1} * A_{+1}) + (w_{+2} * A_{+2})$$

...where T is the *sleep score* being calculated, w is the weight for a given epoch, and A is the AC for a given epoch, with the subscripts defining the epochs based on their position relative to the current epoch being scored (e.g. w_{-2} refers to the epoch that came two epochs before the current epoch being scored) (Fekedulegn et al., 2020). The wake threshold value for determining sleep has three default settings provided in Actiware - low = 20, medium = 40, and high = 80 - though the specific number can be set by the user. The Actiware algorithm has been found to have comparable sensitivity and specificity in comparison to other algorithms (Benson et al., 2004; Meltzer et al., 2012; Tonetti et al., 2008), such as the Cole-Kripke algorithm (Cole et al., 1992), though another study comparing these two algorithms concluded that the Cole-Kripke had "nominally better agreement with PSG" (Rupp & Balkin, 2011). Note that these studies were principally concerned with comparing the Actiwatch to other actigraphs; since the Actiwatch's data can only be processed through the proprietary Actiware algorithm, this resulted in an indirect comparison of the Actiware algorithm to whichever publicly available sleep scoring algorithm was used to analyze data from the other actigraph.

There are several publicly available algorithms in use today; amongst the most popular are the Cole-Kripke algorithm (Cole et al., 1992), the University of California San Diego (UCSD) algorithm (Jean-Louis et al., 2001), and the Sadeh algorithm (Fekedulegn et al., 2020; Sadeh et al., 1994). Briefly, the Cole-Kripke and UCSD algorithms[23] use the

[23] Although developed and evaluated separately, the Cole-Kripke and UCSD algorithms are nearly identical except for the specific weights they use.

same basic “moving average” strategy as the Actiware algorithm, with three major differences. First, both algorithms are explicitly designed for ZCM epoch data - although Actiware’s AC are likely calculated with ZCM, the specifics of their ZCM algorithm are proprietary and thus cannot be generalized to other ZCM data as easily as the Cole-Kripke and UCSD algorithms can be. In addition, the UCSD algorithm is the only one of the four algorithms to be compatible with PIM and TAT epoch data. Second, both the Cole-Kripke and UCSD algorithms use a broader window than the Actiware algorithm, including the “-3” and “-4” epochs when calculating *sleep score*. Third, both algorithms scale the sliding average/sum by the multiplicative constant *P* to derive the *sleep score*, where-as the Actiware algorithm simply uses the raw sliding average/sum (Cole et al., 1992; Fekedulegn et al., 2020; Jean-Louis et al., 2001). The Sadeh algorithm is distinct in that it simplifies the sliding window calculation by using a uniform weight for all epochs, expands the sliding window to 11 epochs (compared to Actiware’s five epoch and UCSD and Cole-Kripke’s seven epoch windows), and integrates three additional measures: the standard deviation of the first six epochs (including the current epoch being scored), the number of epochs in the sliding window whose activity levels fall within a moderate activity range, and the natural log of the activity level of the current epoch being scored. All of these measures are subtracted from a constant positive value, and a given epoch is scored as *asleep* if the difference is ≥ 0 (Fekedulegn et al., 2020; Sadeh et al., 1994). All three algorithms have been shown to have high sensitivity and moderate specificity for the correct identification of sleep epochs as determined by gold standard PSG (de Souza et al., 2003; Fekedulegn et al.,

2020; Haghayegh et al., 2019; Quante et al., 2018)[24]. However, all three have reduced sensitivity for correctly detecting wake epochs and thus tend to overestimate the amount of sleep, although this is not as severe in the Sadeh algorithm and can be reduced through structured *post-hoc* rescoring of the dichotomized *asleep/awake* epochs (Webster et al., 1982).

Algorithmic Derivation of Sleep Characteristics from Actigraphy

Once a sleep period is segmented into *asleep* and *wake* epochs, a number of *sleep characteristics* can be calculated that reflect distinct dimensions of sleep behavior (Berger et al., 2005; Fekedulegn et al., 2020)[25]. This begins by defining the *Sleep Period* (SP); i.e. the difference in units of time between the *Sleep Onset* (SON) and *Sleep Offset* (SOFF) times. Actiware defines SON/SOFF as the first/last epoch of the first/last series of n consecutive epochs scored *asleep*, with n being a customizable number known as the *immobile minutes value* (by default, $n = 10$). Alternatively, Actiware can determine SON/SOFF using a *mobility threshold*, which categorizes an epoch as *mobile* if its AC $\geq m$ or as *immobile* if its AC is $< m$, where m is the predetermined mobility threshold (by default, $m = 4$). These dichotomized epochs are then analyzed in the same way as the sleep scoring method: i.e. SON/SOFF is defined as the first/last epoch of the first/last series of n consecutive epochs scored immobile (Fekedulegn et al., 2020; Mini Mitter Company, Inc., 2006). *Sleep Onset*

[24] The similarities between the Actiware algorithm principally used in this manuscript and the publicly available Cole-Kripke and UCSD algorithms allow us to tentatively extrapolate these findings to our interpretation of the Actiware algorithm

[25] Unless otherwise stated, the definitions presented here are for the Actiwatch and Actiware sleep segmentation algorithm

Latency (SONL) and *Sleep Offset Latency* (SOFFL) represent the time it took for the individual to fall asleep after going to bed and the time it took them to get out of bed after waking up, respectively. While it is technically defined as the time elapsed between when the individual reported going to bed (either through a sleep diary or by pressing their actigraph's marker button) and the first epoch scored as *sleep*, Actiware can automatically calculate SONL via the number of immobile, awake epochs flanking the SP. By adding SONL and SOFFL to SP, the *Time in Bed* (TiB) can be calculated; i.e. $TiB = SONL + SP + SOFFL$, where $SP = SOFF - SON$ (Fekedulegn et al., 2020; Mini Mitter Company, Inc., 2006). TiB can also be expressed as the sum of *Total Sleep Time* (TST) and *Wake After Sleep Onset* (WASO), themselves defined as the cumulative duration of all sleep epochs and all wake epochs, respectively. This allows *Sleep Efficiency* (SE), a general measure of sleep quality (Berger et al., 2005), to be calculated thusly: $SE = TST / TiB$ or, written differently, $SE = TST / (SONL + (SOFF - SON) + SOFFL)$. *Percent Sleep Time* (PST) is a similar – and often conflated (Fekedulegn et al., 2020) – measure calculated thusly: $PST = TST / SP$. In other words, PST is SE without the inclusion of SOFFL and SONL (Mini Mitter Company, Inc., 2006).

Numerous other sleep characteristics can be derived via simple arithmetic: the number of *awake bouts* and *sleep bouts*, their average duration, their variance in duration, and maximum/minimum durations observed in a night, activity levels, including peak activity and average activity throughout the night, during wake, and during sleep, as well as absolute time, percent time, and number of epochs spent above and below the predetermined

mobility threshold (Fekedulegn et al., 2020; Mini Mitter Company, Inc., 2006). This enables the calculation of *Fragmentation Index* (FI), a measure of how likely a person is to transition between sleep and wake periods throughout the night (Fekedulegn et al., 2020; Natale et al., 2009), which can be derived thusly: *FI = ([number of mobile bouts] + [number of immobile bouts ≤ 1 minute]) / [number of immobile bouts]* (Mini Mitter Company, Inc., 2006). However, FI has been calculated differently; e.g. *FI = [number of wake bouts] / TST* (Fekedulegn et al., 2020). This serves as a reminder that many of the sleep characteristics reported in the literature – especially those reported without an accompanying equation – were produced using unknown or unverified equations due to insufficient methodological reporting (M. T. Smith et al., 2018).

Cosinor Models

Three-Parameter "Basic" Cosinor Model

When analyzing time-series data to identify and/or quantify a rhythmic feature, it is helpful to fit the data to an oscillating regression model from which the rhythm's parameters and estimates of its statistical significance can be derived (Cornelissen, 2014). The three-parameter "basic" cosinor is amongst the simplest such models[26]. The term *cosinor* was coined by Halberg and colleagues (1965) as a derivation of the term *sinor*, which refers to the vectorial plots used to modelling rhythmicity in voltages and currents (LePage, 1949),

[26] This is often referred to as simply the "cosinor model" or just "cosinor"; the terms "basic cosinor" and "three-parameter cosinor" appear but are not extant in the literature. They are used in this manuscript for clarity to distinguish between the basic three-parameter cosinor and the extended five-parameter cosinor models.

due to the similarities in applying rhythmic functions to model and visualize oscillations in time-series data. Since then, the basic cosinor has become a common tool employed by chronobiologists for the quantification of biological rhythms, especially the circadian rhythm (Cornelissen, 2014)[27]. Any rhythmic signal with a constant period can be modelled using the basic cosinor, but the most common signals are homeostatic (e.g. temperature), hormonal (e.g. cortisol), physiological (e.g. heart rate), and behavioral (e.g. physical activity) measures that exhibit a circadian rhythm. Cosinor models are usually fit to data with a duration ≥ 2 * period, providing an averaged model that "smooths out" the expected normal inter-daily variance; this is analogous to the application of signal averaging to produce evoked potentials in electroencephalography. Uniperiodic cosinors are also used.

The basic cosinor is a parametric function that assumes a normal distribution of data, and is most often fit using linear least squares regression (Cornelissen, 2014; Neikrug et al., 2020). The core formula of the basic cosinor model is:

$$Y(X) = MESOR + (Amplitude * cosine((X * 2 * \pi) + Acrophase)) + e(X)$$

...where *Y* is the measured signal being modeled, *X* is the time associated with the time-series data, *cosine* is the trigonometric cosine function, and e(X) is the error term. In addition, there are three fundamental parameters that are defined in a basic cosinor model: the *Midline Estimating Statistic of Rhythm* (*MESOR*) is the average value of *Y* across the time-

[27] Interestingly, the basic cosinor was first applied to model circaseptan rhythms in 17-ketosteroid secretion (Franz Halberg et al., 1965).

series, the *Amplitude* (Amp) is the difference between the maximum value of *Y* and the *MESOR*, and *Acrophase* (*Acro*, AKA *Phi* or *Φ*) is the temporal offset (i.e. phase-shift) of the model relative to some constant arbitrary reference (e.g. midnight). As the parameter's values are selected by fitting the model to data through regression (e.g. ordinary least squares), an R^2 value[28] representing model fit can be calculated. A higher *MESOR* indicates a higher average activity across the day and night, a higher *Amp* indicates a higher maximum activity and "more rhythmic changes", a later *Acro* indicates a later period of "peak activity" in the model and can reflect a shift in the model's temporal phase, and R^2 is a conventional statistical endpoint where higher values indicate a better (more accurate) model fit. In the context of rhythmometric analysis, higher R^2 values are often interpreted to reflect a more robust circadian rhythm - i.e. one that exhibits consistent high amplitude sinusoidal oscillations (Neikrug et al., 2020). Cosinors are usually reported by presenting it's best-fit parameters, often accompanied by a graphical representation of the model overlaid on a plot of *Y* by *X*.

The basic cosinors simplicity is both its greatest strength and its greatest weakness. Requiring only three parameters (*MESOR*, *Amp*, and *Acro*), it is not computationally intensive to fit and the details of its pre-processing and application can be easily reported and replicated. This also allows the basic cosinor to be run on a wide variety of scripting languages (e.g. R, Python), analysis programs (e.g. MATLAB, PRISM), dedicated circadian analysis toolkits, and other software. Cosinors also do not require equidistant data and can

[28] Occasionally referred to as the "Circadian Rhythmicity Index" (Grierson et al., 2016; Robillard et al., 2016)

tolerate missing data, giving it great flexibility especially in situations where the data can only be measured sporadically (e.g. salivary melatonin). However, the basic cosinors simplicity entails several restrictive assumptions, most notably that the oscillating signal exhibits a continuous, symmetrical, and sinusoidal "rise" and "fall" in amplitude with equidistant peaks/nadirs that remains constant over multiple periods. However, biological rhythms are rarely symmetrical and are frequently characterized by non-sinusoidal patterns (Marler et al., 2006; J. Martin et al., 2000; Refinetti et al., 2007; Smagula, Boudreau, et al., 2015). For example, the basic cosinor is often applied to model human Rest-Activity Rhythms (RARs) using actigraphic data collected via wearable sensors. While human RARs are strongly rhythmic and possess readily distinguishable "high" and "low" activity periods, they are not sinusoidal: activity is low to nonexistent during sleep, then rapidly increases upon waking and "plateaus" for most of the waking day with intermittent periods of higher- and lower-than-average activity (e.g. exercising and napping, respectively), before rapidly decreasing with sleep onset (Dowling et al., 2005). Human RAR's are also not symmetrical, as demonstrated by the fact that we only spend ~33% of the day in low-activity torpor and sleep. Put simply, human RAR's resemble "square waves" more-so than the inflexible symmetrical sinusoid assumed by the basic cosinor model; this causes it to over- or under-estimate activity levels for most of the day, especially during sleep/wake transitions when the most rapid changes in activity level occur. Many signals (e.g. actigraphy) are also not normally distributed; e.g. actigraphy is usually heavily skewed due to

infrequent and brief moments of very high activity[29]. Lastly, the basic cosinor has been criticized for its poor model fit; one exemplar study found that their basic cosinor model accounted for less than a quarter of the observed variance in actigraphy data (Neikrug et al., 2020; Satlin et al., 1995). This contributes to the difficulty in translating basic cosinor models into clinical applications.

Five-Parameter "Extended" Cosinor Model

The extended cosinor is an expansion of the basic cosinor model (Franz Halberg et al., 1965) developed to more accurately model the waveform of human RARs in actigraphy data (Marler et al., 2006; J. Martin et al., 2000). The first use of the so-called "extended cosine function" was in 2000 (J. Martin et al., 2000), and the model was later expanded in 2006 (Marler et al., 2006)[30]. As with the basic cosinor, the extended cosinor is used to model rhythmic signals in time-series data by fitting them to a cosine function; unlike the basic cosinor, the extended cosinor uses non-linear least squares regression and therefore requires initial starting values (Marler et al., 2006). Moreover, the extended cosinor includes two additional parameters (*Alpha* and *Beta*) that modulate the waveform to better fit the data, and which are incorporated into the model via a "sigmoidal transformation" of the data[31]. The original authors proposed three versions of the extended cosinor, each using

[29] This can be partially corrected for using log transformations and/or by reducing excessively high activity data to a uniform maximum threshold using a "high-pass filter"

[30] Except where stated otherwise, Marler et al.'s (2006) terminology is used to describe components of the extended cosinor in this manuscript.

[31] The original paper that introduced the extended cosinor referred to it as the "sigmoidally transformed cosinor" for this reason (Marler et al., 2006)

a different sigmoidal transformation: the Hill function, the anti-logistic function, and the arctangent transform (Marler et al., 2006). The authors also noted that no function can perfectly recreate a model generated by a different function, but clarified that these inevitable qualitative differences between sigmoid functions may be negligible. While most articles employing extended cosinors do not state which sigmoidal transformation they used (Grierson et al., 2016; Reimúndez et al., 2018; Robillard et al., 2014, 2016; Rodriguez-Zas et al., 2012; Spira et al., 2015; Walsh et al., 2014), the anti-logistic function is the most common amongst those that do provide this information (Davoudi et al., 2018; Paudel et al., 2010; Smagula, Ancoli-Israel, et al., 2015; Smagula, Boudreau, et al., 2015); the Hill function is also rarely used (Pagani et al., 2016). Although the additional parameters and flexibility of the modelled waveform improves the accuracy of the model and the richness of its information, it is still subject to the same assumption of normality in the data which most biological signals do not adhere to (Neikrug et al., 2020).

MESOR, *Amp*, and *Acro/Phi* represent the same general rhythmometric properties in the extended cosinor as they did in the basic cosinor (i.e. average, range, and timing, respectively), but *MESOR* and *Amp* are calculated differently (Marler et al., 2006): *MESOR* is the average of *Y*'s maximum value and minimum value (rather than the average of all *Y* values), and *Amp* is the difference between the model's maximum *Y* value and minimum *Y* value (rather than maximum *Y* value and *MESOR*). The two new parameters affect the waveform's shape: *Alpha* is the width of the modelled sinusoid's trough (higher *Alpha* indicates a longer in-bed/sleep/somnolescent period), and *Beta* is the steepness of the transitions between troughs and peaks (higher *Beta* indicates a quicker transition from low-

magnitude nocturnal activity to high-magnitude diurnal activity, and vice versa). Since the extended cosinor allows "peaks" and "troughs" to have different durations, two additional endpoints can be derived by calculating when the modelled activity crosses the *MESOR*: the time when modelled activity exceeds *MESOR* is referred to as *Up-MESOR*, and it's descending corollary is *Down-MESOR*. These are often interpreted to represent the approximate onset and offset of waking activity, respectively (Marler et al., 2006; Neikrug et al., 2020; Smagula et al., 2018)[32]; similarly, the slope of the modelled activity at the *MESOR* intercepts has been interpreted to represent the . Note that *Up-MESOR* and *Down-MESOR* can be derived from the basic cosinor as well; however, since the basic cosinor is symmetrical, *Up-MESOR* and *Down-MESOR* would be exactly 12 hours apart from each other, and fall exactly 6 hours before and after *Acro/Phi* (respectively), and thus offer no information not already provided by *Acro/Phi*. An R^2 value indicative of the accuracy of the fitted model can be calculated *a la* the basic cosinor. Lastly, a *Pseudo-F Statistic* can be derived from the residual sums of squares of a basic and extended cosinor modelled on the same data; this represents the extended cosinors improvement in model fit relative to the basic cosinor (Marler et al., 2006).

Clinical Evaluation of Parkinson's Disease

In the absence of validated biomarkers of Parkinson's disease (PD), clinimetric assessment remains the primary means of evaluating disease status and translating clinical presentation into analyzable data (Espay et al., 2016). Generally, this entails a trained and experienced

[32] These are also referred to as UP Slope Time and DOWN Slope Time per Neikrug et al. (2020)

clinician observing the subject's clinical presentation and subjectively rating the severity of individual symptomatic domains using predetermined criteria, often accompanied by a patient/informant interview and discrete motor tasks. However, PD's marked heterogeneity, broad array of motor and non-motor symptoms, and fluctuating symptomatic severity (whose variability is exacerbated by dopaminergic therapy, a common means of controlling PD motor symptoms) have complicated the clinimetric assessment of PD and the integration of these observations into standardized, sensitive, and clinically relevant summary scores (Opara et al., 2017). Both the clinical validation of potential neuropathological biomarkers (e.g. alpha-synuclein) and the refinement of existing methods for quantifying disease severity are considered high-priority goals of the PD research community (Lana M. Chahine & Stern, 2017; Espay et al., 2016). Currently, PD is assessed through a combination of gross staging (e.g. Hoehn and Yahr scale [HY]) (Hoehn & Yahr, 1967), disease-specific detailed clinical scales (e.g. Unified Parkinson's Disease Rating Scale [UPDRS]) (Goetz et al., 2008), patient- and informant-reported outcomes (e.g. Hauser diaries) (Hauser et al., 2000), and quantitative motor tasks that evoke parkinsonian symptoms (e.g. Timed Up-and-Go [TUG]) (S. L. Mitchell et al., 2000).

Hoehn and Yahr Scale

Although PD was first described in 1817 (Parkinson, 1817), the H&Y was the first attempt at using clinical symptoms to stage PD into a standardized disease severity scale. The original H&Y was published almost exactly 150 years after Parkinson's seminal work to address the growing need to classify, quantify, and monitor clinical progression in PD (Hoehn

& Yahr, 1967); specifically, the lack of a common nomenclature and standard clinical criteria created controversy regarding the efficacy of therapeutic interventions and descriptions of PD's natural history and progression. Initially the H&Y consisted of five stages - denoted as I, II, III, IV, and V - representing increasing levels of "clinical disability" (Hoehn & Yahr, 1967); these ranged from "unilateral involvement ... with minimal or no functional impairment" (Stage I), to "fully developed [symptoms]" where the patient is "markedly incapacitated" (Stage IV), and ultimately "confine[d] to bed or wheelchair" (Stage V). Hoehn and Yahr acknowledged that these did not necessarily reflect distinct pathophysiological stages, and that functional impairment and disability were chosen as staging criteria to support reproducibility, simplify assessment, and emphasize clinical relevance (Goetz et al., 2004; Hoehn & Yahr, 1967). A modified H&Y that updated the criterion language and added two intermediate stages - 1.5 and 2.5 - gained popularity in the 1990's after it was employed in several clinical trials (Jankovic et al., 1990). However, the Movement Disorder Society (MDS) recommends the original H&Y be used until the modified H&Y can be clinimetrically validated (Goetz et al., 2004; Poewe, 2012).

While the H&Y has been largely eclipsed by the significantly larger and more detailed Unified Parkinson's Disease Rating Scale, both the original and the modified H&Y continue to see widespread use, especially as screening tools in research studies and clinical trials (Goetz et al., 2004; S. L. Mitchell et al., 2000). This is primarily due to its simplicity and brevity (Goetz et al., 2004), its pivotal role in PD research before the development of the UPDRS (e.g. most models of PD's natural history and progression were generated us-

ing the H&Y), its use as a gold standard for the development of subsequent clinical instruments (Ramaker et al., 2002), and its correlation with other measures of disease progression such as the UPDRS (P. Martínez-Martín et al., 1994) and MDS-UPDRS (Skorvanek et al., 2017), neuropathological markers such as fluorodopa positron emission tomography (Vingerhoets et al., 1994), motor impairment (Reynolds & Montgomery, 1987), and quality of life (M. Welsh et al., 2003). However, its basic structure limits its ability to capture all of PD's diverse clinical presentations and precludes its use as a sensitive measure of therapeutic efficacy. Moreover, it's focus on posture and laterality to stage patients over-emphasizes PD's motor symptoms at the cost of its historically undervalued non-motor symptoms. Nonetheless, the H&Y remains a valuable and accessible tool that will remain a mainstay in basic and clinical PD research for the foreseeable future (Goetz et al., 2004).

Movement Disorders Society's Unified Parkinson's Disease Rating Scale

The Unified Parkinson's Disease Rating Scale (UPDRS), is considered the gold standard for assessing PD's clinical features. Originally published in the 1980's, the scale was extensively revised by the Movement Disorder Society (MDS) in 2008 (Goetz et al., 2008). The updated "MDS-UPDRS" consists of a structured interview and motor examination, during which 50 items are scored on a rating scale from 0 ("no symptoms") to 4 ("severe"). Due to its comprehensive nature, compatibility with clinical practice, and clinimetric validation, the MDS-UPDRS has seen widespread use as a measure of disease severity and progression in clinical research (Espay et al., 2017). However, attempts to validate poten-

tial biomarkers (such as alpha-synuclein) against the MDS-UPDRS have produced inconsistent results (Espay et al., 2017; Kalia & Lang, 2015). Methodological concerns, such as inconsistent assay methods, have been cited as possible explanations (Lana M. Chahine & Stern, 2017).

The MDS has recommended that each of the MDS-UPDRS' sub-sections be reported separately and not condensed into a single summary score due to their unstable factor structure (Goetz et al., 2008). Nonetheless, the MDS-UPDRS is usually reported as the sum of all of its item's scores, meant to represent the overall disease burden of the subject. Several other summary scores have been developed that quantify the severity of specific symptoms and classify patients into different disease phenotypes. For example, the bradykinesia sub-score is the sum of the scores of items assessing bradykinesia (Zampieri et al., 2010), and the normalized ratio of scores of items assessing postural instability to items assessing tremor is used to classify subjects into "Tremor Dominant", "Postural Instability/Gait Difficulty", or "Indeterminate" phenotypes (Stebbins et al., 2013). In addition, total scores of the MDS-UPDRS' individual sections are often reported and interpreted as representing some aspect of the patient's clinical presentation; e.g. the total score for Section III (the motor assessment) is frequently used to represent the severity of motor impairment. Cut-off scores for each of the MDS-UPDRS's sections have been proposed to grossly categorize disease severity into three tiers: mild, moderate, and severe[33] (Pablo Martínez-Martín et al., 2015).

[33] Section I: 10/11 and 21/22, Section II: 12/13 and 29/30, Section III: 32/33 and 58/59, Section IV: 4/5 and 12/13

Sit-to-Stand Task

Arising from a seated to a standing posture is one of the most common physical movements humans engage in. The Sit-to-Stand (SitS) postural transition requires expending a relatively large amount of energy to facilitate rapid movement of the body, and recruits several major muscle groups to do so (Goulart & Valls-Solé, 1999; W. G. Janssen et al., 2002). This makes SitS mechanically demanding and thus easily impaired in those with restricted mobility, postural instability, and/or motor disorders (Kerr et al., 1997; Riley et al., 1991). Subsequently, SitS is frequently impaired in PD and is used as an indicator of motor disability (Parisi et al., 2015). Given its ubiquity in activities of daily living and integral role in human locomotion, impairment of the SitS likewise impairs functional independence, and thus is clinically relevant to many populations and a key factor in their reduced quality of life (van Lummel et al., 2016). As a result, SitS transitions are widely used in scientific research and clinical practice, either as a standalone assessment or as part of a larger battery (e.g. the MDS-UPDRS), and are increasingly instrumented with kinematic and actigraphic sensors (Parisi et al., 2015; van Lummel et al., 2016). The primary outcomes of SitS tasks are duration and success of the transition; some tasks require multiple consecutive SitS (e.g. the "5x SitS") or provide a set window of time during which as many SitS transitions as possible should be executed (e.g. the "60 Second SitS"), and so have additional outcomes related to frequency and success rate.

Functionally, SitS is the ability to independently transition from a stable and stationary sitting posture to a stable and stationary standing posture, from which one can (and

often does) easily transition to walking. SitS is therefore an essential for functional independence and an important activity of daily living, as it is the basic obstacle a person needs to overcome before they are able to begin walking, an energy-efficient and primary method of independent locomotion (Kerr et al., 1997; van Lummel et al., 2016). Kinematically, SitS is a dynamic state where the Center of Mass (CoM) is mobile and the body is unstable - if one were to stop halfway through a SitS, it would require significant energy to hold the CoM stable - and so it can be defined as the period between the first and last significant shift of the CoM. Unbalanced muscle contractions exert a net force on the CoM through their fibers and tendons, and this momentum is transformed (i.e. the direction of the CoM's movement and movement speed is changed) by the agonistic and antagonistic forces of other stabilizing muscles. SitS can thus be described by the changes in momentum with respect to the CoM, allowing its kinematics to be simulated in rigid-body biomechanical models (Matthew et al., 2018). Neurologically, the SitS is a complex and physically demanding task that requires the coordinated actions of multiple muscle groups in parallel and in sequence, and is executed by a combination of different neuromotor systems involving both conscious and reflexive action (Goulart & Valls-Solé, 1999). Actions such as flexion of the trunk, stabilization of the head, and flexion/dorsiflexion of the lower limb are executed in preparation of a SitS sequence to reduce the energy required and stabilize the body, and include both conscious actions and anticipatory postural adjustments. In order to provide the force needed to accelerate the body vertically, the SitS employs some of the largest muscle groups in the body, including hamstrings, quadriceps, and lumbar extensors, in a stereotyped and consistent pattern (Goulart & Valls-Solé, 1999; W. G. Janssen et al.,

2002). Throughout the SitS, reflexive postural stabilizers activate as needed to maintain stability.

The SitS has been divided into four main stages (W. G. Janssen et al., 2002; Kerr et al., 1997; Matthew et al., 2018). The "Flexion-Momentum" phase involves the generation of forward momentum via flexion of the torso, ending when the person's weight is fully transferred to their feet (i.e. their CoM has shifted forward). The "Momentum Transfer" phase continues the production of forward momentum, and additionally generates vertical momentum through flexion of the thigh and extension of the knees; this vertical momentum is reinforced by antagonistic muscle action redirecting forward momentum vertically. In the "Extension" forward momentum is no longer being generated, while the extension of the lower limbs and torso continues to generate vertical momentum. The "Stabilization Phase" marks the transition from momentum generation to stabilization where the body, now fully upright, bleeds off any residual momentum by swaying until the CoM is fully within the individual's base of support. These gross stages have also been further subdivided into discrete movements (Kerr et al., 1997).

Self-Reported Questionnaires

Parkinson's Disease Questionnaire, 8-Item

The Parkinson's Disease (PD) Questionnaire (PDQ) is a self-administered disease-specific questionnaire designed to evaluate health domains impacted by PD in order to determine the respondent's health status and Health-Related Quality of Life (HRQOL). The original PDQ was developed and validated in 1995 (C. Jenkinson et al., 1995; Peto et al., 1995) and

contained 39 questions scored on a five point ordinal scale; this version is referred to as the PDQ39. A factor analysis of the PDQ39 during its validation grouped questions into eight distinct "dimensions" of health: mobility, activities of daily living (ADL), emotional well-being, stigma, social support, cognition, communication, and bodily discomfort (Peto et al., 1995). A short-form version of the PDQ39 was developed in 1997 by selecting, for each health dimension, the question whose score best correlated with that dimension's total score (Crispin Jenkinson et al., 1997); this short-form version is referred to as the PDQ8. In both the PDQ8 and PDQ39, a summary index (SI) representing the respondent's health status for each dimension can be calculated by averaging all scores in that dimension (Crispin Jenkinson et al., 1997). An SI can also be calculated for the respondent's overall health status by averaging the dimensional SI's[34]; these are referred to as the PDQ8SI and PDQ39SI. While these scores are recommended for assessing HRQOL in PD, some analyses have found that SI is multidimensional and thus influenced by confounding factors (Franchignoni et al., 2008; Hagell & Nilsson, 2009; Kuspinar et al., 2019); this has resulted in some authors advising caution when using the PDQ and interpreting its SI in clinical research. One early review criticized the PDQ's lack of items addressing self-image, sleep problems, sexual activity, and postural transitions, yet nonetheless concluded that the PDQ would usually be the most appropriate instrument for assessing HRQOL in PD (Kuspinar et al., 2020; Marinus, 2002).

[34] The number of questions varies between dimensions in the PDQ39; by taking the average of the dimensional SI's, the PDQ39 normalizes each dimension's contribution to the respondent's overall health status gives them equal weighting.

Morningness-Eveningness Questionnaire

The Morningness-Eveningness Questionnaire (MEQ) is a self-administered questionnaire designed to evaluate the respondent's psychological preference for when they engage in certain behaviors (Di Milia et al., 2013; Kantermann et al., 2015). Said another way, the MEQ assesses the respondent's morningness-eveningness preference (J. A. Horne & Östberg, 1977) - also known as their diurnal preference, phase of entrainment, chronotype, circadian phenotype, circadian typology, and, in the original MEQ and other older literature, as simply "morningness" (Di Milia et al., 2013; Kantermann et al., 2015). The MEQ consists of 19 questions that ask the respondent to identify their preferred time for certain activities such as sleeping and exercising, their perceived "best" and "worst" times of day, the timing of certain subjective sensations like alertness and hunger, and how they would react to hypothetical scenarios such as going to bed at a different time or choosing their ideal exercise time. The questions have between four and six potential responses, and each response has a predetermined score between zero and six points. The respondent's total score is calculated by summing the chosen scores for all questions, with a potential range of 16 to 86 points divided into five categories: Definite Evening (16 - 30), Moderate Evening (31 - 41), Intermediate (42 - 58), Moderate Morning (59 - 69), and Definite Morning (70 - 86).

The MEQ is considered the gold standard for self-reported morningness-eveningness (Di Milia et al., 2013). It has been validated against physiological and cognitive indicators of circadian rhythm, including body temperature (S. L. Bailey & Heitkemper, 2001; Griefahn et al., 2001; J. A. Horne & Östberg, 1977; Ishihara et al., 1987; Neubauer, 1992),

secretion of cortisol (S. L. Bailey & Heitkemper, 2001) and melatonin (Griefahn et al., 2001), sleep timing (Ishihara et al., 1987), and alertness (Adan, 1991; Natale & Cicogna, 2002). Although it has seen widespread use, been translated into multiple languages, and is frequently used as a benchmark against which other instruments are validated, the MEQ has been criticized for the author's ambiguous rationale for selecting the final questions and responses, the potential multidimensionality of its ostensibly unidimensional score, and it's original cutoff scores, which were based off a relatively small (n = 150) and age-restricted (18 - 32 years old) cohort (Di Milia et al., 2013)[35]. To address the multidimensionality of the MEQ, a "reduced MEQ" (rMEQ) was produced that contains only those questions shown by a factor analysis to directly relate to morningness-eveningness (Adan & Almirall, 1991). Other instruments, notably the Composite Scale of Morningness (CSM) and the Munich ChronoType Questionnaire (MCTQ), were partially derived from the MEQ (Di Milia et al., 2013). Despite its drawbacks, the MEQ's frequent use in the literature, its role as the "gold standard" for validating other instruments, and its simplicity and ubiquity continue to make it a popular and valuable means of assessing respondents' morningness-eveningness preference.

Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) is a self-administered questionnaire with eight items covering various daily activities (e.g. driving), each ranked by the respondent on a four-

[35] Numerous other cutoff scores have been proposed based on larger samples, other age cohorts, different statistical segmentation techniques, and/or different numbers of categories.

point ordinal scale according to how likely they are to doze off. The main outcome of the ESS is the sum of scores for all items, and represents the respondent's degree of daytime sleepiness, also referred to as their Average Sleep Propensity (ASP). The ESS was developed as a simple instrument for measuring the subject's general level of daytime sleepiness (Murray W. Johns, 1991)[36], and was initially validated in Obstructive Sleep Apnea (OSA): the ESS successfully distinguished subjects with OSA from those without OSA, and after treatment those with OSA scored similarly to the healthy controls (M. W. Johns, 1992). Due to its simplicity, brevity, and prior validation, the ESS has seen widespread use in clinical sleep research, especially OSA, (Hirshkowitz et al., 2011), has been adapted to various populations - most notably children and adolescents (K. C. Janssen et al., 2017; M. Johns, n.d., 2015) - and has been translated into dozens of languages beyond its original Australian English, including Arabic (Ahmed et al., 2014), Urdu (Surani et al., 2012), Italian (Vignatelli et al., 2003), and Brazilian Portuguese (Bertolazi et al., 2009).

Although it has been validated and continues to see widespread use, the ESS has several notable drawbacks that have led to criticism of its liberal application in clinical research, especially in the context of OSA (Omobomi & Quan, 2018; Quan, 2013). Perhaps the most obvious drawback is the fact that the ESS is a self-evaluation along an ordinal scale with no objective delineation between low, moderate, and high chances of dozing, which introduces considerable subjectivity in the subject's response (Omobomi & Quan, 2018). One of the ESS' main advantages - the fact it can be self-administered and thus does

[36] The ESS's instructions were revised in 1997 to encourage the subject to complete all questions, which is required to calculate an accurate score

not require physician labor - also predisposes it to human error on the part of the subject (Omobomi & Quan, 2018), with one study examining self- vs physician-administration reporting that nearly a quarter of self-administered ESS' contained an error that prevented full, accurate scoring (Marra et al., 2018)[37]. In addition to anthropogenic errors and biases associated with self-administered questionnaires, the ESS also exhibits a gender bias due to women being more likely to emphasize fatigue when reporting symptoms of OSA (Quan, 2013; Ye et al., 2009), an educational bias with less education being associated with a greater likelihood of making an error - thus preventing calculation of a score and subsequently under-representing less educated subjects (Marra et al., 2018; Omobomi & Quan, 2018), and an observer bias respondents such as commercial drivers may underscore their sleepiness for fear of professional repercussions (Colvin & Collop, 2016; Omobomi & Quan, 2018). Moreover, one's ESS score can vary across repeated administrations (Campbell et al., 2018; Kendzerska et al., 2014; Omobomi & Quan, 2018), and studies examining its expected association with physiological measures of sleepiness (e.g. the multiple sleep latency test) and clinical endpoints of OSA (e.g. respiratory disturbance index) have produced inconsistent results (Fong et al., 2005; Quan, 2013). Despite these drawbacks, many insurance companies have made the ESS a requirement for covering clinical sleep studies, most of which are diagnostic screens for OSA; this requirement has been criticized due to the non-negligible risk of persons with (undiagnosed) OSA scoring too low on the ESS to qualify for a diagnostic sleep study (Quan, 2013).

[37] Errors included dichotomous Yes/No responses instead of an ordinal score, skipped questions, "cross[ed] against" questions, and inability to self-administer the survey due to illiteracy; no errors were found in the physician-administered ESS

While the ESS is still recognized as a useful, flexible, and low-burden means of quickly assessing daytime sleepiness, it is increasingly recommended that it be used in combination with (or supplanted by) other measures, especially in the context of OSA (Omobomi & Quan, 2018; Quan, 2013).

Mini-Mental State Examination

The Mini-Mental State Examination (MMSE) is a 30-point questionnaire principally used as a rapid assessment of cognitive ability, especially screening cognitive impairment and dementia (Carnero-Pardo, 2014; Folstein et al., 1975). The questionnaire is filled out by an administrator - usually a clinician or researcher, though minimal training is required to administer the MMSE - who prompts the subject with questions and scores their responses according to predefined criteria. The MMSE consists of eight items, each assessing a specific cognitive ability and with different scoring amounts: orientation to time (5 points), orientation to place (5 points), registration - AKA memory encoding (3 points), attention and calculation (5 points), recall (3 points), language (2 points), repetition (1 point), and complex commands (6 points). The MMSE was first developed in 1975 as a quicker alternative to existing cognitive assessments[38], such as the Wechsler Adult Intelligence Scale (WAIS), which were difficult for subjects with dementia to complete due to their length (Folstein et al., 1975). This was accomplished by excluding other mental functions, such

[38] This is the reason it is referred to as the “Mini”-Mental

as mood, to solely focus on cognitive function (Folstein et al., 1975). This original MMSE contained 11 items, which were eventually pared down to the current eight items.

The MMSE is arguably the most widely used cognitive screening instrument ever developed, and its seminal article is amongst the most frequently health science articles ever published (Carnero-Pardo, 2014; Folstein et al., 1975; Nilsson, 2007). It has been translated into over 50 languages and adapted to various populations, such as the blind (Carnero-Pardo, 2014). The MMSE has been included in the main clinical practice guidelines published by the American Academy of Neurology (Petersen et al., 2001), the British National Institute for Health and Care Excellence (National Collaborating Centre for Mental Health (UK), 2007), and the Spanish Sistema Nacional de Salud (Ministerio de Sanidad, Política Social e Igualdad, 2018), among others (Carnero-Pardo, 2014). It's simple design and brief administration time have made the MMSE an attractive choice for medical and research organizations, and it's widespread use facilitates replication and inter-study comparisons in a broad variety of contexts. Despite its popularity, the MMSE was not initially developed as a screening tool for dementia. For example, a third of its points concern orientation, but only 10% concern memory, which is usually the first cognitive ability to be noticeably impaired in common dementias such as Alzheimer's disease. It's reliability is impacted by the fact that the MMSE does not have standardized instructions (e.g. the original MMSE did not specify which words to use in the recall task), and the requirement that the subject be literate in the administered language restricts its generalizability, causes an ascertainment bias, and contributes to the MMSE's significant educational attainment bias (Carnero-Pardo, 2014; O'Bryant et al., 2008). The MMSE continues to see high usage,

although alternatives such as the Montreal Cognitive Assessment (MoCA) are continually being developed and evaluated.

EuroQol 5-Dimension

The EuroQol 5-Dimension (EQ-5D) is a self-administered questionnaire consisting of five items scored on a three point ordinal scale[39], as well as a single 0-100 Visual Analogue Scale (VAS). Developed by the eponymous EuroQol, an international research group formed in 1987 (EuroQol, 1990), the EQ-5D was specifically designed as a quick, simple, scalable, standardized, and disease-agnostic assessment of Health-Related Quality of Life (HRQOL)[40] to facilitate the generation of common data-sets that can be shared and analyzed across international, clinical, and disease boundaries. The EQ-5D's primary outcome is a composite "health index" score representing the impact of a respondent's health state on their Quality of Life (QOL) (EuroQol, 1990). The health index is the concatenation of the scores of the EQ-5D's five items, with each item representing one of five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Rabin & Charro, 2001). For example, a health index of "13212" translates to a score of 1 (no problems) in mobility, 3 (extreme problems) in self-care, 2 (some problems) in usual activities, 1 in pain/discomfort, and 2 in anxiety/depression (Rabin & Charro, 2001).

[39] A version with five point ordinal scales - referred to as the EQ-5D-5L - also exists

[40] HRQOL, also styled as HRQoL or HRQL, is defined as "the subjective assessment of the impact of disease and treatment across the physical, psychological, social and somatic domains of functioning and well-being" (Revicki et al., 2000)

Health indices can be converted ("valuated") into a one-dimensional index value representing the respondent's overall health state, which can then be used as a summary endpoint. The index value represents the value of a given health state in some context; in the simplest sense better health is more valuable, though the respective contributions of each health domain varies by population and application (Kind, 2003; Weinstein et al., 2009). For example, the contribution of mobility impairment to QOL is likely more severe in athletes than non-athletes, QOL in a culture that values independence and autonomy would be more impacted when self-care is impaired compared to a more interconnected and collectivist culture, and these weights can vary between sub-populations (e.g. people with PD may be more sensitive to mobility impairments than someone with clinical depression). Similarly, a clinician monitoring a patient's QOL would be more interested in valuations based on their patient's clinical sub-population, a public health economist allocating limited resources would prefer valuations based on the general population, and a hospital may use valuations based on the caregiver's - rather than the patient's - perspective when assessing the efficacy of new staff policies (Kind, 2003). Numerous value sets - i.e. algorithms for converting a health index into an index value - have been generated for different clinical populations and countries using a variety of techniques. The EQ-5D's VAS (EQ-5D-VAS) was the original valuation metric, though more refined methods such as time-trade-off and the development of standardized protocols have eclipsed VAS valuation in most contexts (Kind, 2003).

In summary, the EQ-5D is a flexible instrument with diverse applications that has seen widespread use in clinical research, public health, and economics. It produces three

main outcomes: a categorical health index representing the respondent's health profile, a standardized index value derived from the health index using valuation sets, and the VAS, which represents the respondent's valuation of their overall health state (Hurst et al., 1997). The EQ-5D is primarily used for assessing HRQOL by health domain - with extensive valuation data for adapting outcomes to specific populations of interest - though its simplicity and ease of use make it suitable as a coarse measure of HRQOL in a wide variety of contexts.

Video Analysis and Annotation

Video annotation, the systematic identification and quantification of signals in video recordings, is a broad category of observational methods with diverse scientific and non-scientific applications. Video data is generated passively through recording a scene - be it a social interaction, a natural phenomenon, or a clinical assessment - and can be analyzed qualitatively or quantitatively. As a video is nothing more than a series of still-images captured in rapid succession, it can capture subtle, small-amplitude, and/or brief events that might be missed by a contemporaneous observer. These images can be quantitatively analyzed in a number of ways - e.g. profile tracing, machine vision, image analysis, etc. - independently from the video they were derived from, or collectively played back as a continuous stream of visual data from which patterns and/or events may be qualitatively discerned by a human observer. Herein, video annotation is discussed in the context of qualitatively categorizing physical movements in humans - more specifically, clinical behaviors in Parkinson's disease (PD) - using human raters.

Video recordings can be easily stored and shared, allowing them to be repeatedly used; e.g. by different research teams seeking to replicate findings, in the evaluation of newer and/or alternative methods, or to consistently document a specific item of interest. Unlike contemporaneous observation, multiple observers can annotate the same video in a controlled manner fully divested from the physical, social, and temporal circumstances the recording was made in. For example, the inter-rater agreement of a new clinical scale could be estimated by having clinicians individually score the same video recording of a patient, thus removing the myriad circumstantial factors that could unduly influence in-person scoring (e.g. different patients, different times of day, different symptomatic severity, different viewing perspectives/durations, etc.) (Rodby-Bousquet et al., 2014). Although it's been used throughout the sciences, video annotation is particularly common in psychology due to its ability to objectively capture behaviors used to measure psychological processes, such as social interactions or behavioral tics (Gilmore & Adolph, 2017). Having access to both the interpretation and the subject of interpretation allows for the direct replication of methodologies and the rigorous assessment of their validity by others; this is necessary because the inherent subjectivity of the observables, their interpretations, and the methods of generating them cannot be fully captured with written language.

The study of how human movement and its impairments are clinically assessed faces a similar problem in that the interpretation of specific 'behavioral biomarkers' (e.g. "bradykinesia") relies on qualitative assessment on the part of the clinician, who must interpret their observations in the context of some external schema (e.g. MDS-UPDRS) in order to draw a conclusion. Even with strict and clearly defined criteria, the uncontrolled

nature of human movement and the innumerable ways it can be altered, disrupted, or impaired makes its evaluation a qualitative process that cannot be fully defined objectively with written language or mathematical formulae. Likewise, video annotation of movement requires a human observer to subjectively interpret the visual information in the video according to predefined criteria. While this subjectivity introduces variance and uncertainty, video annotation is nonetheless well-suited to the categorization of complex behaviors - be they social interactions, psychological states, or physical movements - due to the remarkable human ability to rapidly integrate contextual information.

The process of video annotation can be grossly separated into three phases. First, the signal(s) of interest must be identified and rigorously defined to minimize ambiguities (Y. Yang et al., 2013). These definitions may incorporate subjective and objective elements (e.g. "*walking* starts with the first visible forward movement of the leading foot, or the first postural adjustment demonstrating the subject's intent to begin walking") and may be quantitative or qualitative in nature (e.g. "*long walking* is when the subject takes 10 or more steps while *walking*; if the step lengths appear uneven, annotate as *long walking, uneven gait*"). In the abstract sense, definitions bridge the gap between the objective reality of the video recording and the subjective perception of the human annotator, and thus should integrate discretely quantifiable visual criteria (e.g. "*standing* requires both feet to be flat on the ground") into colloquial qualitative descriptions (e.g. "*standing* is when the subject is upright in a stationary vertical posture"). Ideally, definitions will also clarify ambiguous circumstances (e.g. "If the subject appears to be *standing* but you cannot verify their feet are flat on the ground because they're out of frame, annotate as *standing*").

Second, human raters review videos to identify any events/behaviors/etc. that meet these predefined criteria, determine *when* they meet these criteria, and segment the behavior accordingly (Holle & Rein, 2015). Depending on the complexity of the annotations and the amount of expertise required, annotators may be trained on practice videos (previously annotated by an experienced rater) until they meet some predetermined level of accuracy. Annotations can consist of continuous periods of time (e.g. "subject *walking* from frame 100 to frame 200") or discrete instants (e.g. "subject transitioned from *standing* to *walking* at frame 100"), and may include additional qualitative information or sub-categorization (e.g. "subject *walking* with *shuffling gait*").

Third, annotations made by different raters on the same video are compared for agreement in both their segmentation (i.e. start/end times) and qualification (i.e. "*walking* with *shuffling*"); the rate of agreement can be statistically quantified, and disagreements may be arbitrated by a senior rater so that a "final" annotation is chosen for future use. Alternatively, a "primary" annotator may be selected *a priori* based on their experience or *post-hoc* based on statistical inter-rater reliability; the primary's annotations are then used as the final data-set, and the secondary annotators are used for determining inter-rater reliability (Fokkenrood et al., 2014; Orfanos et al., 2017). In order to determine agreement, annotations from multiple raters must be "linked" together; i.e. determined that both were made based on the same segment of video. This is not an issue in case-by-case data (e.g. two clinicians independently score a video recording of a patient performing a motor task) as there is no ambiguity in what the annotations were based off of. In time-series data,

however, raters may disagree on when certain behaviors began or how they should be classified (Bakeman et al., 2009). For example, Rater A makes a single *walking* annotation, where-as Rater B believes the subject paused shortly after starting and so makes two *walking* annotations, one short and the other long. Rater A's single annotation can be paired either with Rater B's first annotation (due to their similar start times), Rater B's second longer annotation (due to their significant overlap), or both (Holle & Rein, 2015). The choice is not trivial, as it limits what statistical metrics of agreement can be calculated and affects their interpretation. This "linking problem" remains unsolved; although there are algorithmic ways of automatically linking annotations in time-series data, none are always correct due to the sheer variety of contextual information that could influence pairing and the subjective manner in which the annotations were originally made.

Statistical Tests and Other Analytical Considerations

Where-as individual chapters describe the analytical procedures pertinent to their content, this subchapter will provide an overview of the general analytical methods, considerations, and practices used throughout the work described herein. Data processing and grooming will not be covered in this subchapter. Unless otherwise stated, all statistical analyses were conducted in Stata (versions 15 – 16, StataCorp, Inc., College Station, TX, USA) on a Mac operating system. Excel (Microsoft, Inc., Redmont, WA, USA) and MATLAB (MathWorks Inc., Natick, MA, USA, R2018a) were used to array, groom, store, and visualize the data; MATLAB was also used to generate cosinor models (see Chapters 4-5).All analyses involved an initial descriptive analysis to characterize the distribution of data through

measures of central tendency and variance; mean and standard deviation were used for continuous or near-continuous data[41]. This also involved the visualization of data, both raw and under different transforms (e.g. log-transform). Skewness and kurtosis were calculated for continuous data, including the use of skewness-kurtosis tests to dichotomize samples as either "normally distributed" or "abnormally distributed". When necessary, the variance of different samples were compared using an equal variances test to determine the appropriate statistical test. Exact p-values were generated and reported where possible, and two thresholds were used for reporting significance: $p = 0.05$ was the default significance threshold, although $p = 0.10$ was used for data with poor signal-to-noise ratios and/or small sample sizes. For the purposes of interpretation and reporting, $p \leq 0.05$ was considered "statistically significant" and $0.05 < p \leq 0.10$ was considered "approaching significance". For the purposes of determining normality and equality of variances, a p-value of 0.05 was used. Significant digits were not constrained during analysis, but to improve readability the data were presented with two or three significant digits.

Due to the nature of the data collected (i.e. from human subjects), outliers were usually identified based on participant feedback and/or researcher observations at the point of data collection. No outlier detection algorithms were consistently used, though some basic outlier criteria - such as being ≥ 3 standard deviations from the mean (for normally distributed data) or ≥ [1st/3rd quartile] +/- [1.5 * interquartile range] from the median (for

[41] "Near-continuous" refers to ordinal data with a large number of ranks that are conventionally treated as continuous for the purposes of statistical analysis; this includes, but is not limited to, variables such as the MDS-UPDRS total score and the MEQ total score. For the rest of this sub-chapter, "continuous" includes both continuous and near-continuous data

abnormally distributed data) - were used in exploratory and descriptive analyses to quickly evaluate the variance in the data. Potential outliers identified during *post-hoc* descriptive and exploratory analyses were evaluated on a case-by-case basis through review of study documents and excluded if they were deemed to be artifacts, spurious, or otherwise altered by a factor outside of the analytical scope of the study. Missing data was quantified and reported whenever possible. No missing data was imputed; however, certain samples were omitted from analysis due to excessive missing data that precluded accurate analysis.

Between-group comparisons were conducted for the purposes of quantifying the probability that two or more samples have the same mean and distribution. Two-sample comparisons of continuous variables were conducted using the Student's t-distribution; i.e. t-tests. Paired and unpaired t-tests were used for paired and unpaired samples, respectively. Welch's t-tests or Wilcoxon Rank Sum tests (AKA Mann-Whitney U tests) were used for samples with unequal variances as demonstrated via an equal-variance test. The Wilcoxon Signed-Rank test was used for paired samples with unequal variances. For comparisons involving three or more samples with continuous data, Analyses of Variance (ANOVAs) were conducted; one-way, two-way, *n*-way, and repeated measures ANOVAs were used as needed. ANOVAs were also employed to model the effects of certain categorical/ordinal factors on the variable of interest, and likewise used to model the influence of continuous covariates on categorical variables of interest. Chi-square tests were used to identify relationships between categorical-ordinal and categorical-categorical variables.

Associations and correlations were quantified using simple and multiple-variable linear and logistic regressions. Linear regressions were used to model the associations between continuous variables, and logistic regressions were used for associations between dichotomous (dependent) and continuous (independent) variables. For associations between ordinal (dependent) and continuous (independent) variables, simple and multiple-variable ordered logistic regressions were used. All multiple-variable regressions were preceded by simple regressions to quantify the pairwise associations between the multiple variables to be used. In addition, simple linear, logistic, and ordered logistic regressions were used extensively for exploratory analyses to identify potentially meaningful associations.

Linear mixed-models were used to model the relationships in complex multi-level nested and repeated measures data (see Chapter 5 Methods). Inter-rater reliability was initially monitored by calculating simple percent agreements using annotation endpoints (i.e. start time, end time, and annotation value) for annotations paired by trained arbitrators (see Chapter 3 Methods). Percent agreement for start and end times included tolerance windows due to the difficulty in reliably determining the exact frame a behavior began; i.e. if two paired times were within 5 frames (~0.167 seconds) of each other, they were considered in agreement. Inter-rater reliability was formally quantified via Cohen's kappa using different agreement criteria (see Chapter 3 Methods).

CHAPTER THREE: QUANTIFICATION OF DISCRETE BEHAVIORAL COMPONENTS OF THE MDS-UPDRS

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Abstract

Introduction

The Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is the current gold standard means of assessing disease state in Parkinson's disease (PD). Objective measures in the form of wearable sensors have the potential to improve our ability to monitor symptomology in PD, but numerous methodological challenges remain, including integration into the MDS-UPDRS. We applied a structured video coding scheme to temporally quantify clinical, scripted, motor tasks in the MDS-UPDRS for the alignment and integration of objective measures collected in parallel.

Methods

25 PD subjects completed two video-recorded MDS-UPDRS administrations. Visual cues of task performance reliably identifiable in video recordings were used to construct a structured video coding scheme. Postural transitions were also defined and coded. Videos were independently coded by two trained non-expert coders and a third expert coder to derive indices of inter-rater agreement.

Results

50 videos of MDS-UPDRS performance were fully coded. Non-expert coders achieved a high level of agreement (Cohen's $\kappa > 0.8$) on all postural transitions and scripted motor

tasks except for Postural Stability ($\kappa = 0.617$); this level of agreement was largely maintained even when more stringent thresholds for agreement were applied. Durations coded by non-expert coders and expert coders were significantly different ($p < 0.05$) for only Postural Stability and Rigidity, Left Upper Limb.

Conclusions

Non-expert coders consistently and accurately quantified discrete behavioral components of the MDS-UPDRS using a structured video coding scheme; this represents a novel, promising approach for integrating objective and clinical measures into unified, longitudinal datasets.

Keywords

Parkinson's disease

Video coding

MDS-UPDRS

Wearable Sensors

Introduction

Parkinson's Disease (PD) is the second most common neurodegenerative disease, affecting 1% of the Western population over 60 years of age (de Lau & Breteler, 2006). The gold standard for the evaluation of PD symptomology is the Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz et al., 2008; Jankovic,

2008). A novel approach to PD symptom monitoring has emerged in Technology-based Objective Measures (TOMs) of movement obtained using accelerometers, gyroscopes, and other motion detectors housed in mobile platforms worn on the body (de Azevedo et al., 2016; Dewey et al., 2014; Espay et al., 2016; Patel et al., 2009; Piro et al., 2016). As they are capable of continuously measuring movement, gait, and posture outside of the clinic, wearable sensors are well suited for monitoring the variable symptoms of PD. However, the use of TOMs in the MDS-UPDRS is largely unexplored, and, in fact, the MDS-UPDRS is often used as an outcome measure for sensor validation (Johansson et al., 2018). In addition, the methodological challenges of wearable sensors remain a significant obstacle to their translation into routine clinical practice (Espay et al., 2016; Horak & Mancini, 2013). Specifically, their high resolution and sensitivity leaves them susceptible to noisy interference. Complicated and time-consuming analytical techniques are required to derive clinically meaningful endpoints from the large amounts of data they produce and the lack of standards has led to isolated "islands of expertise" (Lana M. Chahine & Stern, 2017; Espay et al., 2016, 2017; Horak & Mancini, 2013; Papapetropoulos et al., 2015; Rabuffetti et al., 2011). These challenges are amplified in the MDS-UPDRS, as the scale's semi-standardized motor tasks introduce significant noise into the signal and its loosely structured format complicates interpretation.

Human-directed behavior coding in video recordings of clinical assessments and functional tasks is often used to validate TOMs captured within a clinical setting (Aminian et al., 1999; Fokkenrood et al., 2014; Heldman et al., 2014; Lyons & Tickle-Degnen, 2005; S. T. Moore et al., 2011; Piro et al., 2016). Video coding enables the temporal alignment

of diverse datasets (e.g. TOMs and MDS-UPDRS task ratings) to a "ground-truth" time series of coded behaviors, which allows for greater accuracy and confidence in analyses between and across these data. Video coding therefore has the strong potential to enhance ongoing research on the use of wearable sensors for the continuous measurement of PD symptomatology (S. T. Moore et al., 2011; Piro et al., 2016), and, in fact, is often used to validate the output of prototype sensors. Nonetheless, the use of video coding to validate TOMs has been slowed by study-specific coding schemes, variance in the training and expertise of human coders, and the diversity of the definitions and methods to guide coding.

Through a structured protocol, we have defined reliable visual cues for specific motor tasks in Section III of the MDS-UPDRS, and trained non-clinician coders to recognize and code them in video recordings. Our objective was to construct and apply a detailed, consistent and transparent video coding scheme capable of reliably generating precise timestamps of tasks and behaviors used in the MDS-UPDRS assessment for future alignment with TOM datasets.

Methods

Participants and Video Recordings

25 persons with PD underwent a video-recorded administration of Section III ("Motor Examination") of the MDS-UPDRS, as well as a five times sit-to-stand task. The tasks were administered by a trained medical physician who was an expert in movement disorders. The number of subjects, order of assessments, and the video recordings (with no audio) were transferred to the study group, who were blinded to the clinical details of the subjects.

All videos were de-identified prior to transfer to the study group and all subjects gave informed consent as per institutional study requirements.

Each video recording was constructed from raw footage recorded at 30 frames per second by two separate cameras: a mobile Microsoft Kinect™ camera (640 x 480-pixel resolution) mounted on a tripod, and a stationary Microsoft Kinect™ (640 x 480-pixel resolution) mounted at the end of the hallway used for walking tasks. Both cameras provided full-body views of the subject from a front facing angle.

Development of the Coding Scheme

To facilitate consistent frame-by-frame coding of behaviors of interest, a structured Coding Scheme (CS) was constructed before receipt of the video recordings (Figure A.1). The CS contained definitions for two categories of behavior: Scripted Motor Tasks adapted from Section III of the MDS-UPDRS, and the sit-to-stand and stand-to-sit Postural Transitions.

Each definition consisted of a general definition of the task or transition, a description of prominent visual cues identifiable in a video recording, and the specific events, movements, and/or stimuli coders should use to determine the task's onset and offset frames. Variations of the task (e.g. left hand, right hand) and any expected deviations and how they should be coded were also included in the CS. Anatomical landmarks were used to guide identification of the onset and offset frames where possible. The full list of definitions can be found in Figure A.1.

Coder Training Protocol

All coding was performed using ELAN (v 5.0.0-beta for Mac iOS), a linguistic annotation software capable of frame-specific annotation of video. Coders were trained in the use of the CS (Figure A.1) and ELAN using a structured protocol and the guided coding of a series of training videos (Figure 3.1). Coders were required to use a predetermined configuration of ELAN settings to maintain consistency. The training videos ranged between 5 and 45 minutes in duration and contained exemplars of motor behaviors in patients with PD, with each video focusing on a new category of behavior (Figure 3.1). Raters were required to achieve an accuracy of 80% before they were granted approval to independently code videos for use in data analysis.

Figure 3.1: Flow Sheet Depicting Standardized Training Protocol Used for All Coders prior to participating in study

Coding Process

When coding a motor task, coders working in randomly assigned pairs individually determined its start time, its end time, and the name of the task performed. Frame-specific timestamps for individual behaviors within a task were generated at a resolution of ~ 0.033 seconds, the approximate duration of a frame in the video's 30 frames per second format.

Errors of commission were identified using the following criteria:

- Start timestamp difference between coders was greater than 0.335 seconds.
- End timestamp difference between coders was greater than 0.335 seconds.
- Coders identified different motor tasks were being performed.

Additionally, one-sided codes (i.e. errors of omission) were recorded whenever only one coder made a code that the other coder did not.

All videos were also coded by an expert coder (defined as a neurologist with an expertise in movement disorders) per the CS definitions in order to provide a measure of the internal validity of the definitions generated in the CS.

Statistical Methods

Descriptive statistics were generated using the raw timestamps generated across the entire dataset by individual coders. These included the frequency that a given motor task was coded, it's average duration (Table 3.1), the average difference in start and end times between paired coders, and the frequency of coding (Table 3.2). Paired samples *t*-tests were conducted to compare the mean durations of codes made by non-expert coders and the expert coder as a measure of the internal validity of the CS. These were calculated using all codes made by all non-expert coders across the dataset and therefore did not take into account errors of omission or commission.

Inter-rater agreement was calculated using Cohen's Kappa (κ) (J. Cohen, 1960). The study design allowed for production of a timed-event sequential dataset capable of detecting errors of omission and commission by coders (Bakeman et al., 2009). In order

to account for errors of omission (i.e. only one coder in a pair coded a motor event) codes from both coders were manually linked by the expert rater with expertise in movement disorders. Linked codes were considered in agreement if they met two criteria: (1) both coders identified it as the same motor task, and (2) the segments generated by the coders met or surpassed the overlap threshold of 50% as calculated by the start and end time of the behavior codes (Holle & Rein, 2015). The frequencies of agreement for each type of behavior were collated into agreement matrices, from which proportions of agreement for each type of behavior were derived. Three matrices with overlap thresholds of 50%, 70%, and 90% percent overlap were constructed and used to calculate κ.

Results

25 subjects with PD each underwent two video-recorded assessments, producing a total of 50 videos. Each video was independently coded by two trained coders using the CS, resulting in a dataset of 100 coded videos. Table 3.1 summarizes the frequency of coded tasks within the 100 videos as well as the mean and median durations.

Durations of Coded Behaviors

Scripted Motor Tasks had a median timestamp of between 4-12 seconds while Postural Transitions were between 1-2 seconds in duration (Table 3.1).

Table 3.1: Descriptive Statistics for Coded Tasks for 100 Video Files

Category	Coded Tasks	Frequency of Coded Task**	Timestamp Mean (SD)	Timestamp Median (IQR)	Timestamp Mean Expert (SD)	Timestamp Median Expert (IQR)
Scripted Motor Task*	Rigidity, Neck	97	4.900 (0.996)	4.853 (1.200)	4.972 (1.158)	4.900 (1.250)
Scripted Motor Task	Rigidity, Right Upper Limb	101	7.210 (1.754)	6.697 (1.750)	7.261 (1.862)	7.000 (1.584)
Scripted Motor Task	Rigidity, Left Upper Limb	98	7.470 (2.332)	7.067 (2.433)	7.459 (2.444)	6.900 (2.289)
Scripted Motor Task	Rigidity, Right Lower Limb	99	6.596 (1.745)	6.383 (1.909)	6.661 (1.764	6.433 (1.958)
Scripted Motor Task	Rigidity, Left Lower Limb	99	5.916 (1.526)	5.616 (1.683)	5.929 (1.541)	5.603 (1.742)
Scripted Motor Task	Finger Tapping, Right Hand	113	3.819 (2.301)	3.100 (1.934)	3.653 (2.025)	3.084 (1.717)
Scripted Motor Task	Finger Tapping, Left Hand	105	4.165 (2.636)	3.166 (2.633)	3.918 (1.998)	3.150 (2.558)
Scripted Motor Task	Fist Open and Close, Right Hand	103	5.172 (2.017)	5.067 (2.217)	5.182 (1.965)	5.000 (2.051)
Scripted Motor Task	Fist Open and Close, Left Hand	105	5.005 (2.180)	4.766 (2.033)	5.271 (2.966)	4.867 (1.934)
Scripted Motor Task	Pronation and Supination, Right Hand	106	5.695 (3.133)	4.967 (2.501)	5.859 (2.996)	4.971 (2.633)
Scripted Motor Task	Pronation and Supination, Left Hand	99	5.652 (2.640)	5.200 (2.232)	5.811 (2.556)	5.317 (2.225)
Scripted Motor Task	Toe Tapping, Right Foot	102	4.239 (1.594)	4.000 (1.642)	4.445 (1.816)	4.101 (2.117)
Scripted Motor Task	Toe Tapping, Left Foot	103	4.456 (1.556)	4.133 (1.667)	4.562 (1.544)	4.167 (1.699)
Scripted Motor Task	Stomping, Right Foot	101	4.332 (1.527)	4.067 (1.634)	4.536 (1.640)	4.433 (1.6)

Scripted Motor Task	Stomping, Left Foot	101	4.462 (1.906)	3.934 (1.800)	4.582 (2.063)	3.967 (1.866)
Scripted Motor Task	Postural Tremor, Right and Left Hands	123	11.89 (3.293)	12.412 (1.406)	12.209 (3.148)	12.400 (1.200)
Scripted Motor Task	Kinetic Tremor, Right Hand	94	5.231 (2.166)	4.769 (1.952)	5.501 (2.154)	4.934 (2.258)
Scripted Motor Task	Kinetic Tremor, Left Hand	96	5.034 (1.570)	4.649 (1.950)	5.201 (1.588)	4.900 (2.000)
Scripted Motor Task	Postural Stability*	177	2.373 (2.110)	1.633 (1.366)	1.870 (1.222)	1.466 (0.818)
Postural Transition	Sit-to-Stand	1201	1.834 (1.150)	1.600 (0.667)	1.915 (1.304)	1.633 (0.700)
Postural Transition	Stand-to-Sit	1012	1.114 (0.597)	1.000 (0.466)	1.117 (0.604)	0.967 (0.460)

* As defined in the MDS-UPDRS Section III

** Total number of times motor behaviors were assessed in 100 coded files (50 videos independently annotated by two Coders each)

*** Average κ values

A paired samples *t*-test was performed to compare mean duration between tasks coded by an expert coder to the raw values coded by independent, non-expert coders. Table 3.2 reports the p values for each task; only the coded tasks Postural Stability (p=0.015) and Rigidity, Left Upper Limb (p=0.005) displayed a significant difference in the mean duration.

Table 3.2: Comparison of Mean Coder Duration (Timestamp ss.ms) to Expert Coder for Scripted Motor Tasks and Postural Transitions for all 50 videos

Category	Coded task	Confidence Interval (95%)	*t*-value	Degrees of Freedom (df)	Significance (p<-.05)
Scripted motor task	Rigidity, Neck	[-0.660, 0.185]	-1.129	50	0.264
Scripted motor task	Rigidity, Right Upper Limb	[-0.754, 0.579]	-0.264	50	0.793
Scripted motor task	Rigidity, Left Upper Limb	[-1.727, -0.322]	-2.927	50	0.005*
Scripted motor task	Rigidity, Right Lower Limb	[-0.875, 0.353]	-0.855	49	0.397
Scripted motor task	Rigidity, Left Lower Limb	[-0.610, 0.569]	0.070	49	0.945
Scripted motor task	Finger Tapping, Right Hand	[-0.676, 1.051]	0.434	57	0.666
Scripted motor task	Finger Tapping, Left Hand	[-0.865, 0.715]	-0.190	51	0.850
Scripted motor task	Fist Open and Close, Right Hand	[-0.716, 0.932]	0.264	51	0.793
Scripted motor task	Fist Open and Close, Left Hand	[-1.242, 0.684]	-0.582	52	0.563
Scripted motor task	Pronation and Supination, Right Hand	[-1.129, 1.714]	0.413	52	0.681
Scripted motor task	Pronation and Supination, Left Hand	[-1.099, 0.658]	-0.504	49	0.617
Scripted motor task	Toe Tapping, Right Foot	[-0.449, 0.953]	0.721	51	0.474
Scripted motor task	Toe Tapping, Left Foot	[-0.584, 0.566]	-0.031	52	0.975
Scripted motor task	Stomping, Right Foot	[-0.502, 0.581]	0.146	50	0.884
Scripted motor task	Stomping, Left Foot	[-0.585, 0.841]	0.360	50	0.720
Scripted motor task	Postural Tremor, Right and Left Hands	[-1.190, 1.156]	-0.029	52	0.977
Scripted motor task	Kinetic Tremor, Right Hand	[-0.844, 1.055]	0.223	47	0.825
Scripted motor task	Kinetic Tremor, Left Hand	[-0.710, 0.736]	0.037	48	0.971
Scripted motor task	Postural Stability**	[0.129, 1.148]	2.485	98	0.015*
Postural Transitions	Sit-to-Stand	[-0.122, 0.182]	0.383	608	0.702
Postural Transitions	Stand-to-Sit	[-0.702, 0.091]	0.256	510	0.798

Inter-Rater Reliability of Annotated Tasks

We observed high levels of agreement for all Scripted Motor Tasks, with $\kappa > 0.8$, indicating strong agreement (Table 3.1), with the exception of Postural Stability ($\kappa = 0.617$). These high κ values were maintained at the more stringent 70% and 90% overlap thresholds for most Scripted Motor Tasks, while Postural Transitions demonstrated good agreement at the 50% and 70% overlap thresholds and poor agreement at the 90% overlap thresholds (Figure 3.2).

Figure 3.2: Cohen's κ values of IRA for individual tasks over the 50-video dataset. Each row and column represent an individual coded task and individual video, respectively. Each cell is colored to reflect the κ between the two independent coders who coded that task in that video. Yellow cells indicate a strong IRA as indicated by a high κ approaching 1, green cells a moderate IRA with κ approaching 0.5, blue cells a low IRA with κ approaching 0, and white cells indicate that the task was not coded by either coder in that video.

Errors of Omission and Commission

Differences in the frequency of errors were dependent on the motor activity being coded (Figure A.2). The most frequent error observed was a difference in the identification of the start time of Kinetic Tremor, Right Hand and Kinetic Tremor, Left Hand. The motor task Postural Stability possessed the highest frequency of inter-rater disagreement on the end of

the behavior. Postural Tremor, Right and Left Hands possessed the highest frequency of errors of omission, meaning it was only identified by one coder in a pair.

Discussion

Here we provide an analysis of a novel, detailed, and precise video coding scheme capable of quantifying the duration of selected motor tasks of MDS-UPDRS Section III and related behaviors sensitive to impairment in PD. MDS-UPDRS Scripted Motor Tasks were coded with a high degree of agreement between coders, as indicated by kappa values of 0.80 and above, with the exception of Postural Stability, which showed a moderate level of agreement.

Video coding of discrete behaviors has been extensively used in the behavioral and social sciences, but has only been used sparingly in the study of PD behavior. Djikstra and colleagues used video coding to validate multiple sensor platforms, with a focus on gait parameters including gait speed and distance (Dijkstra et al., 2008, 2010). Other groups have used force plates to define postural transitions based on force generation (Zijlstra et al., 2012).

This study used anatomical landmarks and visual cues extracted from the MDS-UPDRS' instructions to create a detailed coding scheme defining the onset and offset times of motor behaviors. Using this methodology we were able to show that anatomically based definitions for video coding can be recognized by trained non-expert raters to a high level of precision. The high agreement we achieved suggests that video coding, when given sufficiently accurate definitions, can reliably quantify subcomponents of the MDS-UPDRS.

As objective measures of impairment aligned to large video datasets such as this may be easily synchronized with other neurobiological datasets – e.g. those derived from bioimaging, genomics, histology, or biomarkers – video coding may allow for the functional impairments observed in MDS-UPDRS subcomponents to be more accurately related to primary measures of neuropathology in PD. Such a unified systems approach would encourage reproducibility, facilitate the integration of multimodal data, and allow for more powerful scientific hypotheses to be generated and tested, ultimately leading to the development of more detailed models of how they arise from PD's neuropathology.

Video coding studies in PD typically rely on coders with varying degrees of expertise in movement and movement disorders in order to code specific movements. Moore et al. (2011) used video annotation to detect gait abnormalities in a group of PD patients over 24 hours and used graduate level students with moderate expertise in movement measurement to code specific movements. Similar to our findings they were able to code specific tasks to a high level of precision using specific definitions. In our study, we have shown that, with minimal training, non-expert coders can generate these timestamps in video recordings of PD patients to the level of accuracy of an expert rater. These video segments may now able to be individually reviewed for specific clinical indicators, such as tremor, or range of motion, and their timestamps aligned to TOMs generated by sensors worn during the assessment. An example of the use of video annotation can be seen in analysis of postural instability. Analysis of video coding sets such as this can provide insights into both the cause and possible solutions to the variability observed in quantification of this cardinal PD symptom. Although postural instability was accurately identified as a motor

behavior by non-expert coders , the end time of the behavior was inconsistently recognized. The retropulsion test used to assess postural stability, which requires the examiner to destabilize the patient with a forceful backwards pull and observe their ability to recover, is difficult to consistently administer and as a result the true "end time" of this task demonstrates subjectivity in its definition and measurement (Nonnekes et al., 2015). Like many UPDRS tasks, kinematics, wearable sensors, and other objective measures have been applied to quantify aspects of the retropulsion test, adding an objective measurement to enhance the subjective score obtained from the MDS-UPDRS. Due to its low cost, simple training, and reliance on objective definitions, video coding can also provide an accurate, consistent definition of postural instability as assessed using the retropulsion test in order to validate the sensor-based algorithms needed to objectively measure PD impairment. Quantification of task duration in this way can allow for the measurement of the variability of their performance, an essential clinical endpoint that can be aligned to and used to better understand objective physical measures of variability.

Sub-components of task performance may reflect discrete impairments sensitive to a single neural control system (Curtze et al., 2015; Peterson & Horak, 2016). As a result, objective measures of task performance using "wearable sensors" are increasingly viewed as necessary to improving the precision and sensitivity with which we can monitor disease state (Horak & Mancini, 2013). Body-mounted accelerometers or "wearable sensors" are well positioned to objectively measure these sub-components . However, the use of wearable accelerometers in the MDS-UPDRS is largely unexplored, and in fact the MDS-UPDRS is often used as an outcome measure for sensor validation (Johansson et al., 2018).

Video annotation provides a compromise between the objective precision of wearable sensors and the subjective flexibility of the MDS-UPDRS's clinical ratings. The flexibility in video playback and reviewing allows for subtle characteristics of behaviors, such as subcomponents not reliably detectable during clinical assessments, to be precisely measured with little uncertainty in their interpretation (Bussmann et al., 1998). Although it cannot reliably measure amplitude or distance, video coding has granular resolution for temporal measurements (e.g. duration) and frequency (e.g. counting instantaneous events) far beyond what is available to an observer or clinician rater. While video coding falls short of wearable sensors in temporal precision, it avoids many of the challenges posed by wearable accelerometers, such as complicated analytical processes and expensive equipment, and in fact is frequently used to validate the outputs of prototype sensors (Heldman et al., 2014). Additionally, the flexibility in video playback and reviewing afforded to video coders allows them to identify characteristics of behaviors, including subtle or transient movements not reliably detectable during clinical assessments. This provides the opportunity for precise feature extraction necessary for machine learning algorithms.

Limitations

The technical limitations of this study are important to discuss. The assessments performed in this study were dependent on the equipment and personnel used for the clinical examinations. For example, when assessing the reasons for the differences observed between the timestamps generated by the expert rater and the non-expert raters it was found that a frequent, temporary obstruction of the camera was present when the clinician was assessing

rigidity on the left side, due to their blocking the camera's view of the subject. Future studies using this methodology should take care to ensure clear and continuous lines of sight, and to accurately disclose the camera equipment and angles used in order to ensure reproducibility. The definitions used for coding in this article represent a pilot attempt to perform a deep classification of tasks and behaviors sensitive to PD. This remains a major limitation which deserves further study, with models for accurate identification of discrete behaviors necessary. However, they do provide insight into this methodology's precision for quantifying motor behavior in PD. Lastly, the analysis methods used to evaluate reliability for video coding remain important to discuss. The algorithms for linking codes between coders are not well suited to continuous coding, which will be encountered by all studies attempting to provide continuous measurements for discrete behaviors (Albinali et al., 2009; Aminian et al., 1999; Fokkenrood et al., 2014). Future work directed at advanced analytical methods such as Bayesian or forest plot methods may be more suitable for analysis of reliability in video coding.

Future Directions

Video coding allows for objective quantification of behaviors contained within the MDS-UPDRS which has the potential for enhancement of clinical measurements of PD, alignment with sensor derived end-points and generation of improved neuropathological models for individual behaviors in PD. This provides multiple opportunities for clinical translation in PD allowing the capture of discrete behaviors in PD and objective measures of each of these behaviors. In combination with wearable sensors, detailed video coding provides a

common language by which potential biomarkers may be validated, providing powerful objective endpoints for accompanying the MDS-UPDRS clinical assessment.

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Author Contributions

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CHAPTER FOUR: VARIATIONS IN REST-ACTIVITY RHYTHM ARE ASSOCIATED WITH CLINICALLY MEASURED DISEASE SEVERITY IN PARKINSON'S DISEASE

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Abstract

The continuous, longitudinal nature of accelerometry monitoring is well-suited to capturing the regular 24-hour oscillations in human activity across the day, the cumulative effect of our circadian rhythm and behavior. Disruption of the circadian rhythm in turn disrupts rest-activity rhythms. Although circadian disruption is a major feature of Parkinson's disease (PD), rest-activity rhythms and their relationship with disease severity have not been well characterized in PD. 13 PD participants (Hoehn & Yahr Stage [H&Y] 1 – 3) wore a Philips Actiwatch Spectrum PRO continuously for two separate weeks. Rest-activity rhythms were quantified by fitting an oscillating 24-hour cosinor model to each participant-day of activity data. One-way ANOVAs adjusted for demographics revealed significant variation in the amount (MESOR, $F = 12.76$, $p < 0.01$), range (Amplitude, $F = 9.62$, $p < 0.01$), and timing (Acrophase, $F = 2.7$, $p = 0.05$) of activity across H&Y Stages. Those with higher H&Y Stages were significantly more likely to be active later in the day, where-as those who shifted between H&Y Stages during the study were significantly more active

than those who did not change H&Y Stage. Being active later in the day was also significantly associated with higher scores on the Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Section III (motor symptom severity, $p = 0.02$), Section II (self-reported impact of motor symptoms on daily living, $p = 0.01$), and Total Score ($p = 0.01$) in an adjusted linear regression model; significant associations between MDS-UPDRS scores and activity levels were observed only in the unadjusted model. These findings demonstrate that continuous actigraphy is capable of detecting rest-activity disruption in PD, and provides preliminary evidence that rest-activity rhythms are associated with motor symptom severity and H&Y Stage.

Keywords

Parkinson's disease

actigraphy

rest-activity rhythm

cosinor

rhythmometry

Introduction

The circadian rhythm is thought to be associated with underlying neurodegenerative processes and is increasingly recognized as a major component of Parkinson's disease (PD) (Videnovic & Golombek, 2013). Diurnal oscillations are present in PD's characteristic mo-

tor and non-motor symptoms, circadian biomarkers such as melatonin and body temperature exhibit a depressed diurnal amplitude, and the neurological processes underlying circadian rhythm are altered by the dopaminergic treatments used to mitigate parkinsonian symptoms (Baumann-Vogel et al., 2017; Gros & Videnovic, 2017; K. Suzuki et al., 2007; van Someren et al., 1996). Circadian disruption is associated with a myriad negative sequelae, including metabolic, cardiac, and endocrine syndromes, mental and neuropsychiatric disorders, and sleep disruption (Korshunov et al., 2017; Vetter, 2018).

Actigraphy, the process of monitoring activity using body-worn sensors, has been used to study circadian disruption through altered sleep patterns in multiple populations, such as adolescents (Arora & Taheri, 2015) and shift workers (Hulsegge et al., 2019). Although actigraphy has the disadvantage of inferring behavior through movement, it permits continuous and longitudinal measurement that would be infeasible with methods such as clinical scales and polysomnography. Actigraphy also provides an objective measure of behavior in place of self-report motor and sleep diaries, which are often considered subjective in nature (Horak & Mancini, 2013). Due to their small size and capacity to continuously record activity for days to weeks at a time, actigraphy has seen increasingly extensive use in PD research (Espay et al., 2017; M. Suzuki et al., 2017) to objectively quantify motor symptoms (Johansson et al., 2018), measure sleep disruption (Baumann-Vogel et al., 2017), and provide objective measures of gait and balance during motor tasks (Zampieri et al., 2010).

Without exogenous zeitgebers (e.g. regular light-dark cycles), the human circadian rhythm has an endogenous period of approximately 24.2 hours (Burgess & Eastman, 2008;

Czeisler et al., 1999), which would gradually desynchronize it from the 24-hour day. A combination of exogenous cues – e.g. light and social interaction – and endogenous mechanisms – e.g. clock gene feedback loops – continuously entrain the circadian rhythm, effectively synchronizing it with the environment. However, artificial zeitgebers such as light-emitting technology and readily accessible social media, which are ubiquitous in modern societies, can desynchronize the circadian rhythm from the calendar day (Vetter, 2018). In addition, the timetables and obligations of our modern industrial society often diverge from natural light-dark cycles and thus can disrupt biological rhythms. The continuous, longitudinal nature of actigraphic monitoring is well-suited to capturing such disturbances, both through sleep disruption and through assessment of Rest-Activity Rhythms (RAR), the regular 24-hour oscillation in human activity across the daily sleep-wake cycle. RAR can be parametrically modelled by fitting a sine-cosine function with a 24-hour period to time-series accelerometry data, allowing the average, range, and phase-shift of activity to be quantified. Actigraphic evaluation of RAR in neurodegenerative disease is not a new approach – actigraphy has been used to monitor changes in the stability of RAR in Alzheimer's disease (van Someren et al., 1996) – and the continuing advancement and ubiquity of wearable sensors has enabled larger and more detailed datasets to be produced.

Herein we continuously assessed RAR using wrist-worn actigraphy in persons with PD collected over two full weeks in a prospective study. Our objective was to further characterize circadian disruption in PD and determine its associations with disease severity, with the broader aim of developing a methodological and statistical model to characterize circadian disruption in PD and its relationship to disease severity in future work.

Materials and Methods

Participants

This paper is a retrospective analysis of an observational study performed in 2016 whose primary objective was to evaluate the feasibility of an electronic application (app) for reporting quality of life and disease symptom outcomes. The participants, 5 older healthy controls (not included in this paper's analysis) and 15 persons with a diagnosis of idiopathic PD (Hoehn & Yahr Stage 1 – 3), were enrolled on a "first come first serve" basis so long as they met criteria. All participants underwent in-home and in-lab activity monitoring with a Philips Actiwatch Spectrum PRO and a network of BioSensics PAMSys devices (only persons with PD were included in this analysis). Herein we present an analysis of the Philips Actiwatch data, specifically aimed at extracting rest-activity rhythms from the longitudinal and continuous actigraphic recordings.

A single Philips Actiwatch recording accelerometry at 32 Hz was worn by participants on the wrist of their symptomatically least-affected side for two seven-day at-home periods. The recording weeks were separated by an average of 36.31 days (standard deviation = 4.80, range = [28 - 49]). Participants were instructed to wear the devices as often as possible except when they would be submerged in water (e.g. showering, swimming). Participants were also instructed to maintain their normal routine and behavior, and asked to complete electronic quality of life and motor diaries, while wearing the sensors at-home. All participants gave their written informed consent before participating in the study (BUSM IRB H-34656), and all study activities were performed in accordance with the

Declaration of Helsinki (World Medical Association, 2013). Each at-home recording period was followed by an in-lab visit where participants underwent clinical assessments.

Perceived daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS), quality of life was assessed using the Euro-QoL 5-Dimension (EQ-5D) instrument and the Euro-QoL Visual Analogue Scale (EQ-5D-VAS), perceived severity of parkinsonian symptoms was evaluated with the Parkinson's Disease Questionnaire, 8-Point (PDQ8), and disease state was assessed using the Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS). The MDS-UPDRS was administered by one of three trained neurologists during the participant's in-lab visit immediately before each week of recording; participants were assessed while ON medication. Demographics, including daily intake of levodopa medication (in milligrams), were obtained from the participants through self-report. Overall cognitive function was assessed using the Mini-Mental Status Examination (MMSE) on their first in-lab visit before the at-home recording period.

Descriptive Rhythmometry

Tri-axial accelerometry data from the Philips Actiwatch was downloaded using the Philips Actiware 5.0 and transformed into Activity Counts (AC) binned into 15-second epochs[42]. The AC time-series was segmented into days (n = 5760 epochs per day). In order to maximize available data, days were defined as starting with the 18:00:00 – 18:00:15 epoch and

[42] Actiware uses a proprietary algorithm to automatically extract AC from raw accelerometry data, which are not directly accessible.

ending with the 17:59:45 – 18:00:00 epoch (due to scheduling, participant recording began in the late morning to late afternoon). For clarity, models will be referred to by their starting day (e.g. Sunday cosinors start at 18:00:00 and end at 17:59:45 on Monday). Oscillating sin-cosine models with periods of 24-hours (a "cosinor model") were fitted to the daily AC time-series using the least squares method (cheart, 2008; Nelson et al., 1979). The cosinor produces three parameters that characterize the participant's rest-activity rhythms: the Mid-line Estimating Statistic of Rhythm (MESOR) represents the midline of the fitted cosinor function, that is the average AC across the model's sample (i.e. a day) and about which the cosinor function oscillates; Amplitude (Amp) is equal to difference in the average peak (or trough) of the cosinor function and it's midline; Acrophase (Acro) is the relative phase-shift of the peak amplitude from the reference time marking the start of the cosinor function (in this case, 18:00). Cosinor models were generated for all of those days with no more than 15% missing data (i.e. 864 epochs or 3.6 hours), which was usually caused by the participant removing the Actiwatch.

Baseline and Clinical Characteristics

Before the primary analysis, descriptive statistics were generated for the baseline variables collected at enrollment (Age, Sex, Handedness, BMI, MMSE Score, and Levodopa In-take)[43] and clinical endpoints collected after each week of in-home recording (ESS, PDQ8,

[43] Circadian rhythm undergoes a forward phase-shift with increasing age and has a slightly longer period in men; chronic circadian disruption is associated with increased BMI and impaired cogni-tion; while there is little evidence implicating handedness as a modulator of circadian rhythm, it may affect data collected through wrist-worn actigraphy; levodopa therapy can alter circadian rhythm.

EQ-5D, MDS-UPDRS, and H&Y Stage). To determine if clinical characteristics significantly varied between the two in-home recording weeks, paired sample t-tests were conducted for continuous variables (ESS, EQ-5D-VAS, and MDS-UPDRS Section Scores) and Wilcoxon Mann-Whitney rank-sum tests were conducted for non-continuous variables (PDQ8, EQ-5D , and H&Y Stage).

Participants were sorted into sub-groups by their H&Y Stage. Participants whose H&Y Stage changed between the two weeks were defined as their own groups: either H&Y Stage 1/2 (for those who were rated at Stage 1 and Stage 2) or H&Y Stage 2/3 (for those who were rated at Stage 2 and Stage 3). No participant's H&Y Stage changed by more than one between the two weeks. While some participants were evaluated by multiple neurologists during the study due to scheduling and availability, all participants who changed H&Y Stage were evaluated by the same neurologist at both time points. To determine if baseline characteristics significantly varied by H&Y Stage, one-way Analyses of Variance (ANOVAs) were conducted for the analysis of continuous variables (Age, BMI, MMSE Score, and Levodopa Intake) and Pearson's chi-square analyses were conducted for categorical variables (Sex and Handedness).

Rest-Activity Rhythm

Cosinor rhythmometry was performed in MATLAB v9.4 (MathWorks Inc., Natick, MA, R2018a). Data were arranged and visualized in Microsoft Excel v16.16.7 (Microsoft Inc., Redmond, WA) and analyzed using Stata/SE v15.1 (StataCorp LLC, Texas, USA). The threshold for statistical significance was set to $p < 0.05$. All summary statistics are reported

as Average (± Standard Deviation) for continuous data and Number (Percent) for categorical, ordinal, and dichotomous data.

Univariate analysis of cosinor parameters and their association with clinical variables was calculated using one way ANOVA and linear regression. Bivariate models were subsequently performed between cosinor parameters and baseline characteristics. Associations with continuous variables (age, BMI, MMSE score, ESS score, and daily levodopa intake) were quantified with simple linear regressions, and for dichotomous variables (sex and handedness) odds ratios were calculated using simple logistic regressions.

The primary analytical question was whether the participant's rest-activity rhythm significantly varied by disease severity, as measured by H&Y Stage sub-group and by MDS-UPDRS Sections. For the former, one-way ANOVAs were conducted for each of the cosinor parameters (MESOR, Amplitude, and Acrophase) with H&Y Stage as the independent grouping variable. Simple linear regressions were used to measure the degree of association between each cosinor parameter and each MDS-UPDRS Section, including Total Score.

ANOVAs and regressions except for bivariate associations with baseline and clinical characteristics were performed twice: once in an unadjusted model with no predictors besides H&Y Stage or MDS-UPDRS score, and then repeated in a model adjusted by age, BMI, ESS score, daily levodopa intake, and sex.

Results

Missing Data

Two participants were excluded at the beginning of analysis due to excessive missing data, resulting in an analytical sample of 13 participants. Out of a total possible 182 participant-days (14 in-home study days * 13 participants), 58 (31.87%) participant-days were excluded from the cosinor analysis due to greater than 15% missing data within a given day (Table A.1). Across all participants, the greatest proportion of excluded participant-days was on Monday (n = 24, 92.31%). This could be ascribed to being the day participants began and ended study activities with an in-lab visit, resulting in much of the day usually not being recorded. The next greatest proportion of excluded participant-days was on Saturday (n = 10, 38.46%), with Thursday having the least excluded participant-days (n = 2, 7.69%). Across all days, H&Y Stage 3 had the highest percent excluded (n = 17, 40.48%) and H&Y Stage 2 the lowest (n = 10, 23.81%).

Baseline Characteristics

The participant's age, sex, hand dominance, BMI, cognitive status, and daily levodopa intake did not significantly vary by H&Y Stage (p = 0.22 – 0.94; Table 4.1).

Table 4.1: Demographic characteristics of the final analytical cohort and outcomes of statistical tests by H&Y Stage.

	H&Y Stage 1/2	H&Y Stage 2	H&Y Stage 2/3	H&Y Stage 3	All	Comparison of Means Between H&Y Stages	
	n = 1	n = 6	n = 3	n = 3	n = 13	One-Way ANOVA or Pearson χ^2 test	
Age (Years) †	62.00 (-)	61.5 (4.72)	59.33 (9.24)	59.67 (3.79)	60.62 (5.20)	F(3, 9) = 0.14	p = 0.94
Sex (Male) ◊	1 (100.00%)	4 (66.67%)	1 (33.33%)	1 (33.33%)	7 (53.85%)	z = 2.27	p = 0.52
Hand Dominance (Right) ◊	1 (100.00%)	6 (100.00%)	2 (66.67%)	2 (66.67%)	11 (84.62%)	z = 2.76	p = 0.43
BMI (kg/m^2) †	21.11 (-)	27.22 (3.82)	28.88 (4.43)	25.47 (1.72)	26.73 (3.76)	F(3, 9) = 1.31	p = 0.33
MMSE (Total Score) †	29.00 (-)	29.83 (0.41)	28.00 (2.00)	28.00 (2.00)	28.92 (1.50)	F(3, 9) = 1.80	p = 0.22
Levodopa Intake (mg/day) †	800.00 (-)	501.04 (441.17)	683.33 (395.99)	400.00 (173.21)	542.79 (358.68)	F(3, 9) = 0.44	p = 0.73

Abbreviations: ANOVA (Analysis of Variance), BMI (Body Mass Index), H&Y (Hoehn and Yahr), kg (kilogram), mg (milligram), MMSE (Mini-Mental Status Examination), PD (Parkinson's Disease).

Age, BMI, MMSE, and Levodopa Intake provided in Mean (Standard Deviation); Sex and Hand Dominance provided in: Number (%).

† Summary statistics are provided in Mean (Standard Deviation); between-group comparison made with a One-Way ANOVA

◊ Summary statistics are provided in Number (%); between-group comparison made with a Pearson χ^2 test

Clinical Characteristics, Change Across Study Weeks

The participants did not significantly vary in their MDS-UPDRS scores between the two weeks ($p = 0.26 - 0.68$; Table 4.2). Although some participants transitioned between H&Y Stages between the two weeks, this was not significant across the sample ($p = 0.17$). Patient-reported disease state, quality of life, and daytime sleepiness did not significantly vary between the two weeks (PDQ8: $p = 0.84$, EQ-5D: $p = 0.90 – 0.97$, ESS: $p = 0.92$). Six of the 13 participants presented with unilateral tremor (as identified by MDS-UPDRS Item 3.17 “Resting Tremor”) – four on the left side, two on the right side (data not shown). The remaining seven participants presented with no resting tremor in their limbs. No participants presented with bilateral resting tremor during the study.

Table 4.2: Clinical and quality of life characteristics of the final analytical cohort and outcomes of statistical tests between the two week-long recording periods.

	Week 1	Week 2	All Weeks	Comparison of Means Between Weeks Paired t-test or Wilcoxon Mann-Whitney Rank-Sum Test	
	n = 13	n = 13	n = 26		
Hoehn & Yahr Stage ◊	2.46 (0.52)	2.15 (0.55)	2.31 (0.55)	z = 1.38	p = 0.17
MDS-UPDRS Section I †	9.69 (6.76)	10.15 (6.89)	9.92 (6.69)	t = -1.07	p = 0.31
MDS-UPDRS Section II †	10.08 (5.48)	11.15 (8.09)	10.62 (6.79)	t = -0.94	p = 0.37
MDS-UPDRS Section III †	22.23 (8.81)	23.23 (11.61)	22.73 (10.11)	t = -0.43	p = 0.68
MDS-UPDRS Section IV †	4.54 (2.40)	5.15 (3.46)	4.85 (2.94)	t = -1.10	p = 0.29
MDS-UPDRS Total Score †	46.54 (18.55)	49.69 (23.97)	48.12 (21.06)	t = -1.17	p = 0.26
PDQ8 (Total Score) ◊	6.00 (4.20)	6.62 (4.89)	6.31 (4.48)	z = -0.21	p = 0.84
EQ-5D (Total Score) ◊ ‡	6.25 (1.36)	6.42 (1.93)	6.33 (1.63)	z = 0.12	p = 0.90
EQ-5D-VAS † ‡	79.58 (13.56)	79.42 (19.97)	79.50 (16.69)	t = 0.03	p = 0.97
ESS (Total Score) † ‡	7.75 (3.31)	7.67 (3.92)	7.71 (3.54)	t = 0.10	p = 0.92

Abbreviations: CI (Confidence Interval), ESS (Epworth Sleepiness Scale), EQ5D (Euro-Quality of life, 5 Dimension), MDS-UPDRS (Movement Disorder Society's Unified Parkinson's Disease Rating Scale), PD (Parkinson's Disease), PDQ8 (Parkinson's Disease Questionnaire, 8-point), VAS (Visual Analogue Scale).

† Summary statistics are provided in Mean (Standard Deviation); between-group comparison made with a paired t-test

◊ Summary statistics are provided in Number (%); between-group comparison made with a Wilcoxon Mann-Whitney Rank-Sum Test

‡ Week 2 data for one participant was not included for these assessments due to data loss, and were excluded from the summary statistics and statistical tests for those assessments.

Rest Activity Rhythm, Association with Baseline Characteristics

Bivariate linear regressions (Table A.2) demonstrated a significant association between higher MESOR and lower age ($p < 0.01$, Coef. = -1.83 AC/year), lower BMI ($p < 0.01$, Coef. = -1.88 AC/kg/m^2), lower MMSE score ($p < 0.01$, Coef. = -3.41 AC/point), increased daily levodopa intake ($p < 0.01$, Coef. = 0.02 AC/mg levodopa/day), being female ($p < 0.01$, Male Odds Ratio = 0.95), and being left-handed ($p < 0.01$, Right Hand Odds Ratio = 0.95). A greater range of activity (Amplitude) was significantly associated with lower age ($p < 0.01$, Coef. = -1.71 AC/year), lower BMI ($p < 0.01$, Coef. = -1.67 AC/kg/m^2), lower MMSE score ($p < 0.01$, Coef. = -4.11 AC/point), lower ESS score ($p = 0.04$, Coef. = -0.96 AC/point), increased daily levodopa intake ($p < 0.01$, Coef. = 0.02 AC/mg levodopa/day), being female ($p < 0.01$, Male Odds Ratio = 0.95), and being left-handed ($p < 0.01$, Right Hand Odds Ratio = 0.95). A forward-shifted Acrophase was significantly associated with a lower MMSE score ($p = 0.02$, Coef. = -16.12 minutes/score) and a higher daily levodopa intake ($p < 0.01$, Coef. = 0.08 minutes/mg levodopa/day).

Rest-Activity Rhythm, Association with MDS-UPDRS, Unadjusted

Bivariate linear regressions demonstrated that an increased MESOR was significantly associated with a higher Section I score ($p = 0.05$, Coef. = 0.56 AC/score) and Section IV score ($p < 0.01$, Coef. = 3.16 AC/score) in Week 1, a higher Section IV score ($p < 0.01$, Coef. = 3.27 AC/score) in Week 2, and a lower Section III score ($p = 0.03$, Coef. = -0.35 AC/score) and higher Section IV score ($p < 0.01$, Coef. = 3.27) in a sample containing both

weeks. A higher range of activity (Amplitude) was significantly associated with a higher Section I score ($p < 0.01$, Coef. = 0.75 AC/score), Section IV score ($p < 0.01$, Coef. = 2.84 AC/score), and a higher Total Score ($p = 0.04$, Coef. = 0.21 AC/score) in Week 1, a higher Section IV score ($p < 0.01$, Coef. = 3.25 AC/score) in Week 2, and a higher Section I score ($p = 0.04$, Coef. = 0.49 AC/score) and a higher Section IV score ($p < 0.01$, Coef. = 3.02) in a sample containing both weeks. A forward-shifted Acrophase was significantly associated with a higher Section I score ($p < 0.01$, Coef. = 5.18 minutes/score) in Week 1, a higher Section I score ($p < 0.01$, 6.40 minutes/score), higher Section II score ($p < 0.01$, 5.68 minutes/score), higher Section III score ($p < 0.01$, 3.45 minutes/score), and higher Total Score ($p < 0.01$, 2.13 minutes/score) in Week 2, and a higher Section I score ($p < 0.01$, 5.78 minutes/score), higher Section II score ($p < 0.01$, 4.80 minutes/score), higher Section III score ($p < 0.01$, 2.45 minutes/score), and higher Total Score ($p < 0.01$, 1.75 minutes/score) in a sample containing both weeks.

Table 4.3: Cosinor parameters of the final analytical cohort***, tabulated by Study Week and by H&Y Stage, and the outcomes of one-way ANOVAs conducted by H&Y Stage, and linear regressions conducted by MDS-UPDRS score across all participants.**

Table 4.3A MESOR	H&Y Stage 1/2 n = 1	H&Y Stage 2 n = 6	H&Y Stage 2/3 n = 3	H&Y Stage 3 n = 3	All n = 13	Comparison of Means Between H&Y Stages One-Way ANOVA, Unadjusted		Association with MDS-UPDRS Section I Linear Regression, Unadjusted		Association with MDS-UPDRS Section II Linear Regression, Unadjusted		Association with MDS-UPDRS Section III Linear Regression, Unadjusted		Association with MDS-UPDRS Section IV Linear Regression, Unadjusted		Association with MDS-UPDRS Total Linear Regression, Unadjusted	
Week 1	36.52 (7.37)	22.03 (7.28)	44.75 (21.23)	34.15 (9.33)	31.62 (15.44)	F(3, 57) = 11.17	p < 0.01*	Coef. = 0.56	p = 0.05*	Coef. = 0.11	p = 0.77	Coef. = -0.25	p = 0.27	Coef. = 3.16	p < 0.01*	Coef. = 0.08	p = 0.44
Week 2	43.48 (13.54)	19.98 (5.67)	41.27 (34.58)	24.87 (12.55)	28.90 (21.61)	F(3, 59) = 5.47	p < 0.01*	Coef. = 0.26	p = 0.52	Coef. = -0.26	p = 0.44	Coef. = 0.09	p = 0.09	Coef. = 3.50	p < 0.01*	Coef. = -0.04	p = 0.71
All Weeks	40.00 (11.01)	20.99 (6.53)	42.90 (28.71)	29.70 (11.75)	30.24 (18.80)	F(3, 120) = 13.52	p < 0.01*	Coef. = 0.40	p = 0.10	Coef. = -0.17	p = 0.48	Coef. = -0.35	p = 0.03*	Coef. = 3.27	p < 0.01*	Coef. = -0.00	p = 0.95

Table 4.3B Amplitude	H&Y Stage 1/2 n = 1	H&Y Stage 2 n = 6	H&Y Stage 2/3 n = 3	H&Y Stage 3 n = 3	All n = 13	Comparison of Means Between H&Y Stages One-Way ANOVA, Unadjusted		Association with MDS-UPDRS Section I Linear Regression, Unadjusted		Association with MDS-UPDRS Section II Linear Regression, Unadjusted		Association with MDS-UPDRS Section III Linear Regression, Unadjusted		Association with MDS-UPDRS Section IV Linear Regression, Unadjusted		Association with MDS-UPDRS Total Linear Regression, Unadjusted	
Week 1	32.26 (9.86)	22.21 (9.66)	42.40 (17.75)	32.87 (10.56)	30.44 (14.57)	F(3, 57) = 8.94	p < 0.01*	Coef. = 0.75	p < 0.01*	Coef. = 0.26	p = 0.44	Coef. = 0.17	p = 0.43	Coef. = 2.84	p < 0.01*	Coef. = 0.21	p = 0.04*
Week 2	44.50 (15.84)	20.62 (7.47)	39.42 (31.96)	25.39 (15.11)	28.87 (20.88)	F(3, 59) = 4.92	p < 0.01*	Coef. = 0.24	p = 0.53	Coef. = -0.32	p = 0.33	Coef. = -0.36	p = 0.10	Coef. = 3.25	p < 0.01*	Coef. = -0.05	p = 0.65
All Weeks	38.38 (14.11)	21.40 (8.57)	40.82 (25.92)	29.28 (13.23)	29.64 (18.00)	F(3, 120) = 11.10	p < 0.01*	Coef. = 0.49	p = 0.04*	Coef. = -0.15	p = 0.51	Coef. = -0.19	p = 0.22	Coef. = 3.02	p < 0.01*	Coef. = 0.04	p = 0.60

Table 4.3C Acrophase	H&Y Stage 1/2 n = 1	H&Y Stage 2 n = 6	H&Y Stage 2/3 n = 3	H&Y Stage 3 n = 3	All n = 13	Comparison of Means Between H&Y Stages One-Way ANOVA, Unadjusted	Association with MDS-UPDRS Section I Linear Regression, Unadjusted	Association with MDS-UPDRS Section II Linear Regression, Unadjusted	Association with MDS-UPDRS Section III Linear Regression, Unadjusted	Association with MDS-UPDRS Section IV Linear Regression, Unadjusted	Association with MDS-UPDRS Total Linear Regression, Unadjusted
Week 1	12:13 (1:35)	13:32 (1:40)	14:20 (1:44)	13:36 (1:55)	13:37 (1:47)	F(3, 57) = 2.19 p = 0.10	Coef. = 5:11 p < 0.01*	Coef. = 3:05 p = 0.22	Coef. = 0:29 p = 0.76	Coef. = 4:52 p = 0.40	Coef. = 1:09 p = 0.11
Week 2	13:00 (2:10)	13:16 (2:00)	14:00 (1:32)	14:22 (2:27)	13:39 (2:01)	F(3, 59) = 1.25 p = 0.30	Coef. = 6:24 p < 0.01*	Coef. = 5:41 p < 0.01*	Coef. = 3:27 p < 0.01*	Coef. = 7:20 p = 0.12	Coef. = 2:08 p < 0.01*
All Weeks	12:36 (1:51)	13:24 (1:50)	14:09 (1:37)	13:58 (2:11)	13:38 (1:54)	F(3, 120) = 2.62 p = 0.05	Coef. = 5:47 p < 0.01*	Coef. = 4:48 p < 0.01*	Coef. = 2:27 p = 0.01*	Coef. = 6:25 p = 0.07	Coef. = 1:45 p < 0.01*

Summary statistics are provided in Mean (Standard Deviation)

**MESOR and Amplitude are reported in *AC* for mean and standard deviation, and in *AC per UPDRS score* for regression coefficients. Note that Acrophase is reported in *hour:minute* for mean and standard deviation, and in *minute:second per UPDRS score* for regression coefficients.

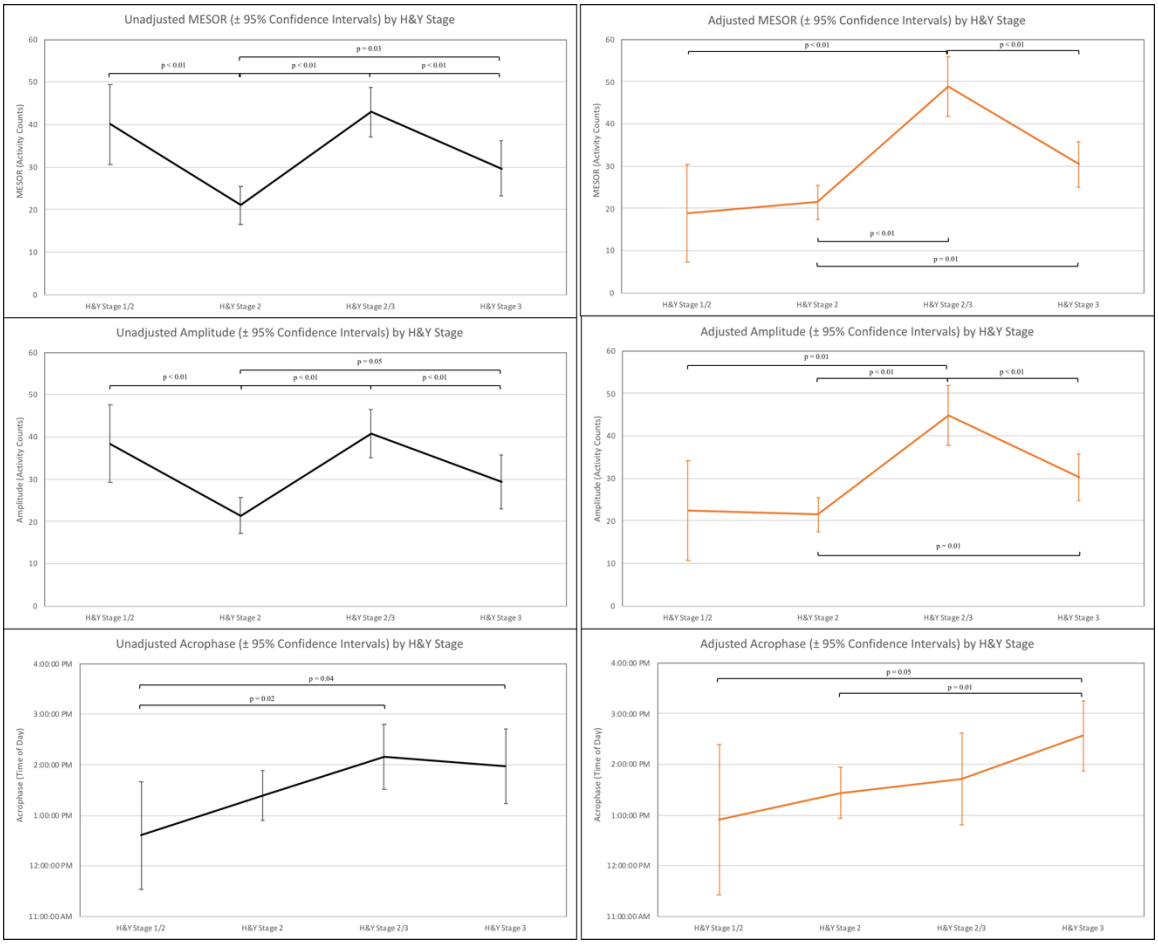
***The sample analyzed contained n = 61 cosinor participant-days and degrees of freedom of F(6, 54) for Week 1, n = 60 and degrees of freedom of F(6, 53) for Week 2, and n = 121 and degrees of freedom of F(6, 114) for both Weeks combined.

Abbreviations: AC (Activity Count), ANOVA (Analysis of Variance), CI (Confidence Interval), Coef = [Regression] Coefficient, H&Y (Hoehn and Yahr), MDS-UPDRS (Movement Disorder Society's Unified Parkinson's Disease Rating Scale), MESOR (Midline Estimating Statistic Of Rhythm). * = $p < 0.05$

Rest-Activity Rhythm, Variation by H&Y Stage

In the models unadjusted for baseline and demographic characteristics (Table 4.3; Figure 4.1), significant variation in mean and range, but not timing, of activity was consistently observed across H&Y Stages for the first week (MESOR: F[3, 57], F = 11.17, $p < 0.01$; Amplitude: F[3, 57], F = 8.94, $p < 0.01$; Acrophase: F[3, 57], F = 2.19, p = 0.10), the second week (MESOR: F[3, 59], F = 5.47, $p < 0.01$; Amplitude: F[3, 59], F = 4.92, $p < 0.01$; Acrophase: F[3, 59], F = 1.25, p = 0.30), and across both weeks of recording (MESOR: F[3, 120], F = 13.52, $p < 0.01$; Amplitude: F[3, 120], F = 11.10, $p < 0.01$; Acrophase: F[3, 120], F = 2.62, p = 0.05). MESOR and Amplitude remained significantly different between H&Y Stages after adjustment of the model for age, sex, ESS score, daily levodopa intake, and BMI ($p < 0.01$; Table 4.4; Figure 4.1). Acrophase was not significantly different between H&Y Stages during Week 1 (F[8, 53], F = 0.83, p = 0.48) in the adjusted model, although it achieved significance in Week 2 (F[8, 51], F = 3.92, p = 0.01) and across both weeks (F[8, 112], F = 2.70, p = 0.05).

Figure 4.1: Modelled values for MESOR (top), Amplitude (middle), and Acrophase (bottom) for each Hoehn & Yahr Stage generated from one-way ANOVA models. The left column shows values from unadjusted models and the right column shows values from models adjusted for age, sex, ESS score, daily levodopa intake, and BMI. Significant differences between Hoehn & Yahr Stages ($p < 0.05$) are shown and were calculated using within-model pair-wise comparisons.



Rest-Activity Rhythm, Association with MDS-UPDRS, Adjusted

Adjustment for baseline characteristics (age, sex, BMI, handedness, daily levodopa intake, MMSE score, and ESS score) eliminated all of the significant bivariate associations observed between MDS-UPDRS Sections and MESOR/Amplitude, with the exception of MESOR remaining significantly and negatively associated with Section III scores across both weeks ($p = 0.05$, Coef. = -0.36 AC). The associations between Acrophase and Section I for Week 1 and both Weeks became non-significant after adjustment (Week 1: $p = 0.88$, Coef. = 0.30 minutes; Both Weeks: $p = 0.16$, Coef. = 2.55 minutes). Acrophase remained significantly and positively associated with Section II for Week 2 ($p < 0.01$, Coef. = 4.80 minutes) and across both Weeks ($p < 0.01$, Coef. = 3.73 minutes), with Section III for Week 2 ($p < 0.01$, Coef. = 5.40 minutes) and across both Weeks ($p = 0.02$, Coef. = 0.85 minutes), and with the Total Score for Week 2 ($p < 0.01$, Coef. = 1.93 minutes) and across both weeks ($p = 0.01$, Coef. = 1.28 minutes).

Table 4.4: Cosinor parameters of the final analytical cohort***, tabulated by Study Week and by H&Y Stage, and the outcomes of one-way ANOVAs conducted by H&Y Stage, and linear regressions conducted by MDS-UPDRS score across all participants, adjusted by age, BMI, ESS score, daily levodopa intake, and sex.**

Table 4.4A MESOR	H&Y Stage 1/2 n = 1	H&Y Stage 2 n = 6	H&Y Stage 2/3 n = 3	H&Y Stage 3 n = 3	All n = 13	Comparison of Means Between H&Y Stages One-Way ANOVA, Adjusted		Association with MDS-UPDRS Section I Linear Regression, Adjusted		Association with MDS-UPDRS Section II Linear Regression, Adjusted		Association with MDS-UPDRS Section III Linear Regression, Adjusted		Association with MDS-UPDRS Section IV Linear Regression, Adjusted		Association with MDS-UPDRS Total Linear Regression, Adjusted	
Week 1	36.52 (7.37)	22.03 (7.28)	44.75 (21.23)	34.15 (9.33)	31.62 (15.44)	F(8, 52) = 21.97	p < 0.01*	Coef. = 0.22	p = 0.41	Coef. = 0.30	p = 0.29	Coef. = -0.33	p = 0.16	Coef. = 1.18	p = 0.18	Coef. = 0.02	p = 0.82
Week 2	43.48 (13.54)	19.98 (5.67)	41.27 (34.58)	24.87 (12.55)	28.90 (21.61)	F(8, 51) = 4.64	p < 0.01*	Coef. = -0.01	p = 0.99	Coef. = -0.14	p = 0.66	Coef. = -0.53	p = 0.11	Coef. = 1.34	p = 0.36	Coef. = -0.08	p = 0.49
All Weeks	40.00 (11.01)	20.99 (6.53)	42.90 (28.71)	29.70 (11.75)	30.24 (18.80)	F(8, 112) = 12.76	p < 0.01*	Coef. = 0.10	p = 0.70	Coef. = -0.02	p = 0.94	Coef. = -0.36	p = 0.05*	Coef. = 1.09	p = 0.13	Coef. = -0.04	p = 0.56

Table 4.4B Amplitude	H&Y Stage 1/2 n = 1	H&Y Stage 2 n = 6	H&Y Stage 2/3 n = 3	H&Y Stage 3 n = 3	All n = 13	Comparison of Means Between H&Y Stages One-Way ANOVA, Adjusted		Association with MDS-UPDRS Section I Linear Regression, Adjusted		Association with MDS-UPDRS Section II Linear Regression, Adjusted		Association with MDS-UPDRS Section III Linear Regression, Adjusted		Association with MDS-UPDRS Section IV Linear Regression, Adjusted		Association with MDS-UPDRS Total Linear Regression, Adjusted	
Week 1	32.26 (9.86)	22.21 (9.66)	42.40 (17.75)	32.87 (10.56)	30.44 (14.57)	F(8, 52) = 11.61	p < 0.01*	Coef. = 0.35	p = 0.19	Coef. = 0.31	p = 0.29	Coef. = 0.06	p = 0.80	Coef. = 0.97	p = 0.28	Coef. = 0.11	p = 0.29
Week 2	44.50 (15.84)	20.62 (7.47)	39.42 (31.96)	25.39 (15.11)	28.87 (20.88)	F(8, 51) = 4.38	p < 0.01*	Coef. = -0.08	p = 0.87	Coef. = -0.21	p = 0.49	Coef. = -0.45	p = 0.15	Coef. = 0.29	p = 0.84	Coef. = -0.10	p = 0.41
All Weeks	38.38 (14.11)	21.40 (8.57)	40.82 (25.92)	29.28 (13.23)	29.64 (18.00)	F(8, 112) = 9.62	p < 0.01*	Coef. = 0.14	p = 0.59	Coef. = -0.08	p = 0.71	Coef. = -0.20	p = 0.26	Coef. = 0.76	p = 0.29	Coef. = -0.02	p = 0.74

Table 4.4C Acrophase	H&Y Stage 1/2 n = 1	H&Y Stage 2 n = 6	H&Y Stage 2/3 n = 3	H&Y Stage 3 n = 3	All n = 13	Comparison of Means Between H&Y Stages One-Way ANOVA, Adjusted		Association with MDS-UPDRS Section I Linear Regression, Adjusted		Association with MDS-UPDRS Section II Linear Regression, Adjusted		Association with MDS-UPDRS Section III Linear Regression, Adjusted		Association with MDS-UPDRS Section IV Linear Regression, Adjusted		Association with MDS-UPDRS Total Linear Regression, Adjusted	
Week 1	12:13 (1:35)	13:32 (1:40)	14:20 (1:44)	13:36 (1:55)	13:37 (1:47)	F(8, 52) = 0.83	p = 0.48	Coef. = 0:18	p = 0.88	Coef. = 1:49	p = 0.41	Coef. = -1:38	p = 0.36	Coef. = 1:23	p = 0.84	Coef. = -0:01	p = 0.98
Week 2	13:00 (2:10)	13:16 (2:00)	14:00 (1:32)	14:22 (2:27)	13:39 (2:01)	F(8, 51) = 3.92	p = 0.01*	Coef. = 7:21	p = 0.01*	Coef. = 4:48	p < 0.01*	Coef. = 5:24	p < 0.01*	Coef. = 5:45	p = 0.51	Coef. = 1:56	p < 0.01*
All Weeks	12:36 (1:51)	13:24 (1:50)	14:09 (1:37)	13:58 (2:11)	13:38 (1:54)	F(8, 112) = 2.70	p = 0.05*	Coef. = 2:33	p = 0.16	Coef. = 3:44	p < 0.01*	Coef. = 0:51	p = 0.02*	Coef. = 6:03	p = 0.23	Coef. = 1:17	p = 0.01*

Summary statistics are provided in Mean (Standard Deviation)

**MESOR and Amplitude are reported in *AC* for mean and standard deviation, and in *AC per UPDRS score* for regression coefficients. Note that Acrophase is reported in *hour:minute* for mean and standard deviation, and in *minute:second per UPDRS score* for regression coefficients.

***The sample analyzed contained n = 61 cosinor participant-days and degrees of freedom of F(6, 54) for Week 1, n = 60 and degrees of freedom of F(6, 53) for Week 2, and n = 121 and degrees of freedom of F(6, 114) for both Weeks combined

Abbreviations: AC (Activity Count), ANOVA (Analysis of Variance), CI (Confidence Interval), H&Y (Hoehn and Yahr), MDS-UPDRS (Movement Disorder Society's Unified Parkinson's Disease Rating Scale), MESOR (Midline Estimating Statistic Of Rhythm). * = $p < 0.05$

Discussion

This study has found that rest-activity rhythms, quantified via rythmometric cosinor analysis of actigraphy data, vary with disease severity in PD and are associated with clinical ratings of disease state. MESOR and Amplitude, which measure the average and range of activity, did not increase linearly with H&Y Stage but were instead significantly higher in participants whose H&Y Stage changed over the study period. Participants with more severe and burdensome symptoms (i.e. higher MDS-UPDRS Sections I, II, and III scores) were less active on average and had a smaller range of activity; however this association became non-significant once demographic covariates were accounted for. A consistent relationship was observed between the timing of activity (Acrophase) and increased disease severity as assessed by both H&Y Stage and by MDS-UPDRS scores, which remained significant after including covariates in the model.

Rest-Activity Rhythms are Associated with Disease Severity in PD

Circadian disruption of molecular, neurological, and behavioral systems is increasingly recognized as a major component in PD with implications for symptom management and the development of therapeutic interventions (Fifel & Videnovic, 2019; Videnovic & Golombek, 2017). Although actigraphy has been widely used to characterize both the hallmark motor impairments and non-motor symptoms (i.e. sleep disruption) in PD (Artusi et al., 2018; Horak & Mancini, 2013; M. Suzuki et al., 2017), objective measures of rest-activity rhythms in PD are scarce. Relative to healthy controls, persons with PD have lower daytime activity, increased inter-daily variability in activity, and increased activity during

sleep resulting in sleep disruption (Madrid-Navarro et al., 2018; Niwa et al., 2011; Whitehead et al., 2008). Our results generally support these findings, as we observed a consistent negative association between MDS-UPDRS Sections I - III and average activity and range of activity. Although the depression of rest-activity rhythms may worsen with increasing disease severity (Fifel & Videnovic, 2019), reported associations between activity levels and MDS-UPDRS scores have been inconsistent (Madrid-Navarro et al., 2018; Niwa et al., 2011). A significant positive association between Section IV (Motor Fluctuations) and amplitude of activity was reported by Whitehead et al. (2008), where-as we observed a negative non-significant association. Our use of the revised MDS-UPDRS versus Whitehead et al.'s use of the original UPDRS may explain this. Our results are consistent with Niwa et al.'s (2011) finding that activity amplitude is negatively associated with MDS-UPDRS Section III (Motor Exam). However, Madrid-Navarro et al. (2018) found no significant associations between range of activity and any MDS-UPDRS Section.

Curiously, the association between disease severity and activity did not extend to H&Y Stages: rather, participants whose H&Y Stage changed over the course of the study had higher activity than those who remained in the same Stage (clinically, participants who received two separate H&Y Stages approximates a cohort with a variable disease state, or a cohort with disease severity straddling the division between the two stages). This may indicate that amplitude of activity is affected by fluctuations in disease state in addition to its overall severity. However, it is uncertain if this is a genuine trend, or the result of normal but unaccounted for inter-individual heterogeneity in rest-activity rhythms, which remain a poorly characterized aspect of actigraphic rhythmometry in PD (Fifel & Videnovic, 2019;

Madrid-Navarro et al., 2018). Small sample sizes may amplify the effects of such inter-individual variances, which highlights the need for future studies including larger cohorts.

Biological Implications of Rest-Activity Rhythms

Dopamine is integral to the neuropathology of PD (Fahn, 2008; Hornykiewicz, 1966; Kalia & Lang, 2015; Videnovic & Golombek, 2013); it's depletion due to dopaminergic cell death in the substantia nigra pars compacta is considered the primary cause of PD's characteristic motor symptoms, and the main therapeutic strategies focus on mitigating its sequelae (either directly through dopamine agonists or indirectly through deep brain stimulation). Given that dopamine exhibits circadian rhythmicity with a diurnal morning peak in cerebrospinal fluid (Poceta et al., 2009) and is involved in multiple circadian regulatory systems – e.g. light adaptation in the retina (Witkovsky, 2004) and clock gene expression in the dorsal striatum (Hood et al., 2010) – it has been hypothesized that pathological dopaminergic depletion would inevitably impair the neural regulation of the circadian rhythm (Videnovic & Golombek, 2017). Furthermore, hypocretin-positive cell loss – a neuropathological characteristic of narcolepsy – occurs in the hypothalamus in PD proportional to disease progression (Thannickal et al., 2007), and the concentration of hypocretin in cerebrospinal fluid has been associated with loss of muscle atonia in REM sleep (Bridoux et al., 2013) and excessive daytime sleepiness (Wienecke et al., 2012).

Although actigraphy cannot directly measure these biological markers, it is capable of monitoring rest-activity rhythms as an estimate of circadian rhythm (Ancoli-Israel et al., 2003). Human rest-activity rhythms are a systemic behavioral output produced by many

interacting biological (e.g. sleep drive, temperature, heart rate) and environmental (e.g. work schedule) influences (Vetter, 2018). Rest-activity rhythms therefore provide a generalized measure of circadian integrity in an ecologically valid "real life" setting (J. A. Mitchell et al., 2017), with the acknowledgement that they are the product, not a direct measure, of circadian rhythm (Vetter, 2018). By quantifying the gross output of a complex systems, one trades the biological specificity of biomarkers for the generalizability of a simple behavioral outcome: did their rest-activity rhythm change? Actigraphic rhythmometry has been applied in this way in healthy (J. A. Mitchell et al., 2017), geriatric (Hopkins et al., 2017), and neurodegenerative populations (Musiek et al., 2018) using both parametric (i.e. cosinor) and non-parametric models to monitor gross behavioral change. Generally, older age and neurodegenerative diseases are associated with a reduced amplitude of activity and greater fragmentation of rest-activity rhythms within and across days. These trends are thought to reflect impairment of the neural control mechanisms that synchronize circadian and behavioral cycles to each other and to the environment, either due to normal aging, chronic misalignment (e.g. shift work), or neural insult secondary to injury or pathology (Vetter, 2018).

Limitations

This analysis has several limitations that should be considered when interpreting our findings. First, our analytical model assumes that all of the participants follow a similar rest-activity rhythm, therefore any observed differences may be attributed to covarying characteristics (i.e. disease severity). This is a reasonable assumption given all recorded sleep

times, with the exception of one outlier, fell between 5:18 PM and 10:12 AM; however it's possible that some of our observed results may be due, in part, to normal inter-individual variations in circadian and circaseptan rest-activity patterns. Second, our small sample size limits the power of our statistical tests and restricts our ability to interpret the results. Fortunately, this analytical model can be easily applied to larger cohorts in order to replicate the observed effects. Third, the two weekly data-sets were merged for this analysis. This was done to compensate for the sporadic missing data (~32.14% of participant-days are missing) and requires the assumption that there is no true difference in participant rest-activity rhythms between the two weeks. To ensure no bias was introduced into actigraphically derived circadian rhythm data, imputation was not employed. Finally, we lack valuable lifestyle and health information about our participants, notably their employment and social obligations that could affect their rest-activity rhythms (e.g. Friday-night social events). Opportunities for future research may lie in the inclusion of other factors that could alter their rest-activity patterns, such as sleep disorders or use of substances known to affect sleep behavior (e.g. alcohol, marijuana, stimulants, prescribed medications, etc.), or in the application of algorithms to detect specific behaviors in actigraphy, such as rest tremor during sleep. While we observed no difference between men and women in their daytime sleepiness as assessed by the ESS (data not shown), it may be prudent to include this in other, larger studies.

Conclusion

This study demonstrates that rest-activity rhythms are associated with disease severity and fluctuations in symptom intensity. RAR as measured by actigraphy was able to provide important insights into neurobiological behavior of participants with PD demonstrating associations with phase shifting to later in the day and overall decreases in activity by disease severity. Circadian disruption is a critical non-motor aspect of PD that requires the integration of molecular, neural, pathological, and behavioral research to effectively understand and treat (Fifel & Videnovic, 2019; Vetter, 2018). Actigraphically monitored rest-activity rhythms are an objective and easily scalable measure of circadian rhythmicity that leverages the innate advantages and growing use of actigraphic monitoring in PD. In combination with gold-standard clinical assessments, diagnostic biomarker panels, and in vivo bioimaging, actigraphically measured rest-activity rhythms may enhance our ability to interrogate the neuropathology underlying PD and its relationship with sleep and circadian disruption.

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CHAPTER FIVE: THE IMPACT OF CHRONOTYPE ON CIRCADIAN, REST-ACTIVITY RHYTHM, AND SLEEP CHARACTERISTICS ACROSS THE WEEK

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Abstract

In order to prepare for regular daily behaviors such as eating and sleeping, many animals rely on their circadian ("about day") rhythm, a complex "system of systems" that continuously entrains biological processes with each other and the environment. Although humans predominantly entrain to solar time, individual persons vary in the precise timing of circadian-influenced events, such as sleep timing and physical activity, due to endogenous and exogenous factors. Innate differences in the timing of individual circadian rhythms relative to a common environmental cue are known as chronotypes, ranging from earlier than average (Morningness) to later than average (Eveningness). Furthermore, individual behavior is often constrained by social constructs such as the seven day week: the regular shift between different work and rest days gives rise to chronic circadian disruption such as social jet lag (SJL) and sleep debt, as one's circadian rhythm lags behind abrupt "sociogenic" changes in behavioral rhythms. The impact our social calendar has on our circadian rhythm is modified by chronotype; e.g. Eveningness chronotypes generally wake up earlier than

preferred on work days. However, current gold-standard methods such as polysomnography (PSG) are ill-suited to the type of long-term monitoring needed to collect behavioral rhythms across the week. Our aim in this study was to employ objective actigraphic monitoring across multiple continuous weeks of out-of-clinic normal behavior in order to identify consistent "about weekly" – i.e. *circaseptan* – patterns in rest-activity rhythm and sleep characteristics, including evaluating the agreement between self-reported and objective measures of circadian timing. 24 young male volunteers (mean age 23.46 years) wore a Philips Actiwatch for four weeks while going about their normal lives. Chronotype was primarily assessed through self-report on the Morningness-Eveningness Questionnaire. Sleep characteristics were derived using Actiware; daily rest-activity rhythms were modelled using a basic 3-parameter cosinor function. Linear mixed models were employed to account for the nested, repeated-measures design, and included random effects to account for the considerable variability expected from uncontrolled *in situ* recordings. We observed that both Eveningness and Morningness Chronotypes were more active and slept later on the weekends than on weekdays. Significant between-Chronotype differences in sleep timing and duration were observed within individual days of the week, especially during transitions between weekends and the work-week. Moreover, Chronotypes significantly varied in their circaseptan rest-activity and sleep rhythms: e.g. Morningness Chronotypes generally adapted their sleep duration, timing, and quality between weekends and weekdays quicker than Eveningness Chronotypes. Our results contribute to a growing body of evidence that both day of the week and individual chronotype must be accounted for *in situ*

observational studies of human behavior, especially when chronotype, sleep behavior, and/or circadian rhythms are of interest.

Keywords

Chronotype

Rest-Activity Rhythm

Sleep

Actigraphy

Circaseptan

Week

Introduction

The circadian rhythm is the regular periodic oscillation in behavior and physiological processes synchronized with the geophysical 24 hour solar day ("circadian" = "about day"). Organized as a distributed yet coordinated "system of systems", the circadian rhythm is an interconnected and hierarchical network of periodic molecular, genetic, neurological, and physiological processes embedded in cells, tissues, organs, and neural control networks that synchronize the body's myriad biological and homeostatic functions to each other and to their environment (M. H. Hastings et al., 2014). Functionally, the circadian rhythm prepares biological systems for expected behavioral states; for example, core body temperature in humans peaks during the afternoon and reaches its nadir during the early morning, anticipating daytime activity and nighttime torpor respectively. The human circadian

rhythm has a period of approximately 24.2 hours and, in isolation, would gradually drift out of synchrony with the solar day (Burgess & Eastman, 2008; Czeisler et al., 1999). However, a combination of exogenous cues – predominantly light – and endogenous biological mechanisms receptive to these cues – e.g. translational-transcriptional feedback loops – continuously entrain the circadian rhythm via the hypothalamic Suprachiasmatic Nucleus (SCN), effectively synchronizing our internal biological rhythms to each other and their environment.

While the biology and period of the circadian rhythm are generally consistent between individuals, the *phase* (i.e. timing) of the circadian rhythm can vary greatly from person to person. This can be seen in the colloquialisms of "morning larks" and "night owls", respectively referring to those who prefer to go to sleep and wake up earlier than normal or later than normal. In the chronobiology literature, these concepts are referred to as *chronotypes*, which may refer to a general phenotype (e.g. Morningness) or to a specific measurement of circadian timing (e.g. sleep mid-time) relative to a sample or population (Vetter, 2018). Chronotypes are dependent on several intrinsic and environmental factors, most notably genetic predisposition, age, sex, and the amplitude, timing, and concentration of environmental light exposure (Roenneberg et al., 2015). Every person has an innate preferred chronotype, which predictably shifts earlier or later across the lifetime depending on their age and sex, and which can be acutely modulated by changes in their behavior and environmental *zeitgebers* (German: "time giver", i.e. a stimulus capable of entraining the circadian rhythm).

Ideally, an individual's innate circadian chronotype and rhythm are tightly coupled with both their expressed behavioral chronotype and the solar day; i.e. requires minimal day-to-day resynchronization and which doesn't impinge upon behavioral rhythms (e.g. eating, sleeping). However, artificial zeitgebers such as light-emitting technology can shift the circadian rhythm independently of the solar day (Vetter, 2018). The timetables and obligations of our modern industrial society often diverge from natural light-dark cycles (e.g. shift work, jet lag), and our seven day work week imposes arbitrary changes in behavioral timing that can further decouple one's circadian rhythm from their environment (e.g. waking up for work vs. sleeping in on the weekend). These disruptions vary in severity and frequency by chronotype. For example, both adults and schoolchildren tend to sleep longer, later, and poorer on weekend nights ("2005 Sleep in America Poll – Adult Sleep Habits and Styles," 2015; Bei et al., 2014; Crowley & Carskadon, 2010; Taylor et al., 2008). This effect becomes more pronounced in those with a later chronotype since their preference to go to sleep later conflicts with their social obligations (i.e. work). When this obligation is removed on rest days, they "sleep in" to make up the sleep deficit accumulated during the workweek (Vitale et al., 2015). The biological cost of these circadian disruptions may include increased risk of cardiovascular and metabolic disease, obesity, and depression (Korshunov et al., 2017).

This habitual discrepancy in sleep timing between work and rest days is common form of circadian disruption known as Social Jet Lag (SJL) (Leypunskiy et al., 2018; McMahon et al., 2019; Vetter, 2018; Wittmann et al., 2006; Wong et al., 2015). SJL arises from differences in natural (i.e. biological, environmental) and artificial (i.e. social) timing

systems; while the distribution of chronotypes in the general population is broad, ranging from extreme eveningness to extreme morningness, the distribution of work schedules is far more compact and constrained by artificial factors such as economics, logistics, law, and culture (Roenneberg et al., 2015). The result is that most of the population is forced to adapt to a social/work schedule too early or too late for their natural chronotype, and then revert back to their natural preference once social constraints are removed on rest days. While all chronotypes can develop SJL, Eveningness chronotypes are significantly more likely to do so (Roenneberg et al., 2019; Takahashi et al., 2018; Wittmann et al., 2006; Zerbini et al., 2020). Looking across multiple weeks, this periodic transition between social and biological "time zones" and the SJL it entails may be described as a *circaseptan* ("circa" = about "septan" = seven) rhythm of circadian disruption.

SJL and chronotypes are measured by proxy, usually via changes in the timing of sleep (itself a systemic behavioral output regulated in part by the circadian rhythm) across the week (Roenneberg et al., 2019; Vetter, 2018). While sleep disruption has been traditionally assessed using in-clinic polysomnography (PSG) as it offers the highest resolution and accuracy for sleep measurements, controlled laboratory settings cannot replicate *in situ* sleep behavior for several reasons: the unfamiliar setting, the myriad instruments, and the controlled environment each have poorly understood effects on sleep (Roenneberg et al., 2015). Moreover, while controlled sleep studies have greatly advanced our knowledge of sleep's structure and neurological substrates, they have given relatively little insight into the functional and longitudinal interactions between sleep, behavior, and the circadian

rhythm *in situ* (Roenneberg et al., 2015). In other words, well-controlled in-laboratory studies lack "ecological validity"; they offer unparalleled resolution and specificity, yet this narrow scope inherently limits their generalizability and therefore our ability to translate their findings into clinical and functional applications (Andrade, 2018; Roenneberg et al., 2015; Vetter, 2018).

Actigraphy, the use of wearable accelerometers to continuously measure physical behavior, is increasingly used to monitor sleep behavior in one's normal environment as an alternative to in-clinic polysomnography (Ancoli-Israel et al., 2015). While actigraphy has the disadvantages of inferring sleep via decreased movement, increased risk of missing data due to subject non-compliance, and is a non-specific measure susceptible to background noise, it is capable of continuous longitudinal measurement that would be infeasible with polysomnography and thus has greater ecological validity (Espay et al., 2016; Ibáñez et al., 2018; Roenneberg et al., 2019). In addition to its metabolic, symptomatic, and kinematic applications, actigraphic data can also be used to model the diurnal fluctuations in physical activity known as rest-activity rhythms (RAR), providing an additional approach to objectively assess changes in circadian rhythm (Meyer-Rochow & Brown, 1998).

Herein we present sleep and circadian data derived from actigraphy collected continuously from a cohort of young adult male volunteers across a full month *in situ* to generate a multi-week accelerometry data-set; this study included at-home self-report assessments and in-clinic polysomnography, genetic testing, and cortisol/melatonin assays, which are discussed elsewhere (Marshall et al., 2020 (under review)). Our objectives were to quantify and describe associations between actigraphically assessed RAR and sleep

characteristics derived from the same data-set, their variation across days of the week and self-reported chronotype, and concordance between self-reported and actigraphically assessed measures of circadian timing and chronotype.

Materials and Methods

Participants

24 healthy volunteers underwent in-home actigraphic monitoring for two 14-day in-home periods separated by a 3-day sleep lab phase (Friday evening – Monday morning). Participants wore five Philips Actiwatch Spectrum sensors recording at 32Hz during the in-home period – one on each wrist and ankle (secured by watch-bands) and one on the anterior torso (secured by Tegaderm [3M, Minnesota, USA]). While at-home, participants were instructed to wear the devices as often as possible except when they would be submerged in water and to maintain their normal routine and behavior while wearing the sensors. Only the actigraphic data collected from the Philips Actiwatch Spectrum worn on the non-dominant wrist is analyzed and discussed in this paper; other results from this study are discussed in Marshall et al., 2020 (under review).

Only volunteers who met the following criteria were offered enrollment into the study: Male; Between 18 and 40 years old (inclusive); English fluency; Non-smoker (including both cigarettes and nicotine vaping); Body Mass Index (BMI) < 30 kg/m^2; No self-reported history of sleep, psychological, neurological, or addictive disorders; Not a shift-worker; Does not change time zones frequently or have a highly irregular sleep schedule; No blood-draw contraindications (anemia, iron deficiency, fear of blood or needles); Not

claustrophobic; Does not have a pacemaker; No allergy to nickel or skin adhesive; and Not dependent on or abusing a substance within the previous six months. All participants gave their informed consent before participating in the study (BUSM IRB H-33035).

Demographics and Clinical Endpoints

Age, sex, BMI, and handedness were obtained through self-report during the first visit. Participants also completed several self-report instruments: the Epworth Sleepiness Scale (ESS) to evaluate daytime sleepiness, the Pittsburgh Sleep Quality Index (PSQI) to evaluate sleep quality, and the Morningness-Eveningness Questionnaire (MEQ) to evaluate chronotype (J. A. Horne & Östberg, 1977). Participants were separated into two groups based on their MEQ scores: those with an MEQ score above 52 were assigned to the Morningness group, and the remainder were assigned to the Eveningness group. This division was based on the observation of a bimodal distribution in MEQ scores, with participants clustering around two peaks at MEQ scores of ~40 and ~60, and were was implemented in order to maximize the contrasts between Chronotypes. Since these peaks were close to the MEQ's baseline cutoffs (41/42 and 58/59), the clusters of participants with similar chronotypes would've been split between multiple groups per the MEQ's cutoffs, which would have reduced group homogeneity and potentially obfuscated between-group differences.

Actigraphy

Accelerometry from the Philips Actiwatch was extracted as "Activity Counts" (AC) and binned ("epoched") in 15-second epochs (Brooks et al., 2020); raw accelerometer data (i.e. voltage) from the Philips Actiwatch is inaccessible and can only be extracted by conversion to AC. The AC algorithm Actiware uses to do this is proprietary, though it may be based off of the Zero Crossing Method (ZCM) algorithm – which reports the number of times the accelerometer's voltage crossed a predetermined threshold in a given epoch as that epoch's AC – due to ZCM's high sensitivity when classifying sleep and subsequent popularity in sleep scoring algorithms (Fekedulegn et al., 2020). Using Actiware 5.0's built-in segmentation algorithm, epoched AC data were then temporally segmented into different behavioral "intervals": either Active, Rest (from which one Sleep interval per Rest interval can be derived), or Excluded (i.e. for periods with no data, such as when the Actiwatch was not being worn). The segmentation algorithm for differentiating Active from Rest Intervals is based solely off activity levels, but further information about how the segmentation algorithm works is unknown as it is also proprietary (Chow et al., 2016). Active and Excluded Intervals were omitted from further analysis, and the remaining Rest Intervals were filtered so that only those containing overnight Sleep Intervals would be analyzed. Specifically, sleep characteristics were derived only from Sleep Intervals that started between 1800 and 0600 and which were determined to not be false positives (i.e. short, idle periods misidentified by the algorithm as sleep) by manual review.

While we cannot access the AC algorithm, segmentation algorithm, or the raw accelerometry data directly, Actiware has published its sleep scoring algorithm (Mini Mitter

Company, Inc., 2006). Briefly, it calculates a "Total AC" – more generally referred to as a "sleep score" (Fekedulegn et al., 2020) – for each epoch by summing the weighted ACs of that epoch and those of adjacent epochs using this formula:

$$\text{Total AC for Epoch}_n\ (E_n) = (E_{n-8} * 0.04) + (E_{n-7} * 0.04) + (E_{n-6} * 0.04) + (E_{n-5} * 0.04) + (E_{n-4} * 0.2) + (E_{n-3} * 0.2) + (E_{n-2} * 0.2) + (E_{n-1} * 0.2) + (E_n * 4) + (E_{n+1} * 0.2) + (E_{n+2} * 0.2) + (E_{n+3} * 0.2) + (E_{n+4} * 0.2) + (E_{n+5} * 0.04) + (E_{n+6} * 0.04) + (E_{n+7} * 0.04) + (E_{n+8} * 0.04)$$

Note: the number of epochs summed and their respective AC weights is different for each epoch length; this formula is for the 15-second epochs used in this analysis.

If an epoch's Total AC is less than or equal to a predetermined "Wake Threshold Value", it is classified as Asleep; otherwise, it's classified as Awake. Actiware then applies one of two Sleep Interval detection algorithms, using either continuous periods classified as Asleep or sustained periods of immobility to define the Sleep Interval. Which algorithm is used and some of its parameters are manually customizable. We used the sustained immobility algorithm with the following parameters: Wake Threshold Value = 20 (epochs with Total AC greater than this value are classified as Awake); Immobile Minutes Onset = 10 (the beginning of a given Rest Interval's Sleep Interval is defined as the first epoch of the first continuous series of epochs this many minutes long where no more than one epoch has ≥ 1 AC); Immobile Minutes Offset = 10 (the end of a given Rest Interval's Sleep Interval is defined as the last epoch of the last continuous series of epochs this many minutes long where no more than one epoch has ≥ 1 AC); Enhanced Sleep Statistics = Off (if On, this modifies several sleep characteristics using correction factors derived from PSG and other Rest intervals in the recording; we chose not to use this because what corrections are used and how they're specifically applied is unknown); 1 Major Rest Interval/Day = Off

(If On, this only allows only one Rest Interval ≥ 3 hours – specifically the longest – to be defined in a single 24-hour period); Minor Rest Interval Sensitivity = Medium (a lower sensitivity will detect fewer Rest Intervals); Minor Rest Interval Minimum = 40 (Rest Intervals must be at least this many minutes long).

Sleep Characteristics

Sleep characteristics quantifying the timing, duration, and quality of sleep were generated for each Rest Interval with a valid overnight Sleep Interval: measures of sleep timing included Sleep Onset time (SON), Sleep Mid-time (SMID), and Sleep Offset time (SOFF); measures of duration included Sleep Onset Latency (SONL), Sleep Offset Latency (SOFFL), Sleep Period (SP), Time in Bed (TiB), Total Sleep Time (TST), and Wake After Sleep Onset (WASO); and measures of sleep quality included Sleep Efficiency (SE), Percent Sleep Time (PST), Fragmentation Index (FI), Average AC per minute during sleep (ACm), and Maximum AC per minute during TiB (AC Max).

SON and SOFF approximate the start and end of sleep, and are defined by the Immobile Minutes Onset/Offset options, respectively, as described above; SMID is simply the mean of SON and SOFF. SONL is the time difference between the start of the Rest Interval and the start of the Sleep Interval (i.e. how long it took to fall asleep); SOFFL is likewise the difference between the end of the Sleep Interval and the end of the Rest Interval (i.e. how long it took to wake up). SP is equal to the duration of the Sleep Interval (i.e. SP = SOFF - SON), and TiB is equal to the duration of the Rest Interval (i.e. TiB = SP + SONL + SOFFL). SP can be subdivided into TST/WASO, which are equal to the summed

durations of all Asleep/Awake epochs in the SP, respectively (i.e. SP = TST + WASO). SE is a percentage measure of general sleep quality where SE = TST / TiB, and PST is a similar characteristic calculated by dividing TST by SP; i.e. PST does not include SOFFL or SONL. Due to their similarities in calculation and interpretation, SE and PST are often conflated with each other in the literature (Berger et al., 2005; Fekedulegn et al., 2020). FI is a percentage measure of how likely a person is to transition between Asleep and Awake during their SP, and is calculated (Mini Mitter Company, Inc., 2006) as:

> Fragmentation Index = ([number of mobile bouts] + [number of immobile bouts ≤ 1 minute]) / [number of immobile bouts]

…where a "bout" is a continuous series of epochs of the same type, and where epochs with ≥ 1 AC are considered "mobile". Higher FI is indicative of frequent night-time arousals and/or increased somnolescent movement. ACm is equal to the total number of AC detected during the Sleep Interval (i.e. SP) divided by its duration, and AC Max is equal to the greatest number of AC observed in a 15-second epoch during the Rest Interval (i.e. TiB).

Rest-Activity Rhythm (RAR) Characteristics

The raw epoch-by-epoch AC time-series for each participant-day was fit to a basic 3-parameters cosinor model (Cornelissen, 2014) – a modified sine-cosine function with a period of 24 hours frequently used to model human RARs – and three parameters that characterize the participant's RAR were produced. The Midline Estimating Statistic of Rhythm (MESOR) represents the midline of the fitted cosinor function; i.e. the average AC across

the entire day and about which the cosinor function oscillates. The Amplitude (Amp) is equal to difference between the average peak of the cosinor function and its MESOR. The Acrophase (Acro) represents how phase-shifted the individual's RAR is relative to the other participants. Cosinors were only generated for at-home days with at least 20 hours and 24 minutes (4896, or 85%, of the 5760 15-second epochs in a day) of successful actigraphy data capture; participant-days that contained any time spent in the mid-study weekend sleep clinic were excluded. The time periods cosinors were applied to were selected to provide sufficient data coverage for modelling; since participants typically began the study in the mid-to-late afternoon, we modelled cosinors on 24-hour periods running from the epoch starting at 18:00:00 through the epoch starting at 17:59:45 the next day, for a total of 5760 epochs (or 24 full hours) per cosinor model. This allowed us to ensure that each overnight sleep period was fully encapsulated within a single cosinor model and that each participant's sleep and RAR characteristics were paired within each of their study days for analysis; specifically, sleep characteristics were paired to the cosinor parameters they occurred within. Since sleep periods and our cosinor intervals straddle midnight and therefore overlap two calendar days, we refer to individual days by the name of the following calendar day in this article for simplicity: e.g. results presented under "Saturday" consist of Friday night's sleep period and the cosinor model running from 18:00:00 Friday to 17:59:45 Saturday.

Circaseptan Characteristics

Two endpoints were calculated to estimate sociogenic circaseptan disruption – chronic differences in sleep behavior, timing, and quality resultant from social obligations and the work week: (1) Social Jetlag (SJL) is the absolute difference between one's average SMID on before-work nights (i.e. Sunday through Thursday nights) and on before-rest nights (i.e. Friday and Saturday nights), and (2) Sleep Debt is the absolute difference in average SP between before-work and before-rest nights (Wong et al., 2015). Where-as SJL quantifies the difference in sleep *timing* between weekends and workdays, Sleep Debt quantifies the difference in sleep *duration*.

Statistical Analysis

Descriptive statistics were generated for all variables; unless otherwise stated, all descriptive values reported herein are "*mean (standard deviation)*" for continuous variables and "*number (%)*" for dichotomous, ordinal, and categorical variables. Measures of central tendency consisted of means and medians for normally and non-normally distributed variables, respectively. Processed data were organized and arrayed using Excel 16.16.13 for Mac (Microsoft, Inc., Redmont, WA, USA). All statistical analyses were performed in Stata 16.0 for Mac (StataCorp, Inc., College Station, TX, USA). Normality of distributions was evaluated using skewness-kurtosis tests, and equality of variances between groups was evaluated using equal-variances test. Two-sample comparisons were conducted using two-sample t-tests for normally distributed samples with equal variances, Welch's t-tests for

normally distributed samples with unequal variances, and Wilcoxon rank-sum tests for non-normally distributed samples with a significance threshold of $p = 0.05$.

In order to account for nesting, repeated measures, and the random effects of between-participant and between-day variability, Linear Mixed Models (LMM) were employed to evaluate the variance of sleep and RAR Characteristics between the primary factors of interest (i.e. Chronotype and Day of the Week). Three LMMs were used: two one-way models containing only either the Chronotype factor or the Day of the week factor, and a two-way model containing both factors. LMMs were fit using maximum likelihood and an independent covariance structure in a nested design, with Day nested within Study Week nested within Participant. Continuous variables for Age, BMI, and Date (specifically "days since the first participant's first day") were included as covariates. Holidays observed in Boston, MA, USA, including school vacations and final exam dates (*Boston University Medical Campus Academic Calendar*, 2015)[44], were flagged with a dummy variable ("Special Day") that was included in the model. Although these days likely change the schedule and therefor the RAR and sleep of individuals relative to "normal days", their effects are also likely not uniform; therefore an interaction between Date and the Special Day dummy variable was included in the model to account for the unique fixed effects of individual Special Days.

The significance of between-group differences in the LMMs was assessed with Wald tests using linear combinations of marginal linear predictions via the Stata *contrasts*

[44] Halloween, Thanksgiving, Thanksgiving Break, Last Day of Classes, Fall Final Exam Study Period, Fall Final Exams, Winter Break, Valentine's Day, President's Day, Spring Break

command (Stata 16.0, StataCorp). The amount of variance attributable to each level of nesting in the LMM, as well as the residual variance, was also quantified in the two-way LMM.

Results

Participant Demographics and Self-Report

Descriptive statistics for demographics and self-reported measures, including between-Chronotype comparisons, are presented in Table 5.1. 24 healthy male participants completed the study; based on their MEQ scores, 15 participants were assigned to the Eveningness group (MEQ: 59.44 [2.96]) and 9 participants to the Morningness group (MEQ: 39.8 [7.23]). All demographic and self-report measures were normally distributed ($p > 0.05$), with the exception of Age in the Eveningness Chronotype ($p = 0.03$). Although the MEQ scores across the entire sample were normally distributed ($p = 0.15$), dividing the sample into Chronotypes appeared to improve the normality within each group ($p > 0.81$). Furthermore, MEQ scores and self-reported normal sleep timings on weekends and weekdays were significantly different between the two Chronotypes ($p < 0.01$). BMI and self-reported sleep quality (via the PSQI and ESS) were not significantly different between Chronotypes ($p > 0.43$). The difference in age appeared to approach significance ($p = 0.09$), with Morningness being older on average; this is expected since Chronotype generally shifts toward Morningness as one ages (Foster & Roenneberg, 2008; Roenneberg, 2004). Together, these observations of improved normality, differences in sleep timing, and lack of differences in demographics and sleep quality support the division of the sample by Chronotype; the

greatest differences were observed in measures expected to be sensitive to Chronotype (i.e. sleep timing and Age), with other measures (i.e. BMI and sleep quality) not achieving significance (Table 5.1).

Missing Data

In order to be considered "valid" and eligible for analysis, a participant-day required both a cosinor model and an overnight sleep period. With perfect compliance, the study design allowed for a maximum of 672 participant-days (24 participants * 28 days) of recorded data. In total, 505 (75.15%) valid participant-days were collected (Table A.3). The Eveningness Chronotype had more valid participant-days overall, with 308 (73.33%), although the Morningness cohort had a higher rate with 197 (78.17%) valid participant-days. Valid participant-days were generally more frequent during the work-week, especially in the week immediately following the sleep clinic stay. Lastly, 111 (21.98%) of all valid participant-days were flagged as "Special Days" due to occurring on a holiday, vacation, or academic event.

Table 5.1 – Participant demographics and self-reported sleep timing and quality, presented by Chronotype and including the p-value of between-Chronotype tests.

Demographic Characteristics by MEQ Chronotype	All Participants (n = 24)	Evening Chronotype (n = 15)	Morning Chronotype (n = 9)	Between-Group Comparisons
Measure	Average (Standard Deviation)			Two-Sample Test p-value
Age (Years) [RS]	23.46 (4.77)	22.20 (4.55) [‡]	25.56 (4.61)	0.0853 *
Body Mass Index (Kilogram/Meter^2) [TT]	24.33 (3.00)	24.72 (2.60)	23.68 (3.65)	0.4250
Epworth Sleepiness Scale (Score) [TT]	5.46 (2.43)	5.47 (2.72)	5.44 (2.01)	0.9833
Pittsburgh Sleep Quality Index (Score) [TT]	3.71 (2.01)	3.93 (1.94)	3.33 (2.18)	0.4913
Usual Sleep Time, Weekday (Time) [TT]	23:44 (0:55)	00:13 (0:46)	22:57 (0:28)	0.0002 **
Usual Sleep Time, Weekends (Time) [TT]	01:03 (1:02)	01:34 (0:52)	00:12 (0:38)	0.0004 **
Usual Wake Time, Weekdays (Time) [WTT]	07:49 (1:09)	08:20 (1:08)	06:57 (0:29)	0.0005 **
Usual Wake Time, Weekends (Time) [TT]	09:11 (1:21)	09:54 (1:07)	08:00 (0:45)	0.0002 **
Social Jet Lag, Self-Reported (Hours) [TT]	1.40 (1.01)	1.69 (1.11)	0.94 (0.58)	0.0929 *
Sleep Debt, Self-Reported (Hours) [TT]	0.52 (0.49)	0.58 (0.57)	0.41 (0.32)	0.4091
Morningness-Eveningness Questionnaire (Score) [WTT]	47.17 (11.37)	39.80 (7.23)	59.44 (2.96)	< 0.0001 **

* p-value $0.05 < 0.10$

** p-value < 0.05

[‡] Significantly abnormal distribution (skewness-kurtosis test, p-value < 0.05)

[TT] T-Test: Both Chronotypes were normally distributed (skewness-kurtosis test, p-value > 0.05) and had equal variances (equal variances test, p-value > 0.05); the between Chronotype comparison was conducted with an independent samples t-test.

[WTT] Welch's T-Test: Both Chronotypes were normally distributed (skewness-kurtosis test, p-value > 0.05) and had significantly different variances (equal variances test, p-value < 0.05); the between Chronotype comparison was conducted with a Welch's independent samples t-test.

[RS] Rank Sum: At least one Chronotype was non-normally distributed (skewness-kurtosis Test, p-value < 0.05); the between Chronotype comparison was conducted with a non-parametric Wilcoxon rank-sum test.

Variance in Linear Mixed Models (LMM)

The variance components of each variable at each nested level (i.e. Day of the Week nested in Study Week nested in Participant) were estimated in the univariate LMM (Table A.4). When averaged across all variables within a nested level, the highest average variance component of 56% was observed at the Day of the Week level, and the lowest average variance component of 8% was observed at the Study Week level; i.e. the highest predicted variance was observed between-Day within-Participant and -Week, and the lowest variance was observed between-Week within-Participant and -Day. The greatest variance components of individual variables were observed in MESOR at the Participant level (55%), SOFF at the Study Week level (24%), and SOFFL at the Day level (86%). SE had the highest residual (i.e. unaccounted for in the model and not attributable to any specific nested tier) variance component of 39%.

Rest-Activity Rhythm (RAR) and Sleep Characteristics (SC)

Significant one-way (i.e. between-Chronotype, across-Day) differences were observed in individual RAR and SC variables in the unmodeled raw data (Table A.5): MESOR ($p = 0.0090$), Amp ($p = 0.0040$), Acro ($p < 0.0001$), SON ($p < 0.0001$), SMID ($p < 0.0001$), SOFF ($p < 0.0001$), and FI ($p = 0.0070$); both TiB and TST approached significance ($p = 0.0867$ and $p = 0.0878$, respectively).

One-way comparisons were conducted for individual variables via Wald tests between predicted marginal means generated in one-way LMMs: either between-Chronotype,

or between-Day. Significant between-Chronotype across-Day differences were observed in the "time of day" variables: Acro ($p = 0.0329$), SON ($p = 0.0062$), SMID ($p = 0.0084$), and SOFF ($p = 0.0370$), with Eveningness having later values (Figure A.4; Table A.6A).

Additional significant differences were observed in a larger number of RAR and SC variables in the between-Day across-Chronotype one-way LMM (Figure A.5; Table A.6B)[45]: MESOR ($p = 0.0356$), Amp ($p = 0.0007$), Acro ($p = 0.0003$), SON ($p < 0.0001$), SMID ($p < 0.0001$), SOFF ($p < 0.0001$), TST ($p = 0.0140$), and PST ($p = 0.0348$). To summarize, weekends (Friday 18:00 – Sunday 18:00) had higher activity, later timing of activity, later sleep times, and longer sleep periods with less time spent awake. TiB ($p = 0.0979$), SOFFL ($p = 0.0578$), and SE ($p = 0.0957$) appeared to approach significance.

Significant within-day between-Chronotype differences (Figure 5.1, Table 5.2) were observed in the two-way LMM: SMID ($p = 0.0243$) and SOFF ($p = 0.0095$) on Sundays; Acro ($p = 0.0162$), SON ($p = 0.0022$), SMID ($p = 0.0142$), TiB ($p = 0.0367$), and TST ($p = 0.0291$) on Mondays; SMID ($p = 0.0405$) on Tuesdays; SON ($p = 0.0210$) and SMID ($p = 0.0210$) on Thursdays; and Acro ($p = 0.0101$), SON ($p = 0.0003$), SMID ($p = 0.0028$), TiB ($p = 0.0275$), and TST ($p = 0.0304$) on Fridays. Lastly, SON ($p = 0.0116$), TiB ($p = 0.0263$), and TST ($p = 0.0180$) were jointly significant for Chronotype and Day of the Week (Table 5.2).

[45] All between-Day across-Chronotype p-values reported in-text are joint p-values derived from joint Wald tests conducted across all seven Days. Two-sample Wald tests were used to compare individual Days to Sunday; their p-values are reported in Table A.6B.

Table 5.2 – Predicted marginal means (standard error) for each Chronotype-Day, the p-values of the between-Chronotype within-Day Wald tests, and the p-values of the joint Wald tests.

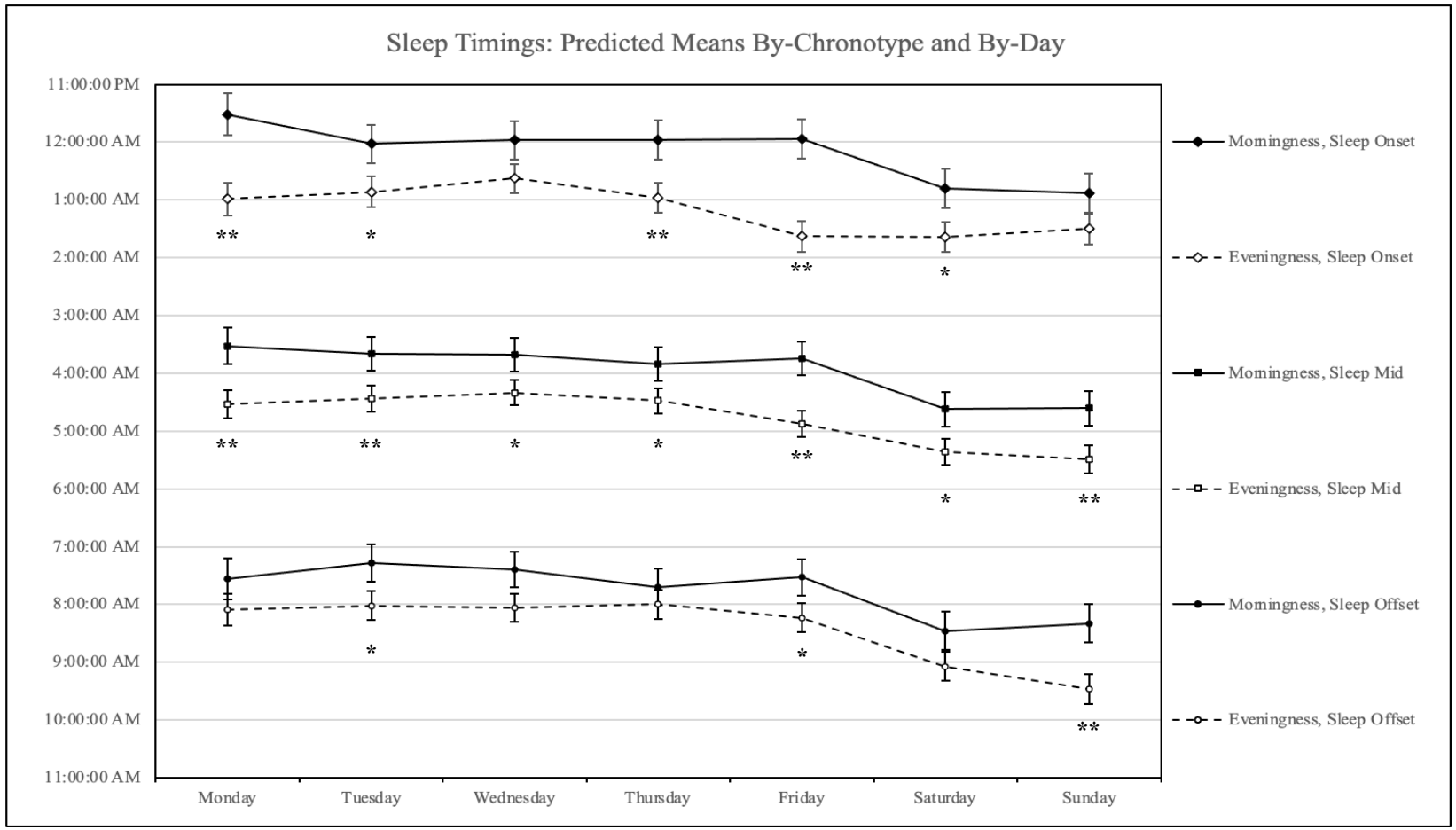
		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Joint p-value
MESOR (AC)	Eveningness	46.39 (3.81)	46.16 (3.67)	45.47 (3.65)	44.23 (3.65)	49.06 (3.69)	47.86 (3.68)	46.35 (3.75)	0.3808
	Morningness	38.78 (4.95)	44.68 (4.79)	40.79 (4.76)	40.30 (4.77)	43.10 (4.78)	46.39 (4.83)	47.17 (4.85)	
	p-value	0.2432	0.8136	0.4546	0.5304	0.3444	0.8171	0.8989	
Amplitude (AC)	Eveningness	39.01 (3.5)	38.45 (3.29)	35.14 (3.24)	32.51 (3.25)	37.54 (3.31)	39.15 (3.29)	40.73 (3.41)	0.6031
	Morningness	32.66 (4.54)	35.17 (4.27)	32.31 (4.21)	32.45 (4.22)	34.36 (4.23)	42.44 (4.33)	41.02 (4.35)	
	p-value	0.2847	0.5567	0.6075	0.9920	0.5687	0.5602	0.9604	
Acrophase (Time)	Eveningness	16:19 (0:21)	16:12 (0:18)	16:14 (0:18)	16:16 (0:18)	16:43 (0:19)	17:05 (0:18)	17:20 (0:20)	0.1895
	Morningness	14:57 (0:26)	15:50 (0:23)	15:43 (0:23)	15:57 (0:23)	15:32 (0:23)	16:18 (0:24)	16:29 (0:24)	
	p-value	0.0160 **	0.4657	0.2895	0.5281	0.0174 **	0.1369	0.1071	
Sleep Onset (Time)	Eveningness	00:59 (0:17)	00:51 (0:16)	00:38 (0:15)	00:58 (0:15)	01:38 (0:16)	01:38 (0:16)	01:30 (0:16)	0.0116 **
	Morningness	23:31 (0:22)	00:02 (0:20)	23:58 (0:20)	23:58 (0:20)	23:57 (0:20)	00:48 (0:21)	00:53 (0:21)	
	p-value	0.0022 **	0.0610 *	0.1225	0.0210 **	0.0003 **	0.0630 *	0.1798	
Sleep Mid (Time)	Eveningness	04:32 (0:15)	04:26 (0:13)	04:20 (0:13)	04:29 (0:13)	04:53 (0:14)	05:22 (0:13)	05:29 (0:14)	0.1597
	Morningness	03:32 (0:19)	03:39 (0:17)	03:41 (0:17)	03:50 (0:17)	03:45 (0:17)	04:37 (0:18)	04:36 (0:18)	
	p-value	0.0142 **	0.0405 **	0.0776 *	0.0888 *	0.0028 **	0.0557 *	0.0243 **	

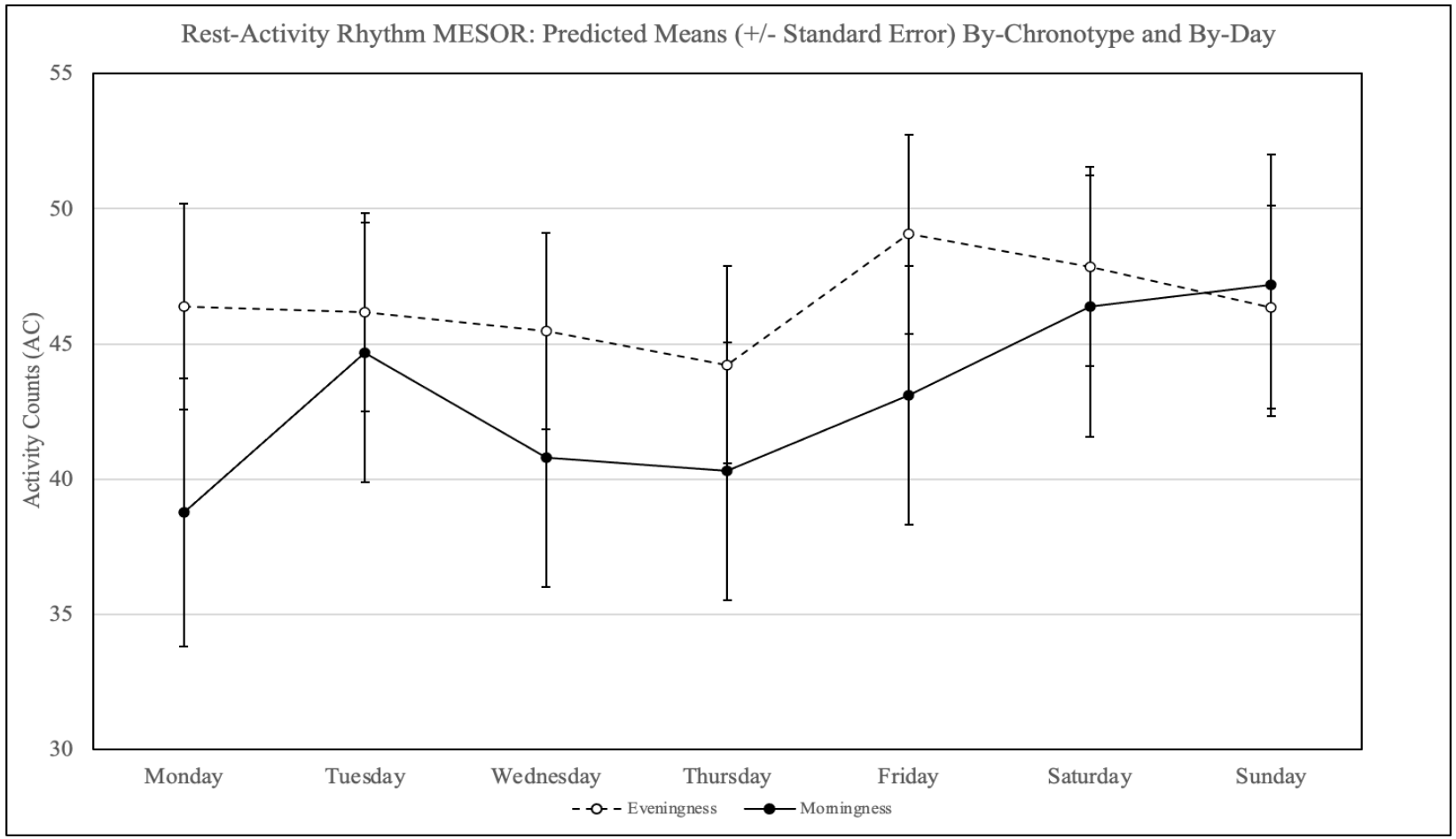
Sleep Offset (Time)	Evening-ness	08:06 (0:17)	08:01 (0:15)	08:03 (0:15)	08:00 (0:15)	08:14 (0:15)	09:04 (0:15)	09:28 (0:16)	0.3057
	Morning-ness	07:33 (0:21)	07:17 (0:19)	07:24 (0:19)	07:42 (0:19)	07:32 (0:19)	08:27 (0:20)	08:20 (0:20)	
	p-value	0.2392	0.0780 *	0.1045	0.4663	0.0938 *	0.1518	0.0095 **	
Time in Bed (Hours)	Evening-ness	7.11 (0.27)	7.20 (0.24)	7.46 (0.23)	7.07 (0.23)	6.71 (0.24)	7.40 (0.24)	7.94 (0.26)	0.0263 **
	Morning-ness	8.05 (0.35)	7.23 (0.31)	7.41 (0.30)	7.73 (0.30)	7.58 (0.30)	7.66 (0.32)	7.44 (0.32)	
	p-value	0.0367 **	0.9337	0.8953	0.0886 *	0.0275 **	0.5304	0.2352	
Average Activity during Sleep (AC per Minute)	Evening-ness	15.13 (1.87)	14.27 (1.73)	12.54 (1.70)	14.13 (1.71)	14.20 (1.75)	11.13 (1.73)	14.25 (1.81)	0.4846
	Morning-ness	10.99 (2.41)	9.25 (2.24)	10.25 (2.21)	13.30 (2.22)	11.84 (2.22)	10.95 (2.28)	11.55 (2.30)	
	p-value	0.1894	0.0875 *	0.4290	0.7767	0.4197	0.9523	0.3727	
	Morning-ness	11.51 (1.30)	9.51 (1.21)	11.16 (1.19)	12.63 (1.20)	11.74 (1.20)	10.50 (1.23)	11.45 (1.24)	
	p-value	0.5866	0.5932	0.5059	0.1480	0.2167	0.8636	0.6516	

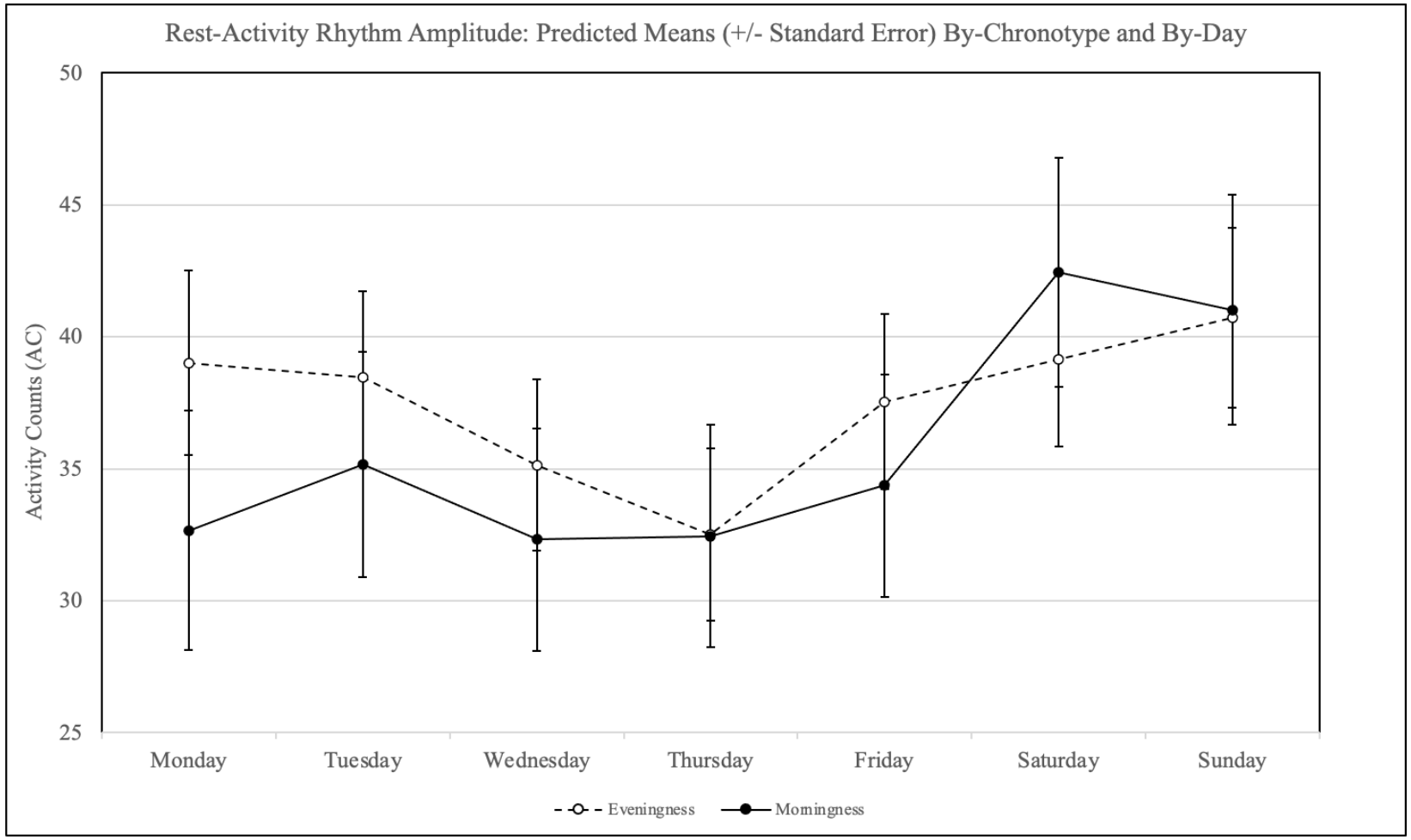
		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Joint p-value
Peak Activity during Rest (AC per 15 Minutes)	Evening-ness	313.02 (30.95)	298.53 (29.17)	286.12 (28.77)	301.29 (28.89)	279.67 (29.38)	264.41 (29.18)	301.75 (30.17)	0.5657
	Morning-ness	265.92 (40.16)	241.73 (37.93)	283.06 (37.47)	277.30 (37.58)	287.76 (37.67)	266.69 (38.46)	266.69 (38.65)	
	p-value	0.3706	0.2539	0.9502	0.6261	0.8705	0.9638	0.4913	
Sleep Onset Latency (Minutes)	Evening-ness	38.71 (11.28)	37.14 (10.20)	45.15 (9.95)	44.94 (10.03)	42.52 (10.34)	26.31 (10.21)	39.72 (10.81)	0.4880
	Morning-ness	44.31 (14.52)	28.50 (13.11)	53.27 (12.78)	25.34 (12.85)	34.71 (12.88)	28.95 (13.44)	60.19 (13.56)	
	p-value	0.7667	0.6133	0.6255	0.2421	0.6461	0.8795	0.2506	
Sleep Offset Latency (Minutes)	Evening-ness	24.35 (7.20)	29.45 (6.34)	27.78 (6.14)	28.52 (6.20)	28.99 (6.46)	30.42 (6.35)	43.15 (6.83)	0.7468
	Morning-ness	21.34 (9.23)	34.66 (8.08)	23.17 (7.80)	45.44 (7.86)	36.41 (7.88)	33.57 (8.35)	46.14 (8.45)	
	p-value	0.8011	0.6187	0.6481	0.0974 *	0.4755	0.7693	0.7873	
Sleep Effi-ciency (%)	Evening-ness	76.34 (1.95)	76.74 (1.77)	76.21 (1.73)	75.95 (1.75)	75.62 (1.80)	79.99 (1.77)	76.32 (1.87)	0.7396
	Morning-ness	78.46 (2.51)	78.85 (2.28)	77.98 (2.23)	77.17 (2.24)	77.40 (2.25)	79.22 (2.34)	73.63 (2.36)	
	p-value	0.5182	0.4791	0.5447	0.6774	0.5467	0.7985	0.3859	
Wake After Sleep Onset (Minutes)	Evening-ness	0.94 (0.09)	0.93 (0.09)	0.90 (0.09)	0.88 (0.09)	0.84 (0.09)	0.77 (0.09)	0.96 (0.09)	0.4515
	Morning-ness	0.98 (0.12)	0.75 (0.11)	0.84 (0.11)	0.99 (0.11)	0.90 (0.11)	0.80 (0.11)	0.84 (0.12)	
	p-value	0.8188	0.2399	0.6745	0.4652	0.6589	0.8411	0.4543	
Total Sleep	Evening-ness	6.17 (0.25)	6.27 (0.23)	6.55 (0.22)	6.19 (0.22)	5.87 (0.23)	6.62 (0.23)	6.99 (0.24)	0.0180 **

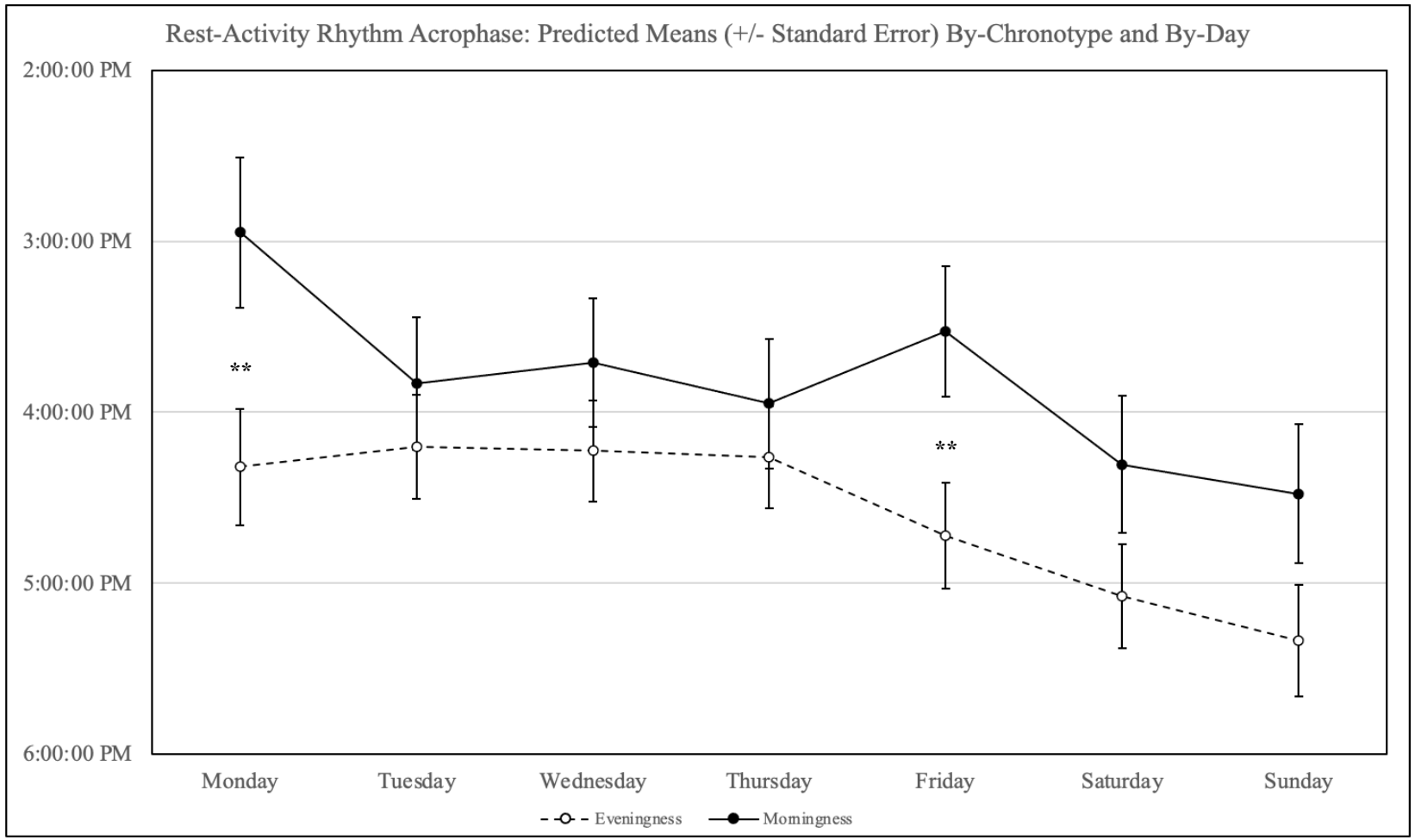
Time (Hours)	Morning-ness	7.08 (0.32)	6.48 (0.29)	6.58 (0.28)	6.75 (0.28)	6.69 (0.29)	6.88 (0.30)	6.61 (0.30)	
	p-value	0.0291 **	0.5695	0.9367	0.1303	0.0304 **	0.5091	0.3410	
Percent Sleep Time (%)	Evening-ness	86.94 (1.17)	87.62 (1.12)	88.11 (1.11)	87.89 (1.11)	87.95 (1.13)	89.57 (1.12)	87.74 (1.15)	0.6113
	Morning-ness	88.24 (1.53)	89.43 (1.46)	88.54 (1.45)	87.20 (1.45)	88.21 (1.45)	89.46 (1.48)	88.49 (1.48)	
	p-value	0.5177	0.3459	0.8198	0.7185	0.8914	0.9570	0.7013	
Frag-menta-tion In-dex (%)	Evening-ness	10.59 (1.01)	10.36 (0.94)	10.12 (0.92)	10.37 (0.93)	9.78 (0.95)	10.22 (0.94)	10.72 (0.98)	0.3669
	Morning-ness	11.51 (1.30)	9.51 (1.21)	11.16 (1.19)	12.63 (1.20)	11.74 (1.20)	10.50 (1.23)	11.45 (1.24)	
	p-value	0.5866	0.5932	0.5059	0.1480	0.2167	0.8636	0.6516	

Figure 5.1: Predicted marginal means (standard error) of cosinor parameters (MESOR, Amplitude, and Acrophase) and sleep timings (Sleep Onset, Sleep Mid, Sleep Offset) by-Chronotype and by-Day of the Week derived from the by-Day by-Chronotype two-way linear mixed model. Between-Chronotype Wald tests were conducted within each Day for all variables; ** indicates p-value < 0.05, * indicates p-value ≥ 0.05 and < 0.10.




Rest-Activity Rhythm MESOR: Predicted Means (+/- Standard Error) By-Chronotype and By-Day
Activity Counts (AC)
55
50
45
40
35
30
Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday
Eveningness
Morningness


Rest-Activity Rhythm Amplitude: Predicted Means (+/- Standard Error) By-Chronotype and By-Day
Activity Counts (AC)
50
45
40
35
30
25
Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday
Eveningness
Morningness


Rest-Activity Rhythm Acrophase: Predicted Means (+/- Standard Error) By-Chronotype and By-Day
2:00:00 PM
3:00:00 PM
4:00:00 PM
5:00:00 PM
6:00:00 PM
**
**
Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday
Eveningness
Morningness

Discussion

In this study, we used data from a single wrist-worn actigraphy device to identify significant differences in Rest-Activity Rhythm (RAR) and Sleep Characteristics (SC) across the seven-day week and between Morningness and Eveningness Chronotypes. We found that certain RAR and sleep characteristics varied significantly between Chronotypes, and that these differences were often dependent on day of the week.

Sleep and Activity Timing Significantly Varies across the Week

We observed substantial changes in SC across the week in both Chronotypes, especially during the "transitions" that separate work from rest days (i.e. Friday/Monday). As might be expected, the strongest between-day differences were observed in the *timing* of activity and sleep; both Chronotypes woke up and were active later during the weekend (Friday and Saturday nights) than during the work-week (Sunday – Thursday nights), suggesting that "sleeping in" was not limited to a specific Chronotype in our sample (Figure 5.1, Table 5.2, Table A.6). Significant day-to-day changes in SMID and SOFF were observed at the transitions between work and rest days for both Chronotypes. Although both Chronotypes went to bed earlier during the work week, Morningness participants adjusted to the work week more quickly, achieving significantly earlier bedtimes within one day. In contrast, Eveningness participants took on average an extra day before their SON were significantly earlier than on the weekend. Interestingly, Eveningness transitioned to their later weekend SON on Thursday night, where-as Morningness began going to bed later on Friday night. Qualitatively, Morningness appears to have a more consistent SON during the work week.

Where-as Morningness shifted within one day, Eveningness gradually went to bed earlier each day from Sunday through Tuesday, then later with each day through the weekend.

In summary, both Chronotypes conform to a similar circaseptan rhythm across the week – i.e. sleep timing advances on weekends – and that this pattern is most consistent in their SOFF. When transitioning between weekends and weekdays, Morningness adjust their SON quicker than Eveningness, who shift incrementally throughout the week. These results may be due to the fact that SOFF are the most directly constrained by the work-week, where-as individual preference plays a larger role SON; i.e. SON is more sensitive to Chronotype than SOFF.

Morningness had significantly greater TiB and TST than Eveningness on Sunday and Thursday nights (Figure 5.1; Table 5.2). These differences are attributable to Chrono-type-specific variations in SON and SOFF: Thursday night's due to the later Eveningness SON without a comparable advance in SOFF, and Sunday night is likewise explained by the significantly earlier Morningness SON. Both Chronotypes experienced a significant and comparable decrease in SOFFL from Sunday morning to Monday morning, perhaps attributable to work constraints as with SOFF (i.e. less freedom to "sleep in").

Eveningness had significantly higher SE on Friday night relative to Thursday night, potentially due to their resumption of their preferred sleep schedule. In contrast, Morning-ness had significantly lower SE on Saturday night relative to Friday night. The unexpect-edly similar advances in sleep timing on the weekend for both Chronotypes may be at-tributable to the fact that the social schedule during the work week is more closely aligned with Morningness preferences. Different social pressures during the weekend (e.g. late-

night social events) resulted in phase-advance of sleep timing in Morningness participants beyond their preferred sleep schedule, resulting in decreased sleep quality. Eveningness participants, however, may experience improved SE on the weekend for the same reason. However, note that other measures of sleep quality – WASO, PST, and FI – did not significantly decrease during the weekend for Morningness, although Eveningness WASO and PST significantly decreased on Saturday nights relative to Friday nights.

Measuring and Interpreting Circaseptan Rhythms

Technological advances have enabled continuous monitoring of authentic, uncontrolled, and out-of-lab behavior. Wearable devices such as the Actiwatch used in this study allow chronobiologists to collect ecologically valid data, better interrogate the complex interactions between circadian cycles and environmental factors, and potentially identify targets for interventional therapy. However, this introduces new problems: which methods are the most reliable and functional, which measures are the most relevant and informative, identifying unknown systemic biases or false assumptions, and ensuring methodological and analytical consistency to allow for replicability and meta-analysis. Our study highlights some of the more pragmatic obstacles to this approach, specifically the large amount of variance observed, the need to account for as many environmental factors as possible, and participant compliance.

Due to the unconstrained nature of continuous monitoring, our main analytical goal was to account for as much variance as possible and isolate the desired signal: RAR and sleep behavior across the week. Our nested design – Day nested within Study Week nested

within Participant – was specifically chosen to detect *circaseptan* rhythms. Analogous to an electroencephalographic technician deriving an event-related potential from the average of hundreds of trials synchronized to a reference time, we derived circaseptan rhythms from the average of many Participant-Weeks "synchronized" to the standard seven-day week. This allows random variability to "average out", where-as effects that are constant across all weeks (e.g. sleeping in on the weekend) remain. While the results in this article are primarily discussed in reference to individual days, these outcomes collectively represent the average pattern across the average week; i.e. circaseptan rhythms.

We derived variance components for each of the three nested levels in our design. The largest variance components were observed at the Day level for all variables, with the exception of MESOR and SON whose largest variance component was at the Participant level (Table A.4). This means that RAR and sleep characteristics varied more between Days within a Participant than they did between Participants, and implies that the largest contributors of variance were at the Day level; in addition to normal between-Day variability, this variance may be attributable to weather, illness, personal events such as birthdays or travelling, and so on. Likewise, Participant-level variance may be explained by normal individual variability and unaccounted for between-Participant factors, such as living situation, employment, or commute. Although we cannot definitively attribute variance to individual factors, variance components allow us to infer the what factors different measurements may or may not have in common. For example, the large Participant-level variance component seen in SON suggests that individual preference is more influential on the time when one goes to bed, where-as the large Day-level variance component observed in

SOFF implies that external day-specific factors (e.g. work) may be more important for predicting when one wakes up.

Our results support the concept that Day of the Week is a significant factor that alters timing of sleep and activity, and therefore should be accounted for when assessing them across multiple days. More generally, study designs must properly account for the social calendar their participants will exist in, whether it's office employees at a 9-to-5 job, nurses on 12-hour shifts, or oil-rig workers on a four week rotation, especially when the observation period includes both rest and work days (Roenneberg et al., 2019; Vetter, 2018). This extends to the natural calendar, i.e. season and daylight hours. Given the widespread control the circadian rhythm has on our physiology and behavior, we argue that most studies of human biology should account for these calendar factors as well, especially observational studies with long data collection periods.

Circadian Disruption in Modern Societies

Circadian disruption is the sustained desynchronization of the circadian rhythm from its environment (Vetter, 2018), and is a significant and widespread burden upon modern industrialized societies (Colten & Altevogt, 2006). Epidemiological studies quantifying its full extent are scarce (D. R. Hillman & Lack, 2013) due its multifaceted and vaguely defined nature (Vetter, 2018); however, epidemiological studies of sleep disruption (which is closely linked to circadian disruption) estimated that over a third of Americans suffer from insufficient sleep (Liu et al., 2016), a similar proportion of Australians suffer from sleep disorders (D. R. Hillman & Lack, 2013), and young and middle aged French adults sleep

~1.5 hours less than recommended (Léger et al., 2011). Moreover, retrospective analyses of Swedish and Finnish cohort studies suggest that sleep duration has declined by as much as 18 minutes/night over a period of ~30 years (Kronholm et al., 2008; Rowshan Ravan et al., 2010), and the prevalence of sleep disruption is expected to continue rising in proportion to at-risk populations (Ferrie et al., 2011). Numerous health issues have been linked to circadian disruption, including metabolic disease (Potter et al., 2016), cardiovascular disease (Portaluppi et al., 2012), neuropsychiatric disorders (Musiek & Holtzman, 2016), neurodegenerative diseases (Colten & Altevogt, 2006; Videnovic, Lazar, et al., 2014), and disruption of the endocrine system (Bedrosian et al., 2016; Vetter, 2018). Generalized symptoms of acute circadian disruption (e.g. fatigue and impaired attention) have contributed to the occurrence of fatal accidents (Gottlieb et al., 2018) - the rate of which has increased in the United States of America (USA) over the past decade (Murphy et al., 2018) – and has been implicated in numerous high profile accidents and catastrophes such as the Three Mile Island disaster, the Chernobyl disaster, the Exxon Valdez oil tanker spill, the Space Shuttle Challenger disaster, and the Union Carbide disaster in Bhopal, India (Colten & Altevogt, 2006; RAND Corporation, 2016). Insufficient sleep has also been linked with seven of the fifteen most common causes of death in the USA (RAND Corporation, 2016) and is associated with worse academic performance in schoolchildren and undergraduates (Okano et al., 2019). The broad extent of sleep and circadian disruption is believed to have a significant economic impact. In 2002, the total economic cost (in terms of lost productivity due to fatigue, absences, accidents, and medical treatment of sleep disorders) was

estimated at $226 billion in the USA alone (Stewart et al., 2003). 14 years later, one international model (RAND Corporation, 2016) estimated that cost had increased to ~$350 billion.

Clearly, there is a need for a better understanding of the causes and consequences of circadian disruption in order to inform the development of new therapies and policies for curtailing it and its deleterious impacts on human society. However, there is a lack of consensus regarding the spectrum of changes to the circadian rhythm, which range from normal intra- and inter-individual *variability* (e.g. behavior and chronotype, respectively), to *adaptive* changes in response to the environment (e.g. seasonal changes in sunlight), to short-term disturbances caused by acute challenges (e.g. jet lag), to chronic *disruption* created by sustained desynchrony between the circadian rhythm and environmental cues (e.g. SJL) (Vetter, 2018). Any discussion of circadian disruption must account for the fact that the circadian rhythm is innately *adaptive*; i.e. it constantly receives and integrates internal and external zeitgebers to optimize the timing and coordination of biological processes. For example, the gradual day-to-day change in sunrise time is a constant challenge that the circadian rhythm easily adapts to with minimal systemic effects (i.e. we are not jet lagged every morning). However, a significant change in sunrise time (e.g. due to normal jet lag) can overwhelm the circadian rhythm's adaptability and result in a period of disruption before the organism is fully resynchronized to their new environment. Therefore any discussion of circadian disruption must distinguish between healthy *adaptation*, normal *variation*, and abnormal *disruption* in the circadian system/endpoint of interest (Vetter, 2018).

This extends to the impact on the biological mechanisms of circadian rhythm: which molecules, cells, tissues, organs, and/or systems are affected by adaptation and disruption, by how much, how consistently, how are disruptions borne and distributed by each level of organization and its sub-components, etc. In other words, the circadian rhythm is a system of systems; inferring its integrity by studying its overall function is analogous to determining the health of an individual by their height alone.

Our data contribute to the considerable evidence indicating our circadian rhythm adapts to the socially-defined seven-day week. Although our sample was small and demographically constrained, we incorporated relevant factors (e.g. chronotype, holidays) and triangulated the circadian rhythm using multiple approaches (i.e. objective monitoring and subjective self-report) and endpoints (i.e. RAR, sleep, and biomarkers (see Marshall et al., 2020 [under review]) to produce a more comprehensive model of sociogenic disruption. This model enabled us to estimate the variance attributable to between-Day, between-Week, and between-Individual effects, which can be used to generate hypotheses targeting specific factors for future work; residual variance components likewise provide an estimate of how much "background noise" can be expected in certain endpoints, which can aid in the informing power analyses.

Moreover, our work emphasizes the highly integrated nature of our biology and our society. Sleep and RAR are systemic outputs that represent the cumulative effects of our conscious decisions, circadian rhythm, social environment, and natural zeitgebers like sunlight and eating (Vetter, 2018). In the same way, certain epidemiological and social trends

may be the cumulative product of the intersection between our social calendar and biological rhythms; e.g. there is a well-documented circaseptan rhythm in suicides and heart attacks associated with the transitions between work- and rest-days (F. Halberg et al., 2005; Refinetti et al., 2007; Rogot et al., 1976). Given that blood pressure exhibits a circaseptan rhythm with a peak on Mondays (Murakami et al., 2004), and that transitions between "social time zones" (i.e. stress of returning to work after the weekend) increases psychosocial – and subsequently physiological – stress, the weekly rhythm in heart attack fatalities may be attributable to the compounded risks borne from biogenic and sociogenic factors (Ayers et al., 2014; Wallert et al., 2017). The presence of a circaseptan rhythm in urinary 17-ketosteroid secretion (Franz Halberg et al., 1965), the approximately circatrigintan rhythm of menstruation, and circannual rhythms in cortisol secretion (Morgan et al., 2017) and the duration of nocturnal melatonin secretion (Stothard et al., 2017) suggest the presence of endogenous infradian rhythms that exist independently of, and thus may become misaligned with, our social calendars. For example, human birth-rates exhibit a profound circannual rhythm, but the amplitude has dramatically decreased since the industrial revolution (Foster & Roenneberg, 2008). This change was undeniably driven by sociocultural factors (e.g. artificial lighting, insulation from seasons, transition to industrialized mass production, implementation of standardized time tables, etc.), but it is unknown if this was because the circannual rhythm in birth-rate is purely an emergent property of human culture with no biological basis, or because the effect of its biological drive has since been eclipsed by societal change and new technology; much like how alarm clocks and year-round stand-

ard work schedules have rendered moot our need to wake with the rising sun, or how artificial lighting has largely abolished our circannual rhythm in nocturnal melatonin secretion (Stothard et al., 2017). In summary, circadian disruption associated with the seven-day week is only one of the myriad ways in which our behavior is shaped by a combination of intrinsic biological and extrinsic social factors, and serves as a microcosm for studying the nature, breadth, and extent of these factors.

Limitations

The study discussed in this article had several limitations. The high level of variability observed between Participants and Days was a natural consequence of the uncontrolled nature of continuous monitoring. We were able to mitigate this by accounting for random effects at the Participant and Day level in our linear mixed model, but this nonetheless limits interpretability of results. This study employed a "basic" 3-parameter cosinor to model RARs; while computationally accessible, the basic cosinor assumes symmetrical rhythms with an idealized cosine waveform. Human RARs are more "block-like" than sinusoidal, with prolonged periods of activity and torpor of different length during the day and night, separated by relatively rapid transitions in activity level. We plan to use the "extended" 5-parameter cosinor model (Marler et al., 2006) in future work, which includes additional parameters to model the rise/fall time and the ratio of sustained activity versus torpor. Sleep characteristics were generated with Actiware, which has many customizable parameters that can hinder generalizability; these should be considered when comparing

our results to other sleep data. The study population was recruited from a limited demographic, consisting mainly of medical and graduate students from the Boston area. While this minimized variance from factors such as age or sex, this is not a representative sample of the population and further limits generalizability. This study required participants to wear additional devices and complete daily diaries at-home, as well as a one-weekend stay in a sleep lab halfway through the study period; although the sleep lab visit was excluded from all analysis in this article, participant behavior may have been altered by the additional devices, in-home diary, or on days adjacent to their stay in the sleep lab. Lastly, we did not collect detailed information on their work schedule during the study, their observation of holidays (official, personal, or otherwise), or other changes in their day-to-day schedule; this required us to assume the cohort had a uniform and consistent weekly schedule throughout the study period, and deviations from this assumption likely contributed to some of the residual variance in our models.

Conclusion

Our observations support the growing literature describing chronic circadian disruption in modern societies. Phenomena such as SJL, sleep debt, and "sleeping in on the weekend" emerge from the mismatch between social and circadian rhythms, whereby individuals oscillate between their preferred chronotype on rest days and a socially enforced chronotype on work days analogously to crossing time zones (Vetter, 2018). The behavioral shift is immediate, where-as the circadian rhythm "lags behind" and requires time to resynchronize. As with normal jet lag, this discrepancy between behavioral and circadian rhythm is

associated with acute cognitive, homeostatic, and metabolic deficits (Roenneberg et al., 2012; Vetter, 2018); unlike jet lag, SJL and similar phenomena presents a challenge at consistent, periodic intervals (i.e. weekly). As a result, sociogenic circadian disruption is a unique challenge to our modern societies that will require widespread data collection, careful identification of relevant factors, improved methodological consistency and replicability, and ultimately fundamental changes to our society informed by biological evidence.

CHAPTER SIX: DISCUSSION

Summary of Main Outcomes

Circadian disruption in humans is widespread in modern industrialized societies due to a combination of sociogenic and pathological factors. In order to translate scientific studies into clinical applications, researchers must be able to accurately quantify and classify circadian disruption, distinguish between disruption and normal variance, and identify potential therapeutic targets. This requires the use of observational approaches that emphasize ecological validity, employ synergistic methodologies, to challenge our assumptions, and to strive to detect and account for the myriad environmental factors that shape our circadian rhythm. Most importantly, researchers must reach a consensus on how to standardize the scientific evaluation of circadian disruption: its definition, its assessment, its reporting, and its interpretation. This harmonization is not only for the benefit of chronobiology, but also for the study and treatment of pathologies such as Parkinson's disease (PD) for whom circadian disruption is a major feature. This is not unique to circadian disruption; as technology continues to improve, methodological diversity increases, and powerful new techniques emerge, scientific work must be consolidated, standardized, and clearly reported lest the field miss the forest for the trees.

A key element in this approach is the integration of diametric methods, such as qualitative self-report with quantitative measurement, subjective evaluation with objective mensuration, cross-sectional evaluation with longitudinal monitoring, and controlled experiments with naturalistic observation. In Chapter 3, this philosophy was applied by integrating qualitative and quantitative approaches in the context of PD and, more specifically,

its assessment via the Movement Disorders Society's Unified PD Rating Scale (MDS-UPDRS). This work showed that behaviors used in the standard evaluation of PD can be systematically defined using key anatomical, visual, and behavioral references to enable their identification and precise temporal quantification in video recordings to a level of detail so that naive raters without prior clinical experience can achieve high inter-rater reliability.

Amongst the challenges of studying circadian disruption is attributing its etiology to discrete factors and causes. While circadian disruption is increasingly recognized as a major feature of PD, relatively little work has been done to characterize its relationship with PD's clinical severity, or to what degree PD's circadian disruption is attributable to pathology or unrelated factors. In Chapter 4, depression and fragmentation of rest-activity rhythms (RAR) in PD were detected via continuous actigraphic monitoring, which further revealed an association between RAR disruption and motor severity and Hoehn and Yahr stage (H&Y).

Misalignment between our biological rhythms and our artificial timetables gives rise to phenomena such as Social Jet Lag (SJL), sleep debt, "sleeping in on the weekend", and "a case of the Mondays". As these occur on a weekly period - potentially due to our use of a seven-day week and/or an endogenous seven-day biological rhythm - they can be described as circaseptan rhythms of circadian disruption. An interim analysis found that persons with PD experienced more sleep fragmentation across the week, but retained the "half-week" or "semicircaseptan" rhythm observed in controls. This implies a common factor; given the circaseptan period, it was hypothesized that the effect was sociogenic and

a product of the seven-day week. To test this, the same general methodology used in Chapter 4 was applied to a population of young, healthy adults with the intent of characterizing the potentially sociogenic circadian disruption observed in the PD cohort. This worked revealed strong circaseptan effects in RAR and sleep related to transitions between weekdays and weekends (i.e. when people's behavioral timing shifts due to a change in schedule), which were further influenced by their self-reported chronotype. These sociogenic and endogenous factors must be quantified and accounted for in order to advance our understanding of, and capacity to minimize, circadian disruption in humans.

Methodological Considerations

Much of our knowledge of chronobiology derives from controlled experiments designed to manipulate the circadian rhythm and measure it in isolation. Technological advancements have led to the development of wearable devices capable of measuring circadian indicators, such as body temperature, sleep, and movement. By measuring authentic (i.e. uncontrolled) human behavior longitudinally, researchers can observe how rhythmic processes - well understood in isolation - are impacted by the myriad intricacies of life. This approach inherently produces highly variable data, and is dependent on well-structured analytical models, integration of secondary lifestyle information to account for individual differences, and the application of sociological theories on human behavior to minimize variance and aid in interpretation.

This subchapter will discuss methodological considerations relevant to the studies and topics covered in earlier chapters. In particular, the importance of methodological harmonization and clarity, the beneficial integration of synergistic measures, the necessity of mitigating unconventional biases, and notable methodological obstacles will be explored in the context of this manuscript's contents and applied more generally to human observational research (especially chronobiological) writ large.

Methodological Diversity: Objective, Subjective, Quantitative, and Qualitative Approaches

As scientists, we strive to measure natural phenomena as objectively and quantitatively as possible. Much of the effort in scientific research is expended in pursuit of developing, assessing, refining, validating, and disseminating novel methods for measuring observables of interest to generate and test hypotheses. *Observation* is fundamentally the acquisition of information from some system, and since every measurement will always have some amount of uncertainty, the methods employed by scientists are incredibly specialized and rely on strategies tailored to the signal of interest and its context. However, as a method becomes more context-dependent and constrained by a conceptual framework, the number of prerequisite assumptions needed for the valid interpretation of its outputs increases. Put simply, the cost of specialization is a loss of generalizability. A natural application of this knowledge is to incorporate both powerful, specialized methods and more non-specific, generalizable methods in parallel, so that their respective strengths can compensate for their counterpart's weaknesses. For example, the Parkinson Associated Risk Study (PARS)

was able to more accurately predict future risk of Parkinson's disease (PD) using a combination of two potential biomarkers - hyposmia[46] and reduction in dopamine (DA) transporter (DAT) binding - than either individually (Lana M. Chahine & Stern, 2017; Danna Jennings et al., 2017). Both hyposmia and a reduction in DAT binding can be detected with high sensitivity, but have poor specificity for PD due to their myriad potential causes. However, since there is little overlap in their potential causes, their integration into a single model can greatly improve their combined specificity by filtering out false positives (e.g. hyposmia secondary to respiratory illness) and "triangulating" the common factor of interest; i.e. PD. Predictive accuracy can be further increased through the inclusion of additional biomarkers such as constipation and cognitive dysfunction (Lama M. Chahine et al., 2016; D. Jennings et al., 2014), which also allows for individual biomarkers to be weighted as risk factors relative to their predictive power (Berg et al., 2015; Lana M. Chahine & Stern, 2017). It has been acknowledged that an effective approach to detecting prodromal PD will likely require a diverse array of biomarkers sensitive to specific symptomatic (both motor and non-motor) and pathological components, requiring a combination of quantitative, qualitative, subjective, and objective methods (Artusi et al., 2018; Espay et al., 2017).

Chapter 3 similarly employed a constellation of complementary methods to triangulate specific endpoints. Instead of integrating prodromal biomarkers to improve specificity, video annotation was applied to quantify the duration of clinical behaviors in combination with subjective clinical evaluations, with the goal of establishing a unified clinical

[46] Hyposmia is the reduction in or loss of the ability to smell, a common prodromal symptom in PD

dataset that could be aligned with objective actigraphic monitoring. By integrating subjective, objective, and quantitative measures, this "multimodal" dataset can characterize these behaviors in detail and allow for equitable comparisons between normally incompatible methods: e.g. the duration of a sit-to-stand can be precisely quantified through annotation, which can then be related to a clinical rating via the MDS-UPDRS, and used to segment objective actigraphic accelerometry for use in algorithm development or machine learning. This unified approach provides essential information that contextualizes and bounds the often difficult-to-discern key features of interest in actigraphy data, facilitating analysis and informing interpretation more efficiently than actigraphy alone.

Chapter 4 employed multimodal measures to assess sleep and rest-activity rhythm (RAR) disruption in persons with PD, whose multifaceted symptoms and multi-system pathological insults require a similarly diverse methodology to comprehensively assess. Consider sleep disruption, a major non-motor symptom in PD that can be quantified with polysomnography (PSG) through objective markers such as sleep stage progression and number of awakenings. Daytime sleepiness is another common non-motor symptom in PD caused, in part, by previous sleep disruption. Although there are objective, quantifiable events that cause daytime sleepiness (e.g. midsleep awakenings, i.e. sleep disruption), it manifests as a *qualia*, an experiential perception (Lou et al., 2009) that can only be subjectively assessed, usually through self-report on a questionnaire. In this context, *subjectivity* means that the signal of interest is dependent on some contextual perspective, such as the beliefs, biases, opinions, memories, and mood of an individual; a subject who has long

experienced disrupted sleep may be so accommodated to daytime sleepiness that they consistently rate themselves as having less daytime sleepiness than another person who recently developed the same level of sleep disruption. While there is no biological difference between these hypothetical subjects, the impact on quality of life would be greater in the latter subject since their subjective perception is more severe.

This highlights the critical and fundamental importance of selecting the appropriate methods to balance accuracy, relevance, burden, validity, and translatability. Consider the myriad ways a researcher could measure the sleep quality of PD patient: they could record how well they slept every morning in a diary, infer sleep quality through the number of conscious awakenings by instructing the patient to press a button on their phone whenever they wake up, have an experienced sleep clinician observer assign a score based on standardized criteria, monitor them with wearable sensors to quantify some behavioral or physiological correlate of sleep like physical activity or respiration rate (respectively), or have them spend the night in a sleep lab with polysomnography (PSG) to directly monitor sleep/wake status via brain activity, the neurological primogenitor of sleep, alongside myriad physiological correlates.

These methods vary along different axes: subjective (e.g. clinical evaluation) to objective (e.g. actigraphy), qualitative (e.g. sleep quality diary) to quantitative (e.g. number of awakenings), low burden (e.g. passive monitoring in-home with actigraphy) to high burden (e.g. PSG), coarse (e.g. self-report) to precise (e.g. clinical scale), and systemic (e.g. brain activity) to system-specific (e.g. respirations). Sleep diaries are subjective because they rely on the subject's recollection, and qualitative because the subject is reporting their

perceived *quality* of sleep. Marking midsleep awakenings is quantitative because it's measuring the *quantity* of awakenings, and objective because the subject always presses the button when they wake up. An expert rating based on standardized criteria is subjective because the expert must interpret their observations to determine which criteria are met, qualitative because they have to assign a score, and also quantitative because the score is - in part - based on quantitative metrics like "number of awakenings". Measuring respiration rate with a wearable respiration belt is objective (because it's observed via an artificial sensor) and quantitative (as it's derived from the number of respirations), but it may not be as precise as other methods since it reflects a single biological system that can be influenced by many different factors beyond sleep. It is also less burdensome as it does not require the subject or researcher to actively measure breathing, and is thus less susceptible to issues of compliance and human error. PSG is also objective and quantitative, but instead of measuring one biomarker of sleep, it assesses many (e.g. movement, respiration, heart rate, cortical activity, etc.); this allows one to triangulate the data (*a la* the previous PD prodromal biomarker example) (Lana M. Chahine & Stern, 2017; Espay et al., 2017) and arrive at a more accurate outcome than just measuring respirations alone, albeit at the cost of high subject burden due to the myriad instruments and monitors placed on them and the need to stay in an unfamiliar environment (i.e. sleep lab).

In theory, one might consider always using PSG due to its systemic scope, objective nature, and quantitative measures - and in fact PSG is considered the "gold standard" (i.e. most accurate and reliable) method for assessing sleep. In reality, the burden, cost, logistics, and complexity of PSG restricts its utility enough so that other, less reliable, methods

are used in some situations. If a scientist is, for example, conducting a quick exploratory study to determine if a certain population has enough sleep disruption to merit a large-scale project, then a sleep diary will probably suffice: it can be easily distributed, is cheap, does not require extensive analysis or post-processing to interpret, and - while it is less accurate and susceptible to more confounds than PSG - a high level of accuracy isn't essential in a prospective exploratory study.

Do not mistake this as an argument against the validity of subjectively evaluated data or an indictment of qualitative scales; rather, this highlights the importance of choosing "the right tool for the job". In other words, seemingly inferior methods - on account of their subjectivity, coarseness, etc. - still have valid applications to which they are well-suited. For example, a questionnaire can capture qualitative data on mood and a thermometer can capture quantitative data on body temperature. While one could theoretically be inferred from the other - given sufficient knowledge of mood-related changes in thermoregulation - this is not feasible in practice because one is a subjective report of perception, and the other an objective measurement of a physical property. While mood can theoretically be reduced to a series of neurochemical processes, their specific nature, the ability to precisely quantify them, and the knowledge to translate these biomarkers into a mood that can be subjectively verified is currently beyond our ability. Pragmatically, it is much easier to simply have the subject complete a structured questionnaire. Philosophically, the epistemological incompatibility of physical biology and intangible consciousness precludes their integration into a cohesive system; i.e. the means by which qualitative experiential con-

sciousness (from which subjective evaluation originates) arises from quantifiable biochemical processes (which can be objectively measured) is unknown and can't be artificially recreated. Put simply, subjective evaluations are the product of an inscrutable "black box" of consciousness, whose internal mechanisms cannot be accurately replicated or objectively measured. Until we can do so (and perhaps not even then), subjective evaluation and qualitative self-report will continue to be powerful and ubiquitous methods.

Mixed Methods Research and Data Triangulation – Actigraphy and Polysomnography

We applied the above-mentioned principles to create a multimodal battery of methods to triangulate sleep and circadian disruption in PD (see Chapter 4) and in young healthy men (see Chapter 5). Specifically, objective and quantitative measures (e.g. actigraphy, PSG) were integrated with subjective and qualitative approaches (e.g. sleep questionnaires) to capture as much data and contextual information as possible.

Although PSG is currently the most direct and reliable means of assessing sleep, it entails significant costs and burden on both the clinicians and patients (M. Mitchell & Werkhaven, 2020). Patients are required to sleep in an unfamiliar environment outside of their homes and are often responsible for arranging travel to the clinic, which can be a significant logistical barrier to some. Trained technicians are needed to set up, monitor, and score the PSG, and the necessary specialized equipment and facilities are both expensive to maintain and outstripped by patient demand (CAREOperative, 2020; Gozal et al., 2015).

Actigraphy has been found to have a sleep-detection accuracy of ~80-90% in comparison to in-laboratory PSG, though this varies slightly by population (Ancoli-Israel et al., 2003; Fekedulegn et al., 2020; Marino et al., 2013; M. T. Smith et al., 2018). However, actigraphy's ability to effectively detect sleep - and whether its efficacy is sufficient to yield valid data - is still debated (Goldstone et al., 2018). Epoch-by-epoch sensitivity is considered very good relative to PSG (i.e. ≥ 90%), yet the specificity of epoch-by-epoch sleep detection over the last 20 years has remained constant at approximately 50% (Goldstone et al., 2018). Although derived metrics (e.g. sleep characteristics) usually have better agreement between actigraphy and PSG than epoch-by-epoch sleep detection, the specificity of derived metrics is lower in sleep periods with more wake time. Furthermore, there is scant literature describing the intricacies of sleep algorithms and how certain sleep characteristics are calculated, leading to confusion and inconsistent reporting in the literature (Berger et al., 2005; Fekedulegn et al., 2020; M. T. Smith et al., 2018). Increased methodological transparency may contribute to a better understanding of how sleep characteristics are generated. improve the validity and consistency of their interpretation and application in future studies, facilitate their iterative refinement with improved algorithms, call attention to underused sleep characteristics, and provide the information needed to develop (and disseminate) novel sleep characteristics tailored to specific applications (Fekedulegn et al., 2020).

Ultimately, actigraphy is a compromise between biological assessment and subjective self-report. It is an objective measurement that is still significantly cheaper and less burdensome than biological assays (i.e. PSG for sleep monitoring), and so can be used

longitudinally in ecologically valid environments. Moreover, it eschews the inherent imprecision of subjectively self-reporting sleep, the inaccuracy of which is further compounded by the fact that sleep is an unconscious behavior, and the tendency for subjects to fill out diaries after significant time has passed. However, it is limited by the lack of a direct biological measure, instead inferring sleep through reduced physical activity, and cannot sample qualitative data such as sleep quality or perceived tiredness. Nonetheless, these drawbacks can be greatly mitigated by the inclusion of complementary measures - namely PSG and self-report sleep diaries - allowing internal validation of their common measures (e.g. sleep timing) and data triangulation to inform more accurate interpretations (Madrid-Navarro et al., 2018).

For example, the work presented in Chapter 5 used a combination of demographic and objective data to inform the division of the sample into Morningness and Eveningness cohorts. Since chronotype represents one's default phase-alignment with external zeitgebers, only measures of circadian timing (e.g. acrophase of RAR, sleep timing) would be expected to vary significantly between the cohorts in an unbiased sample. Thus after comparing and finding no difference in non-timing endpoints (e.g. age, BMI) between the cohorts, it was concluded that there were no significant demographic confounds related to chronotype that would need to be accounted for in statistical analysis and interpretation. In addition, the use of the Morningness-Eveningness Questionnaire (MEQ) to determine chronotype was further supported by deriving chronotype from other sources (specifically self-reported and actigraphically-determined bedtimes on weekends and weekdays) and

verifying that these outcomes were also significantly different between MEQ-defined Morningness and Eveningness cohorts.

Triangulation can also be accomplished by characterizing certain aspects or sub-components within a single measure (e.g. actigraphy). For example, Chapter 5 characterized general "sleep quality" using several different measures algorithmically derived from actigraphy: Sleep Efficiency (SE), Wake After Sleep Onset (WASO), Percent Sleep Time (PST), and Fragmentation Index (Frag). After observing a weekend decrease in SE in the Morningness cohort, its potential causes were considered. SE is the ratio of Total Sleep Time (TST) to total Time in Bed (TiB), therefore a lower SE could be caused by additional time spent awake and/or a greater Sleep Onset/Offset Latency (SONL/SOFFL, respectively). PST is a similar metric that omits SONL/SOFFL and only considers the time spent awake between the time of Sleep Onset (SON) and the time of Sleep Offset (SOFF). A significant decrease in PST on weekends in the Morningness cohort was not observed, which led to the conclusion that the additional time spent awake that contributed to the lower SE occurred within the sleep period. However, a significant increase in WASO – which would be expected if a person spent more time awake at night – was not observed. Since WASO is an absolute sum and SE is a ratio, a change in the latter but not the former suggests that the cohort had similar WASO throughout the week, and thus a decrease in TST is the likely cause of the observed decrease in SE.

Despite these applications, the value of multimodal data triangulation was unfortunately only recognized in hindsight. The analyses throughout Chapter 4 and 5 were complicated by the lack of valuable demographic and lifestyle information related to RAR and

sleep. While it is practically infeasible to measure all of the possible factors that could influence RAR and sleep, due to their being systemic behavioral outputs of the interactions between the individual's natural and social environments and their biological circadian rhythms, many of the most influential factors can be readily assessed through self-report. For example, subjects were assumed to work a uniform Monday - Friday daytime schedule due to a lack of information on their vocation and work schedule. Subjects were not instructed to record deviations from their normal routine or asked to report on noteworthy events that could have potentially affected their sleep and activity (e.g. "woke up early to catch flight"), requiring the assumption that such instances never occurred. National holidays and other "special" days that usually elicit a change in behavior (e.g. day off from work) were accounted for in Chapter 5, though this entailed the assumption that all subjects uniformly observed and reacted to these special days because these data were not collected[47]. Other influential factors that were not collected include timing and amount of substance use (especially caffeine, alcohol, and other stimulants/depressants), long-distance travel (especially across time zones), living conditions (e.g. shared bed), meal content and time of consumption, exposure to artificial light[48], and changes in daily routine between work and rest days (e.g. using an alarm clock only on work days).

The inclusion of even a few of these factors may dramatically alter the outcomes of statistical analyses; for example, most of the bivariate associations between MDS-UPDRS

[47] This was somewhat mitigated by treating each special day as a random effect (see Chapter 5, Methods)

[48] This includes the use of specialized screens to filter out blue light, which has the most influence on entraining our circadian rhythm

scores and RAR cosinor metrics reported in Chapter 4 were accounted for by the inclusion of demographic (age, sex, BMI, handedness) and clinical (daily levodopa intake, MMSE score, and ESS score) covariates. It is possible that the remaining significant associations could be attributable to some of the aforementioned factors, especially those related to environmental conditions and work and rest schedules. Longitudinal and multi-site studies (who sample across long duration or distances, respectively) would especially benefit from the inclusion of local day/night cycles, which vary by time of year and geographic location, and which could be represented by those variables, sunrise/sunset times, and/or day:night ratio. A subtle yet significant confound can occur if the sample is distributed across a time zone: while everyone shares the same social time, individuals at different longitudes and (to a lesser extent) latitudes will have different local sunrise and sunset times. Since humans entrain primarily to solar time, the phase-of-entrainment relative to social time will steadily advance as one travels from west to east across a time zone (Roenneberg et al., 2007). The effect is proportional to differences in local sunrise/sunset times, which can vary by up to an hour in most time zones; e.g. on June 21, 2020 the sun rose 51 minutes later (~3.5% of a day) in Indianapolis, Indiana than it did in New York City, New York, despite both being located in the Eastern Standard Time (EST) time zone. Therefore samples taken across large geographic distances should avoid unnecessary variance by accounting for differences in local solar time, as well as other changes in social time (most notably daylight savings time, but also including leap days and other calendar abnormalities).

Ultimately, observational circadian studies greatly benefit from the relatively straightforward collection of ancillary data about the subject and their environment. In addition to allowing researchers to better characterize their dataset, identify novel factors, and draw more nuanced conclusions, it contributes to the methodological harmonization of the field by advancing toward a standardized array of influential covariates and high-value endpoints, which can be expanded to include relevant population-specific factors (e.g. levodopa use in PD, which can cause sleep disruption via night-time dyskinesias).

Mixed Methods Research and Data Triangulation – Actigraphy and Video Annotation

While automation is clearly more efficient and reliable in known systems that can be algorithmically defined, video annotation's value lies in its ability to classify ambiguous and/or context-dependent visual information (Bussmann et al., 1998). This is possible because humans possess the remarkable ability to rapidly evaluate and accurately classify many kinds of visual information that remain algorithmically challenging to contemporary computational approaches (e.g. facial recognition software). More specifically, humans can flexibly integrate contextual information and use it to inform their judgments; for example, a person can correctly recognize that a fold-out lawn-chair and an antique handcrafted wooden chair are both in fact chairs despite their distinct appearances, but would likely not identify a toilet or a throne as a "chair" based on their contextual knowledge of their functional uses. These properties make human raters much more adaptable, accurate, and flexible than contemporary computer algorithms for the purposes of identifying complex,

open-ended, and contextually dependent behaviors, such as social interactions and natural physical movements.

Video annotation is a valuable hybrid approach that implements both subjective and objective techniques to qualitatively classify and temporally quantify behavior; i.e. it implements data triangulation to accurately characterize ambiguous and/or context-dependent behaviors. Furthermore, the fine control of video playback and granularity of "frame-by-frame" review allows for subtle characteristics not reliably detectable in real-time to be precisely visualized with maximal clarity in their presentation (Bussmann et al., 1998; W. G. Janssen et al., 2002). This level of control gives video annotation a temporal resolution far beyond what is available to a contemporaneous observer and allows brief and instantaneous events to be fully reviewed; however, spatial features (e.g. amplitude or distance) cannot be easily quantified by annotators without objective techniques (e.g. kinematics). Although the temporal resolution of video annotation falls short of quantitative measures of movement (e.g. 125 Hz actigraphy has ~8 millisecond resolution, where-as a 60 frames per second (FPS) video has ~17 millisecond resolution), it avoids many of the challenges posed by wearable accelerometers and similar methods - such as expensive equipment, visualization software, and post-processing/filtering. Moreover, raw video data provides an unaltered visual representation unobtainable with accelerometry, allowing for the easy verification of the data: e.g. one could easily verify that a given subject is in a video by watching the video, but one cannot do the same by looking at just an accelerometry waveform. Because of its rich visual content and minimal abstraction, video recordings are frequently used as a "ground truth" to validate sensor-based behavioral classification

algorithms (Heldman et al., 2014). It's important to note that, in these scenarios, the algorithms are being validated against the definitions and criteria used by the annotators to classify behavior; i.e. in the absence of an objective ground truth, the accuracy of the quantitative algorithm is validated against the accuracy of qualitative video annotation.

While the work presented in Chapter 3 was specifically aimed at assessing the feasibility and reliability of video annotation, it was implemented in the first place to bridge the gap between the subjective clinical gold standard - the MDS-UPDRS - and an objective measure of the physical behaviors it assesses. By using video annotation, the MDS-UPDRS' clinical behaviors were accurately and reliably temporally delimited in such a way that they could be readily aligned to objective accelerometry collected in parallel. This effectively created an internally consistent dataset composed of discrete instances of clinical behaviors and postural states. Each instance has an associated duration, demographic information (e.g. sex), clinical scores from the MDS-UPDRS, objective actigraphy and its associated endpoints (i.e. derivatives like sleep characteristics, and other sensors like temperature) and general study metadata associated with the behavior or subject (e.g. date of observation, self-reported quality of life), all manually reviewed and temporally aligned. Such datasets are powerful tools that allow for equitable and valid comparisons between normally incompatible approaches, leveraging data triangulation to contextualize the subject of interest with multiple modalities. For example, a machine learning algorithm could be trained to predict the clinician's score on the Finger Tapping task using accelerometry from the wrist-mounted actigraph (Criss & McNames, 2011).

Although video annotation is not required to create aligned multimodal datasets, it is well-suited to validating sensor-derived postural segmentation and behavioral detection algorithms (Czech & Patel, 2019; W. G. Janssen et al., 2002): postures and most behaviors are gross movements readily identifiable in video, subjective bias can be minimized through clear predefined criteria as demonstrated in Chapter 3, and disagreements can be thoroughly arbitrated as the video is a permanent, immutable record. While the MDS-UPDRS remains a common feature in validation studies due to its ubiquity and recognition as the gold standard assessment of disease severity, it is not well-suited for validating sensor-derived symptomatic scores (e.g. bradykinesia): the scoring - while guided by clear criteria - often relies on the clinician's subjective interpretation of transient symptoms, the scores are assigned in real time with no opportunity to "rewind" and review an ambiguous clinical presentation, and the most commonly used endpoints (i.e. section scores and total score) are meant to reflect overall disease severity and integrate a broad array of symptoms beyond what's being evaluated. Ultimately, no MDS-UPDRS data is lost through the inclusion of wearable sensors and video recording, but their quantitative nature can help contextualize and validate subsequent analyses of scores from the MDS-UPDRS and other clinical assessments (Criss & McNames, 2011; Goetz et al., 1997; Lyons & Tickle-Degnen, 2005; S. T. Moore et al., 2011).

Maximizing Data Integrity and Value to the Scientific Community

Both PD's pathology and the circadian rhythm are complex, dynamic systems that benefit from data triangulation and multimodal data-sets; however, these systems and the methods

used to assess them are sensitive to myriad extraneous factors that must be considered, controlled, and accounted for throughout the scientific process. In addition to ensuring sound experimental design, drawing reasonable conclusions from the results, and objectively considering previous data, the scientific method demands methodological rigor and replicability.

Of paramount importance is the need to reach a scientific consensus on what measures should be employed to assess circadian disruption, it's associated factors, and it's short- and long-term effects on health and wellbeing (Vetter, 2018). Currently, the study of circadian disruption is plagued by inconsistent terminology and insufficient methodological detail, resulting in discrepancies between peer-reviewed articles in how they generate, present, and interpret their findings (Fekedulegn et al., 2020; Vetter, 2018). Beyond the complications this introduces to scientific communication, such heterogeneity limits the power of systematic reviews and meta-analyses by forcing them to reconcile methodological inconsistencies and account for them in their interpretation.

In order to achieve consensus, different models and methodological paradigms must be replicated, evaluated, and compared; to do so requires abundantly detailed and transparent methodological reporting. For example, there are several algorithms that are commonly used to derive sleep characteristics from actigraphy. These are described in detail in Chapter 2; briefly, raw accelerometry must be condensed into epochs through conversion into some intermediate metric (e.g. AC, ENMO), then these epochs are behaviorally classified (i.e. sleep, rest, active, etc.) using a sleep scoring algorithm to identify and bound the sleep period, from which numerous sleep characteristics (e.g. WASO, SE) can

be derived. Designing the method of data collection and implementing the first two steps - epoching and sleep scoring - entails myriad technical decisions (Ancoli-Israel et al., 2015; Fekedulegn et al., 2020):

- What sampling frequency should be used?
- Where will the device be placed on the subject?
- Will the data be transformed to minimize the effect of non-normal distribution and variability (e.g. log transform)
- Which epoch-level endpoint should be used?
- What epoch duration should be used?
- Will gravity be accounted for? How (e.g. gyroscope, ENMO)?
- Will off-body non-wear periods be identified? How (e.g. manual review, subject self-report)?
- How much missing data will be tolerated before the actigraphy is considered invalid for analysis?
- What is the threshold for distinguishing rest from active states?
- Which sleep-scoring algorithm should be used?
- Should the algorithms parameters be tailored to the specific population being assessed? For example, should the sleep threshold be higher in PD to account for their nighttime tremor increasing their baseline activity?
- Regardless of tailoring, which parameters were *actually* used?

Acknowledging that there is a lack of consensus on the *optimal* answers to these questions, this disagreement can be attributed to, in part, the lack of methodological transparency in peer-reviewed articles assessing sleep through actigraphy. Although many such articles provide answers to some of these questions, few provide sufficient detail to accurately replicate their algorithmic pipeline (Fekedulegn et al., 2020). This lack of detailed reporting leads to "islands of expertise" (Espay et al., 2016), the relatively independent and often redundant iterative development of techniques that grow increasingly incompatible with other "islands" due to the lack of communication and collaboration. Espay and colleagues (2016) applied this term specifically to the producers of "technology-based objective measures" (which includes actigraphy) as part of a larger acknowledgement (Johansson et al., 2018) of the need to improve reporting and standardization of actigraphy derived measures in PD research (including motor, clinical, and physical activity in addition to sleep characteristics); however, this concept is just as applicable to the iterative process of methodological refinement in research. For example, the FI is a common sleep characteristic that is often interpreted to represent the frequency of sleep/wake transitions throughout the night; i.e. it is a measure of how likely a person is to transition between sleep and wake epochs throughout the night (Fekedulegn et al., 2020; Natale et al., 2014). While it is widely reported, there exist multiple variations purporting to be "fragmentation index" or analogous metrics that are derived using different formulas (Fekedulegn et al., 2020; Mini Mitter Company, Inc., 2006). Further confusion is introduced by "spin-off" metrics derived from FI, such as the *rest fragmentation* (k_{RA}) and *activity fragmentation* (k_{AR}) indices (Lim et al., 2011), and the historical use of standard PSG metrics, such as the arousal index and SE

(Moser et al., 2009), to infer sleep fragmentation. Without context, "sleep fragmentation index" could potentially refer to any one of these metrics.

The need to promote abundantly detailed and transparent methodological reporting is by no means limited to actigraphy, but is vital for all aspects of study design. While frequently acknowledged as a limitation (including for the work presented herein), sampling and recruitment biases are nonetheless a significant and widespread confound in observational circadian research that must be accounted for and, whenever possible, mitigated (Di Milia et al., 2013). Unfortunately, the practical constraints of deadlines and budgets often leads to "convenience sampling" in modern human subjects research, where subjects are enrolled as quickly as possible from easily accessible populations (e.g. a study on "healthy adults" recruiting undergraduate students from the laboratory's university). Although the judicious use of appropriate inclusion/exclusion criteria can mitigate the effect of convenience sampling by homogenizing the sample (albeit at the cost of generalizability), and *post-hoc* analysis can potentially account for demographic differences between the cohort and the general population, a convenience sample may differ from the general population in ways not accounted for by the researchers. For example, alcoholics were screened out in Chapter 5, but a cohort of young males is nonetheless significantly more likely to drink to excess than the general population and this must be considered when generalizing Chapter 5's results.

The work presented herein was not immune to this bias, as the data presented in Chapter 5 was obtained from a sample consisting largely of graduate students enrolled at Boston University School of Medicine. Although this helped create a homogenous sample

and thus increased the confidence of conclusions drawn from it, the lack of a representative sample worked to negate the primary strength of observational research by limiting the generalizability of its conclusions. This is not to say that observational circadian research should not be conducted on specific sub-populations - in truth circadian function and disruption varies widely across demographic factors such as age, chronotype, and vocation (Roenneberg et al., 2019; Vetter, 2018) - but that a convenient sample should not be assumed to be a representative sample. Especially now, in this period of methodological consolidation and theoretical harmonization, large representative samples are needed in both the general population and specific subpopulations to provide accurate baseline data to inform future research in observational circadian research. Beyond making informed study design decisions, this also requires clear reporting of the process by which subjects were selected and recruited, the inclusion/exclusion criteria used to screen them, and the rationale for these choices in the context of the study's primary research questions.

Missing data is another serious hindrance to observational circadian research, primarily due to the reliance on methods such as actigraphic monitoring that are susceptible to subject non-compliance (Fuster-García et al., 2013). Considerable missing data was encountered in Chapters 4 and 5, the large majority of which was attributable to subject non-compliance. Although data imputation was considered, it was ultimately decided that it was too unreliable and that the relatively small size of the dataset would introduce unnecessary stochastic bias. Data imputation is common in actigraphy, though conventional imputation methods entail assumptions regarding the distribution of missing data that actigraphy rarely meets, and data imputation in actigraphy is neither standardized nor universal

(Brooks et al., 2020; Herrmann et al., 2014; Jang et al., 2020). There is also no consensus on the amount of missing data that can be tolerated before a given period of actigraphy should be discarded entirely. Chapters 4 and 5 implemented 15% threshold (i.e. 3.6 hours/day) for the purposes of identifying eligible days for cosinor analysis. After failing to identify a consistent reference threshold in the scientific literature, 15% was chosen as it could flexibly accommodate the amount of missing data and participant non-compliance expected to occur due to study protocols (e.g. removal for bathing).

Although there is scant information regarding the treatment of missing data in cosinor analysis[49], there has been some exploratory work in other applications of actigraphy. For example, the minimum amount of "wear time" needed to assess daily physical activity ranges from 2 - 16 hours (Herrmann et al., 2013); a wear time of 12+ hours, based on a 2014 meta-analysis (Herrmann et al., 2014), has recently become more common (Amagasa et al., 2019; Kaufman et al., 2019; Mazzoni et al., 2017). Missing data must be characterized in detail in scientific reporting[50]: it's amount, distribution across the sample, potential causes, and treatment (i.e. imputed or omitted). Not only is this valuable information that can inform future work and meta-analyses (Johansson et al., 2018), it can be applied to better understand the causes of missing data and mitigate its frequency and severity (Herrmann et al., 2014; Morgenthaler et al., 2007).

[49] Cosinor analysis has been described as "robust" to missing data because it does not require equidistant samples (Cespedes Feliciano et al., 2017)
[50] Roberts et al. (2020) is an excellent example of this

Sociogenic Circadian Disruption

Our behavioral rhythms - and therefore our physiology and health - are subtly influenced by factors conventionally taken for granted. Our circadian rhythm is, in many ways, analogous to the social calendar in form and function. According to the French sociologist, Émile Durkheim: *"A calendar expresses the rhythm of the collective activities, while at the same time its function is to assure their regularity."* In the same way, our circadian rhythm is the product of the "collective activities" of our myriad biological processes, and simultaneously serves to "assure their regularity" with respect to each other and the geophysical day. Both provide a common, regular temporal reference that can be used to minimize waste and optimize efficiency; both were derived from the astronomical properties of our planet and sun; and both are a constant pressure that shapes our daily lives and subtly affects our minute-to-minute behavior.

Circadian disruption is the sustained desynchronization of the circadian rhythm from its environment, although it has also been referred to as circadian misalignment, circadian desynchrony, and chronodisruption, among other terms, in the literature (Vetter, 2018). The widespread circadian disruption extant in modern industrialized societies can be partially attributed to interference caused by social calendars, mores, and expectations that shape our behavioral schedules independently of the biological circadian rhythm and the geophysical day. Chapter 4 reported variations in sleep and RAR metrics that appeared to be associated with distinct times of the week, which were characterized as "sociogenic" based on the socially defined nature of the calendar week. Sociogenic circadian disruption specifically refers to desynchronization caused primarily by social and sociological factors,

especially the calendar and the "rhythm of collective activities" it regulates. The work in Chapter 5 explicitly aimed to detect these sociogenic effects in a larger, more uniform sample and found distinct, regular changes in sleep and RAR associated with transitions between weekends and the work-week. Analysis of variance components in each nested tier of Chapter 5's linear mixed models - Participant, Week, and Day - identified consistently large variances at the Day level across RAR and sleep characteristics, suggesting that the most influential factors on sleep and RAR patterns may be at the Day level: e.g. weather, exercise opportunities, inconsistent weekly schedules, etc.

There is abundant evidence of the deleterious effects associated with rhythmic sociogenic factors. For example, there is a well-documented weekly rhythm in heart attack with its peak on Mondays (Rogot et al., 1976), and cardiovascular mortality has been observed to increase on regularly occurring socially significant occasions, such as holidays (Wallert et al., 2017) and major sporting events (Wilbert-Lampen et al., 2008), although similar increases in mortality have been observed in singular periods of social disturbance, such as in the weeks following earthquakes (Takegami et al., 2015). Other socially influenced infradian rhythms have been found in the timing of human activity *vis-à-vis* the normal morning increase in power grid burden occurring ~1 hour later on weekends (Stowie et al., 2015) and a similar delay in peak social media usage (Leypunskiy et al., 2018). Other notable infradian rhythms potentially influenced by social factors include an increase in the mortality rate of acute subarachnoid hemorrhages increasing during the work-week (Turin et al., 2010), a circaseptan rhythm in blood pressure with its peak on Monday (Murakami et al., 2004), and a semicircaseptan (i.e. twice weekly) peak in suicides (F. Halberg

et al., 2005; Refinetti et al., 2007). Myocardial Infarction (MI) with Non-Obstructive Coronary Arteries (MINOCA) events were observed to be more common on Mondays and early mornings (Nordenskjöld et al., 2019); curiously, unlike normal MI's, the frequency of MINOCA's was not associated with holidays. Collectively, these may be caused by sudden increases in psychosocial stress associated with significant social events (e.g. holidays), behavioral transitions (e.g. weekend to work week), and their subsequent physiological stress (Ayers et al., 2014; Wallert et al., 2017).

Circadian disruption is not a new phenomenon, but modern technology has vastly increased the number of ways it may occur. Before the development of steam engines, for example, no human had the means to travel far enough in one day to experience jet lag; now it is a common occurrence for much of the population (Roenneberg et al., 2015). Calendrical abnormalities and social customs such as daylight savings time and holidays, respectively, present challenges to our circadian rhythm that risk acute disruption (Fritz et al., 2020; Kitamura et al., 2016; Wallert et al., 2017). Artificial lighting has a clear confounding effect that interferes with the circadian rhythm's ability to synchronize to photic zeitgebers, and has made it dramatically easier to extend daytime behaviors into the night and further decoupled social and biological time. For example, there are many "time-agnostic" professions whose schedules are almost entirely determined by social factors, including first responders, military personnel, medical specialists, and shift-workers at 24/7 jobs. Competitive fields, such as professional sports and post-graduate education, may encourage personal schedules that prioritize professional advancement over a regular sleep

schedule. At a macro scale, human birth-rates have historically exhibited a strong circannual trend that has all but evaporated: birth-rates fluctuated by ~60% across the year in pre-industrial human societies, where-as modern industrialized nations experience an amplitude of ~0%-5% (Foster & Roenneberg, 2008).

Modern human societies are more secluded from natural zeitgebers than ever before. Through the development of shelter, artificial lighting, social calendars, industrialization, electronics, globalization, rapid long-distance transportation, and near-instantaneous communication, human society has increasingly sequestered itself from the natural cycles present on Earth that shaped the biological rhythms of our global ecosystem and therefore our own species. While our behavior is still dominated by the rising and setting of the sun, our technological advancement has led to our societies becoming more insulated from natural zeitgebers. The rhythm of human society is increasingly determined by logistical (e.g. international shipping), economic, sociopolitical (e.g. work-week), geographic, professional (e.g. shift-work), and other artificial pressures. The increasing independence of our society from natural cycles (e.g. tidal, solar, and seasonal) results in a discrepancy between our social, behavioral, and circadian rhythms from which circadian disruption can arise.

Circaseptan Rhythms and Disruption

Socially motivated changes in the phase of behavioral rhythms across the seven-day week give rise to circaseptan rhythms of circadian disruption. Social Jet Lag (SJL), the difference in average sleep timing between rest and work days (Wong et al., 2015), is perhaps the

most obvious example of sociogenic circaseptan disruption. Most adults in industrialized countries experience at least one hour of Social Jet Lag (SJL) ("2005 Sleep in America Poll – Adult Sleep Habits and Styles," 2015; Roenneberg et al., 2003, 2015). This delay in sleep times on rest versus work days is commonly observed (Monk et al., 2000; Roenneberg et al., 2003) and can cause circadian phase delays of up to 1 hour (Crowley & Carskadon, 2010; C.-M. Yang et al., 2001) that may take several work days to overcome (Crowley et al., 2015; Taylor et al., 2008). This mild forward phase-shift leads to increased daytime sleepiness and fatigue (Taylor et al., 2008), consequently impairing attention, mood (Dinges et al., 1997), memory consolidation (Karni & Sagi, 1993), vigilance, and potentially contributing to an increased risk for accidents (Bonnet & Arand, 1995) and cardiovascular disease (Gallerani et al., 2017) following rest-work transitions. While these outcomes are caused by disruptions associated with discrete parts of the week (specifically the transition between different "social time zones", i.e. work and rest days), it is unclear whether it is purely a product of abrupt changes in behavioral rhythms (e.g. sleep timing) and significant events (e.g. work-related stress) caused by the week, or if they can be partially attributed to the misalignment of an innately circaseptan biological rhythm with the social week exacerbates the sociogenic disruption (Reinberg et al., 2017). In the same way the circadian rhythm predisposes us to be active during sunlight hours in the 24-hour day, an innately circaseptan biological rhythm may predispose us to being more active on certain days of the week.

Humans likely adopted the seven-day week based primarily on cultural and social factors - i.e. not based on a systematic evaluation of scientific evidence of negative health

outcomes associated with weeks of different lengths. Ancient Bayblon implemented a lunar calendar divided into four seven-day weeks - the oldest historical evidence of a calendar week - and the first non-lunar calendar week appeared in Judea; both included a specific "sabbath" or "rest day" dedicated to spiritual and ceremonial activities (Zerubavel, 1989). Perhaps the most famous antecedent of the seven-day week in American society is the story of God's creation of the earth as told in the Book of Genesis:

> "And on the seventh day God ended His work which He had done, and He rested on the seventh day from all His work which He had done." (Genesis 2:2, New King James Bible)

Although it is implicit that the modern week was derived from these historical precedents, it is nonetheless possible that the adoption of the seven-day week was encouraged by an innate biological circaseptan rhythm through its influence on infradian rhythms in human behavior (i.e. work/rest days). Humanity's inquisitive, greedy, and self-preserving nature ensures that our societies are continually adapting to external pressures by exploring, testing, and revising strategies to protect themselves and improve their fitness. For example, prehistoric humans spontaneously formed cities in response to new farming technology and the food surplus they created, as this gave them an immense benefit by allowing specialization and non-agricultural pursuits, and these cities spontaneously formed self-governing coalitions (i.e. states) to protect their shared interests. During World War II, the adoption of "total war" policies and the societal cost it entailed led to dramatic changes in American society, such as a large influx of women into the workforce and the proliferation

of "victory gardens" to supplement rationed food supplies. At the time of writing this manuscript in 2020, ingrained social touch customs such as the handshake are rapidly being replaced with contactless gestures due to the increased risk of viral transmission associated with the global Coronavirus Disease 2019 (COVID-19) pandemic. Human sociocultural mores are enduring yet adaptable, and this extends to our calendars as well.

For most of human history, societal time structures and their subsequent rhythms have been dictated by biological (e.g. circadian rhythm) and natural (e.g. day/night cycle) factors. While artificial considerations such as simplicity, economic efficiency, compatibility with other societies, and the cost of revising an existing system undoubtedly influenced calendar development throughout history, the increased energy made available by the industrial revolution greatly expanded our productive capacity and thus the influence of these artificial factors. In the interest of efficiency, industrialization efforts built upon and standardized pre-existing systems: since the week was the cultural standard in much of the world in the 19th century, it became the basis for the standard modern calendar. Assuming it exists, an innate biological circaseptan rhythm likely influenced the adoption of the seven-day week in human societies, but has since been supplanted by an artificial calendar dependent on non-biological factor: why check the sun's position in the sky when you can look at your watch? While a circaseptan rhythm and the seven-day week are equivalent in duration, the day-to-day activities and normal behaviors across the week are now primarily informed by wholly artificial considerations: i.e. work schedules. In other words, there's no guarantee that the "shape" of our circaseptan rhythm is the same as it was before

the industrial revolution, nor that it possesses the same properties such as adapting to seasonal differences in the day/night cycle.

Origin of Circaseptan Rhythms

It has been proposed that circaseptan rhythms observed in tidal zone organisms, such as the beach beetle (*Chaerodes trachyscelides*), derive from the lunar-driven tidal cycle, and that this may be the origin of circaseptan rhythms in non-tidal animals (Meyer-Rochow & Brown, 1998). Tides are regular oscillations in local water level along coastlines driven primarily by the gravitational force exerted by the moon. Individual tidal cycles (i.e. high tide to the next high tide) occur every ~12.4 hours due to the combined rotation of the earth and the revolution of the moon about the earth - for a given location, high tides generally occur when the moon is directly overhead and directly underfoot, and low tides occur when the moon is perpendicular to the location's ground plane. Tidal dynamics are complex, being affected not only by local conditions (e.g. atmospheric pressure, temperature) and geography (i.e. coastline shape), but also by the sun. Despite its distance, the sun's immense mass allows its gravity to exert a force roughly half as influential as the moon's gravity. This is most noticeable during *spring* and *neap* tides. Twice during the lunar cycle, the earth, moon, and sun align in syzygy, once with the moon between the earth and sun (i.e. a *new moon*), and ~14.5 days later when the earth is between the moon and sun (i.e. a *full moon*). During these syzygies, the gravitational pulls of the moon and sun both work along the same axis, exaggerating the amplitude of high and low tides; these are known as *spring tides*. Likewise, a *neap tide* occurs during the 1st quarter moon and 3rd quarter moon

when the moon is at quadrature (i.e. orthogonal to the sun relative to the earth) and the lunar-solar gravitational reinforcement is at its weakest, resulting in reduced tidal amplitude.

The authors of the aforementioned *C. trachyscelides* study observed a circaseptan rhythm in their physical activity (Meyer-Rochow & Brown, 1998). They further noted that, since *C. trachyscelides* forages in the debris zone left by the ebb tide, and since the debris zone would gradually shift up and down a beach between each neap and spring tide, they would be subject to a natural evolutionary pressure to anticipate and follow these shifts. As previously explained, a single cycle of spring tide --> neap tide --> spring tide takes approximately 14 days to complete; this makes it a *circadiseptan rhythm*, with the acceleration, deceleration, and eventual reversal of the tidal cycle's maximum extent occurring every 7 days - i.e. a circaseptan rhythm. Therefore, the weekly increase in *C. trachyscelides* activity may be a byproduct of their natural chronobiological adaption to the circaseptan harmonic of the naturally occurring circadiseptan rhythm of neap and spring tides. Thus, while natural circaseptan rhythms do not have an obvious astronomical correlate capable of entraining them, they may have ultimately originated from the lunar cycle via the regular circadiseptan oscillation in tidal amplitude caused by the moon's rotation around the earth relative to the sun. While this may indicate a potential biological origin of the circaseptan rhythms, it does not account for how such a rhythm could be biologically preserved and transferred to humans (via evolution, symbiosis, or otherwise). Given that the majority of humans have historically lived on the coast and thus been exposed to this circadiseptan

rhythm, it is possible that this played a role in the sociocultural development of a seven-day calendar unit regardless of the presence of a biological correlate.

Scientific and Clinical Considerations

In order to improve resiliency to the negative effects of sociogenic circadian disruption, we must be able to reliably detect it, precisely measure its magnitude, thoroughly characterize its nature, and quantify its risks and their associations with its negative outcomes, both acute (e.g. fatigue) and chronic (e.g. risk factors for diseases). While it is clear that systemic changes in the ordering of our social calendars is needed to prevent sociogenic circadian disruption (), the nature and extent of these changes are unknown. Until then, more conventional therapeutic interventions are needed to mitigate the deleterious effects of circadian disruption.

Much like "lifestyle diseases" such as obesity and metabolic disorders, circadian disruption can be minimized through practical changes to one's lifestyle. SJL is a widespread form of chronic sociogenic circadian disruption caused by the seven-day week and associated with numerous negative health outcomes. Much like obesity, it is a product of one's behavior (acknowledging also the genetic, metabolic, and neurological systems promoting that behavior) and is best remedied through behavioral modification. In addition to maintaining a constant sleep schedule, daytime exercise and consistent day-to-day RAR's provides a stabilizing effect that strengthens the amplitude of the SCN's latent rhythms and improve mood and performance in Alzheimer's disease (Pévet, 2016); note that circadian disruption (e.g. "sundowning") is a common symptom in Alzheimer's disease.

Amongst the numerous topics of debate in this emerging field is the degree to which sociogenic factors can directly influence the biological circadian rhythm, as opposed to indirectly (e.g. via sleep). Although social calendars and behaviors may influence a person's chronotype, these "social zeitgebers" do not appear capable of independently entraining human circadian rhythms (Roenneberg et al., 2007, 2015), and evidence suggests that the human circadian rhythm is entrained primarily by the solar calendar (i.e. sunrise/set) rather than the social calendar. For example, humans have created arbitrary "time zones" that unify relatively broad ranges of longitude with a common clock, yet local sunrise time is a continuous function of longitude irrespective of time zones; e.g. the sun may have risen in New York City but not in Columbus, a city in the same time zone but ~9° farther west. A study examining self-reported sleep times and chronotypes in Germany found that individuals who lived farther west woke up later than more easterly individuals in the same time zone; i.e. their clocks showed the same time. This effect was inversely proportional to population density, as. people in cities were less entrained to solar time, which the authors theorized was due to light pollution (Roenneberg et al., 2007). The greater importance of solar time versus social time for circadian entrainment is further supported by case studies of blind workers, who have free-running circadian rhythms (due to their insensitivity to light) despite functioning within a social calendar (i.e. work) (Arendt et al., 1988). In other words, social time can influence the phase of the circadian rhythm (and thus disrupt it), but it is not enough to entrain the circadian rhythm by itself (Roenneberg et al., 2007).

Methodologically, the study of circadian disruption benefits from data triangulation and the integration of observational and experimental datasets. In general, animal models

are well-suited to basic biological research, where-as human subjects lend themselves well to translational research. This holds especially true for chronobiology given the presence of numerous artificial zeitgebers (e.g. artificial lighting), widespread use of circadian-modifying substances (e.g. caffeine and alcohol), and other anthropogenic confounds extant in modern human populations (e.g. social media). Moreover, the sheer number of potential confounds limits the generalizability of basic research to functional applications. Observational studies attempt to maximize ecological validity - i.e. minimize observational and experimental biases - to more accurately measure authentic circadian disruption as it exists in the modern milieu, replete with artificial zeitgebers and innumerable potentially confounding variables. Thus observational studies are often epidemiological or translational in nature, relying on gross systemic outputs of the circadian rhythm (e.g. sleep timing) in combination with environmental factors (e.g. presence of artificial zeitgebers) and/or interventions (e.g. sleep medication) to characterize a given population's circadian rhythm, its disruption in a given context, and potential correlates amongst the behavioral (e.g. sleep timing), biological (e.g. body temperature), cognitive (e.g. reaction time), and/or psychological (e.g. perceived sleepiness) outcomes of interest (Vetter, 2018).

In addition to factors and covariates mentioned earlier in this Chapter (see *Methodological Considerations*), the work presented in Chapter 5 reinforces the importance of accounting for chronotype in observational circadian research and contributes to its utility as a circadian endpoint in clinical and epidemiological studies. DLMO is generally considered to be the gold standard marker of one's biological chronotype (Arendt & Skene, 2005; Benloucif et al., 2005). In practice, melatonin concentration is derived from saliva or blood

plasma samples collected in frequent intervals to prevent short-term changes (from, e.g., exposure to artificial light) from "masking" the underlying circadian rhythm. As the process of sampling and processing of samples for DLMO is burdensome, time-consuming, and expensive, self-reported chronotype (e.g. via questionnaires like the MEQ) has become more common. Alternatively, sleep timing on rest days has been used as low-cost low-burden behavioral proxy for inferring chronotype (Vetter, 2018). This approach benefits from its cost-effectiveness, ease of implementation, and applicability to remote in-home monitoring for capturing ecologically valid sleep behavior, with the significant caveat that sleep is a complex systemic behavior only partially mediated by the circadian rhythm. In other words, sleep timing represents a behavioral output influenced by the circadian rhythm, where-as DLMO is a physiological signal directly regulated by the central oscillator and so can be expected to more accurately reflect the circadian phase (Vetter, 2018). When assessing chronotype in humans, chronobiologists must weigh the accuracy and biological validity of DLMO sampling against the utility and ecological validity of questionnaires and sleep timing. The MEQ was employed in Chapter 5 due to the logistical difficulties of sampling DLMO while monitoring subjects during their "normal life". Regardless of whether sleep timing is assessed either subjectively through self-report (e.g. MEQ) or quantified through objective measures (e.g. DLMO, actigraphy), it is essential that chronotypes are derived from sleep timing on rest nights. This is because external factors, such as waking up early to go to work, will change when a person sleeps, where-as one can adhere to their preferred, "chronotypical" sleep timing when there are no restrictions on when they have to wake up.

Lastly, it should be noted that there is a profound historical sex bias in chronobiological research: for example, only 1 in 5 peer-reviewed articles employing mouse models of circadian rhythm included female mice (Kuljis et al., 2013). This systemic bias is exacerbated by the mounting evidence of significant sexual dimorphism in circadian biology; e.g. sex-specific modification of circadian rhythm in the embryo, differences in SCN volume, physiology, and cytoarchitecture between the sexes, and the presence of androgenergic and estrogenergic receptors on neurons in central circadian regulators, including the SCN (M. Bailey & Silver, 2014; Kuljis et al., 2013). Between-sex differences have also been observed in humans; e.g. women have larger and longer SCN's relative to total brain volume.

Circadian Disruption in Parkinson's Disease

Circadian disruption and sleep dysregulation are critical non-motor symptoms of PD that require the integration of molecular, neurological, and behavioral research to effectively understand and treat (Fifel & Videnovic, 2019; Vetter, 2018). Much like PD's other symptoms, the breadth and severity of circadian disruptions are heterogenous. Although sleep and circadian disruption (amongst other non-motor symptoms) have received considerably less attention than PD's hallmark motor symptoms until recently, they were described in a patient with advanced PD by James Parkinson in his seminal work, "An Essay on the Shaking Palsy" (1817):

> "In this stage, the sleep becomes much disturbed. The tremulous motion of the limbs occur during sleep, and augment until they awaken the patient, and frequently with much agitation and alarm. ... It now seldom leaves [a patient] for a moment; but even when exhausted nature seizes a small portion of sleep, the motion becomes so violent as not only to shake the bed-hangings, but even the floor and sashes of the room. ... [The patient's] attendants observed, that of late the trembling would sometimes begin in his sleep, and increase until it awakened him: when he always was in a state of agitation and alarm."

Parkinson described sleep disruption as a consequence of the motor symptoms in particular, though there now exists a burgeoning appreciation that the breadth and diversity of sleep disruptions in PD is considerable and is caused by non-motor factors (i.e. the pathological disturbance of the circadian rhythm). Etiologically, sleep disruptions have been separated into three broad categories: sleep disruption as a consequence of PD's neuropathology and symptoms, sleep disruption as a consequence of dopaminergic medication and its side effects, and sleep disorders that frequently co-occur with PD (Claassen & Kutscher, 2011). The first category includes Excessive Daytime Sleepiness (EDS; described by Parkinson as "constant sleepiness" and "extreme exhaustion"), which may originate from intrinsic the degeneration of central sleep regulators such as the raphe nucleus and locus coeruleus, and/or secondarily by sleep fragmentation caused by urinary incontinence, motor symptoms, etc. (Videnovic, Lazar, et al., 2014). Parkinson's observations (1817) fall in this category. Next, dopaminergic medications (e.g. levodopa) can induce insomnia and reduce time spent in NREM when incorrectly dosed (Brunner et al., 2002; Vetter, 2018), their side effects (e.g. dyskinesia) can interrupt sleep in the same manner as

tremor, and medications for other symptoms and comorbidities (e.g. depression) can further interfere with sleep regulation (Huete & Varona, 1997; Jindal, 2009). Lastly, REM Behavioral Disorder (RBD), Restless Leg Syndrome (RLS), and Obstructive Sleep Apnea (OSA) are more prevalent in persons with PD than those without PD (Claassen & Kutscher, 2011); determining the causal relationship between these disorders and PD - i.e. whether one causes the other - is a major objective of current clinical research.

Dopamine has been identified as a promising research target for exploring the relationship between the pathology and circadian disruption of PD (Videnovic, Lazar, et al., 2014; Videnovic, Noble, et al., 2014). The depletion of dopamine throughout the CNS and particularly in the basal ganglia is a hallmark symptom of PD and thought to be the primary cause of PD's motor symptoms; moreover, dopamine is a major neurotransmitter in the circadian rhythm, and several symptoms have been linked to dopamine loss and dysregulation in PD (see Chapter 4; Discussion).

Limitations

The work presented in this manuscript should be considered in the context of several limitations and assumptions. While these have been described in greater detail throughout the Chapter, they will be briefly summarized here. The use of small sample sizes recruited through "convenience sampling" contributed to the high variance in the data and limited their generalizability, especially in Chapter 4. The Actiwatch used throughout Chapters 4 and 5 is a "black box" actigraph that restricts access to the raw accelerometry data and uses

a proprietary algorithm to epoch and behaviorally segment the data, which greatly restricted analytical options for deriving RAR and sleep characteristics. A significant amount of missing data primarily attributable to subject non-compliance was also encountered; in combination with limited sampling periods of two to four weeks (in Chapters 4 and 5, respectively), this weakened statistical power and increased variance. The basic cosinor model, while common in the literature, is overly simplistic and can only approximate human RAR, which are more "block-wave" than sinusoidal. Due to methodological constraints, several contextual factors known to influence circadian and circaseptan rhythms were not accounted for, most notably employment, weekly work schedule, use of depressants and stimulants, exercise and mealtimes, and "one-off" events that deviated from the subject's normal rhythm.

Future Directions

The work described in this manuscript has highlighted several promising avenues for future research. First, the significant methodological challenges encountered due to inconsistent and opaque reporting in the literature is a significant hindrance to the field – progress demands methodological consolidation, theoretical harmonization, abundantly transparent reporting, and the generation of publicly available datasets to facilitate collaboration and data triangulation – and future work will strive to promote these principles alongside the rest of the field. Second, future work will focus on the refinement of the methodological toolkit, including the use of more accurate models of human RAR (e.g. extended cosinors),

reducing missing data through improving subject compliance, and the integration of synergistic methods to create more robust and comprehensive statistical models. Third, the search for potential biological correlates of infradian rhythms will be aided through identification of infradian trends in unconventional data, including social (e.g. social media usage), demographic (e.g. birth rates), epidemiological (e.g. causes of death), commercial (e.g. media engagement), and civil (e.g. power consumption) data. This also entails the detailed characterization of RAR and sleep characteristics in distinct populations and environments, such as those with different levels of light pollution (e.g. urban v. rural), to identify significant factors that contribute to circadian disruption, and the integration of the sociological perspective to aid in contextualizing and interpreting chronobiological outcomes.

Our future work will be guided by the knowledge that our lives, our behavior, our society, and our health are shaped by factors we all-too-often take for granted - most notably the seven-day week - and fueled by the remarkable abundance of data available to humanity in the information era.

Conclusion

The circadian rhythm is a distributed yet interconnected system of systems that coordinates the timing of biological processes by integrating exogenous and endogenous signals via a self-regulating, adaptive network present at every level of biological organization, from cells to cities. Although we have greatly improved our knowledge of the circadian rhythm's molecular and anatomical components, the mechanisms and consequences of its disruption

in modern societies are less well understood. Moreover, the ubiquity of circadian rhythms in our biology creates innumerable avenues through which it can be pathologically disrupted (e.g. dopaminergic depletion in PD), or through which it can create pathology (e.g. SJL and risk factors). Clinical study of circadian disruption therefore requires a holistic, integrative approach that strives to measure both the circadian rhythm itself and the suspected factors implicated in its disruption. As the circadian rhythm is inseparable from our behavior and environment, its disruption can only be crudely replicated in controlled laboratory settings, and this loss of ecological validity hinders the translation of scientific findings into clinical interventions (Andrade, 2018). Over the last several decades, technological progress has enabled the practical use of wearable devices capable of continuously monitoring circadian signals, such as RARs. While this nascent approach has significant obstacles still to overcome, it has nonetheless encouraged more ecologically valid studies focused on objectively measuring circadian rhythms in the authentic context of day-to-day life and human behavior.

Furthering the scientific community's understanding of sociogenic circadian disruption will be *accomplished* through the integration of complementary designs, synergistic methods, and multimodal datasets to triangulate findings; *motivated* by its ubiquity in modern industrialized societies, it's contribution to negative health outcomes, and its disproportionate impact on critical infrastructure; *facilitated* by methodological consolidation, theoretical harmonization, and integration of sociological and other novel perspectives; and *guided* by an appreciation of the fundamentally important role the circadian rhythm plays in shaping in our behavior, our society, and our health. This is not a novel approach; the

growing acknowledgement that a diverse and broad battery of clinical biomarkers will be needed to accurately diagnose, characterize, and monitor disease progression shows that data triangulation efforts are already being prioritized in PD research, among other fields.

APPENDIX

Chapter 3 Supplementary Information

Figure A.1: Video Coding Scheme

"**Clinician**" refers to the person directly administering and guiding the Subject through the assessments. The Clinician is not face masked.

"**Subject**" refers to the person undergoing the assessments and wearing the wearable sensors. The Subject's face is masked.

Scripted Motor Tasks

Rigidity, Neck – The Clinician manually articulates Subject's neck.

- Initiation Frame: First visible movement of the neck or head clearly caused by the Clinician through physical contact, including when the point of contact is out of view.
- Termination Frame: Last visible movement of the neck or head clearly caused by the Clinician, or when the Clinician is no longer touching Subject's head and neck, whichever comes first.
- MDS-UPDRS Instruction Criteria: Subject in relaxed position, Clinician slowly manipulates major Neck joints, Subject allows passive movement of neck.
- MDS-UPDRS Rating Criteria: Rigidity (w/o Activation Maneuver), Rigidity (w/ Activation Maneuver), Range of Motion, Difficulty of Achieving Range of Motion

Rigidity, Right Upper Limb – The Clinician manually articulates Subject's joints on their right upper limb.

- Initiation Frame: First visible movement of the right upper limb clearly caused by the Clinician through physical contact, including when the point of contact is out of view.
- Termination Frame: Last visible movement of the right upper limb clearly caused by the Clinician, or when the Clinician is no longer touching Subject's right upper limb, whichever comes first.
- MDS-UPDRS Instruction Criteria: Subject in relaxed position, Clinician slowly manipulates Right Wrist and Elbow joints, Clinician does not manipulate other limbs or neck, Subject allows passive movement of RUE, [Subject performs Activation Maneuver]
- MDS-UPDRS Rating Criteria: Rigidity (w/o Activation Maneuver), Rigidity (w/ Activation Maneuver), Range of Motion, Difficulty of Achieving Range of Motion

Rigidity, Left Upper Limb – The Clinician manually articulates Subject's joints on their left upper limb.

- Initiation Frame: First visible movement of the left upper limb clearly caused by the Clinician through physical contact, including when the point of contact is out of view.
- Termination Frame: Last visible movement of the left upper limb clearly caused by the Clinician, or when the Clinician is no longer touching Subject's left upper limb, whichever comes first.

- MDS-UPDRS Instruction Criteria: Subject in relaxed position, Clinician slowly manipulates Left Wrist and Elbow joints, Clinician does not manipulate other limbs or neck Subject allows passive movement of LUE, [Subject performs Activation Maneuver]
- MDS-UPDRS Rating Criteria: Rigidity (w/o Activation Maneuver), Rigidity (w/ Activation Maneuver), Range of Motion, Difficulty of Achieving Range of Motion

Rigidity, Right Lower Limb – The Clinician manually articulates Subject's joints on their right lower limb.

- Initiation Frame: First visible movement of the right lower limb clearly caused by the Clinician through physical contact, including when the point of contact is out of view.
- Termination Frame: Last visible movement of the right lower limb clearly caused by the Clinician, or when the Clinician is no longer touching Subject's right lower limb, whichever comes first.
- MDS-UPDRS Instruction Criteria: Subject in relaxed position, Clinician slowly manipulates Right Hip and Knee joints, Clinician does not manipulate other limbs or neck, Subject allows passive movement of RLE, [Subject performs Activation Maneuver]
- MDS-UPDRS Rating Criteria: Rigidity (w/o Activation Maneuver), Rigidity (w/ Activation Maneuver), Range of Motion, Difficulty of Achieving Range of Motion

Rigidity, Left Lower Limb – The Clinician manually articulates Subject's joints on their left lower limb.

- Initiation Frame: First visible movement of the left lower limb clearly caused by the Clinician through physical contact, including when the point of contact is out of view.
- Termination Frame: Last visible movement of the left lower limb clearly caused by the Clinician, or when the Clinician is no longer touching Subject's left lower limb, whichever comes first.
- MDS-UPDRS Instruction Criteria: Subject in relaxed position, Clinician slowly manipulates Left Hip and Knee joints, Clinician does not manipulate other limbs or neck, Subject allows passive movement of LLE, [Subject performs Activation Maneuver]
- MDS-UPDRS Rating Criteria: Rigidity (w/o Activation Maneuver), Rigidity (w/ Activation Maneuver), Range of Motion, Difficulty of Achieving Range of Motion

Finger Tapping, Right Hand – Subject taps tips of their right index finger and right thumb together in rapid succession.

- Initiation Frame: First visible movement of the right index finger or right thumb of the first tap of the series.
- Termination Frame: Last visible movement of the right index finger or right thumb of the last tap in the series.
- MDS-UPDRS Instruction Criteria: Subject taps right index finger against right thumb, Subject performs 10 taps, Subject taps as quickly as possible, Subject taps as big as possible, Subject does not tap fingers on left hand
- MDS-UPDRS Rating Criteria: Speed, Slowing, Amplitude, Decrementing Amplitude, Number/timing of Hesitations, Number/timing of Halts, Freezes

Finger Tapping, Left Hand – Subject taps tips of their left index finger and left thumb together in rapid succession.

- Initiation Frame: First visible movement of the left index finger or left thumb of the first tap of the series.

- Termination Frame: Last visible movement of the left index finger or left thumb of the last tap in the series.
- MDS-UPDRS Instruction Criteria: Subject taps left index finger against left thumb, Subject performs 10 taps, Subject taps as quickly as possible, Subject taps as big as possible, Subject does not tap fingers on right hand
- MDS-UPDRS Rating Criteria: Speed, Slowing, Amplitude, Decrementing Amplitude, Number/timing of Hesitations, Number/timing of Halts, Freezes

Fist Open and Close, Right Hand – Subject flexes their right fingers as fully as possible to form a fist, then extends ("fist-open") and flexes ("fist-close") their right fingers as fully as possible in rapid succession.

- Initiation Frame: First visible extension or flexion of any of the right fingers as part of the first fist-open or fist-close of the series.
- Termination Frame: Last visible extension or flexion of any of the right fingers as part of the last fist-open or fist-close of the series.
- MDS-UPDRS Instruction Criteria: Subject has right forearm flexed, Subject's right palm is facing the Clinician, Subject makes a fist with right hand, Subject opens and closes right hand, Subject opens right hand as quickly as possible, Subject opens right hand as fully as possible, Subject performs 10 open/closes, Subject does not open/close left hand [If Subject does not open fist quickly/fully, Clinician reminds Subject to do so]
- MDS-UPDRS Rating Criteria: Speed, Slowing, Amplitude, Decrementing Amplitude, Number/timing of Hesitations, Number/timing of Halts, Freezes

Fist Open and Close, Left Hand – Subject flexes their left fingers as fully as possible to form a fist, then extends ("fist-open") and flexes ("fist-close") their left fingers as fully as possible in rapid succession.

- Initiation Frame: First visible extension or flexion of any of the left fingers as part of the first fist-open or fist-close of the series.
- Termination Frame: Last visible extension or flexion of any of the left fingers as part of the last fist-open or fist-close of the series.
- MDS-UPDRS Instruction Criteria: Subject has left forearm flexed, Subject's left palm is facing the Clinician, Subject makes a fist with left hand, Subject opens and closes left hand, Subject opens left hand as quickly as possible, Subject opens left hand as fully as possible, Subject performs 10 open/closes, Subject does not open/close right hand [If Subject does not open fist quickly/fully, Clinician reminds Subject to do so]
- MDS-UPDRS Rating Criteria: Speed, Slowing, Amplitude, Decrementing Amplitude, Number/timing of Hesitations, Number/timing of Halts, Freezes

Pronation and Supination, Right Hand – Subject flexes their right arm with fingers extended and with forearm extended and pronated; Subject then alternates between laterally rotating their right forearm until the palm is facing up ("supination") and medially rotating their right forearm until the palm is facing down ("pronation") in rapid succession.

- Initiation Frame: First visible rotation of the right forearm as part of the first pronation or supination of the series.
- Termination Frame: Last visible rotation of the right forearm as part of the last pronation or supination of the series.
- MDS-UPDRS Instruction Criteria: Subject has right arm (and right forearm) extended in front of themselves, Subject begins with right palm facing downward, Subject turns their

right palm up, Subject turns right palm down, Subject turns right palm up/down as fast as possible, Subject turns right palm up/down as fully as possible, Subject performs 10 up/down palm turns, Subject does not turn left palm up/down
- MDS-UPDRS Rating Criteria: Speed, Slowing, Amplitude, Decrementing Amplitude, Number/timing of Hesitations, Number/timing of Halts, Freezes

Pronation and Supination, Left Hand – Subject flexes their left arm with fingers extended and with forearm extended and pronated; Subject then alternates between laterally rotating their left forearm until the palm is facing up ("supination") and medially rotating their left forearm until the palm is facing down ("pronation") in rapid succession.
- Initiation Frame: First visible rotation of the left forearm as part of the first pronation or supination of the series.
- Termination Frame: Last visible rotation of the left forearm as part of the last pronation or supination of the series.
- MDS-UPDRS Instruction Criteria: Subject has left arm (and left forearm) extended in front of themselves, Subject begins with left palm facing downward, Subject turns their left palm up, Subject turns left palm down, Subject turns left palm up/down as fast as possible, Subject turns left palm up/down as fully as possible, Subject performs 10 up/down palm turns, Subject does not turn right palm up/down
- MDS-UPDRS Rating Criteria: Speed, Slowing, Amplitude, Decrementing Amplitude, Number/timing of Hesitations, Number/timing of Halts, Freezes

Toe Tapping, Right Foot – Subject is Sitting with their right foot on the ground; Subject then lifts their right toes (dorsiflexion) and taps them back onto the ground (plantarflexion) in rapid succession.
- Initiation Frame: First visible dorsiflexion of the right foot as part of the first toe tap of the series.
- Termination Frame: Last visible plantar- or dorsiflexion of the right foot as part of the last toe tap of the series.
- MDS-UPDRS Instruction Criteria: Subject is sitting, Subject is in a straight-backed chair with arms, Subject has both feet on the floor, Subject places right heel on the ground in a comfortable position, (Subject raises right toes off the ground), Subject taps right toes on the ground, Subject taps right toes as fast as possible, Subject taps right toes as big as possible, Subject taps right toes 10 times, Subject does not tap left toes
- MDS-UPDRS Rating Criteria: Speed, Slowing, Amplitude, Decrementing Amplitude, Number/timing of Hesitations, Number/timing of Halts, Freezes

Toe Tapping, Left Foot – Subject is Sitting with their left foot on the ground; Subject then lifts their left toes (dorsiflexion) and taps them back onto the ground (plantarflexion) in rapid succession.
- Initiation Frame: First visible dorsiflexion of the left foot as part of the first toe tap of the series.
- Termination Frame: Last visible plantar- or dorsiflexion of the left foot as part of the last toe tap of the series.
- MDS-UPDRS Instruction Criteria: Subject is sitting, Subject is in a straight-backed chair with arms, Subject has both feet on the floor, Subject places left heel on the ground in a comfortable position, (Subject raises left toes off the ground), Subject taps left toes on the

ground, Subject taps left toes as fast as possible, Subject taps left toes as big as possible, Subject taps left toes 10 times, Subject does not tap right toes
- MDS-UPDRS Rating Criteria: Speed, Slowing, Amplitude, Decrementing Amplitude, Number/timing of Hesitations, Number/timing of Halts, Freezes

Stomping, Right Foot – Subject is Sitting with their right foot on the ground; Subject then lifts their right foot off the ground and stomps it back onto the ground in rapid succession.
- Initiation Frame: First visible movement directly related to lifting the right foot, including flexion of the right thigh, flexion of the right leg, movement of the right foot, or any other movement clearly connected to the preparation and/or execution of the first foot stomp of the series.
- Termination Frame: Last visible movement of the right lower limb as part of the last foot stomp of the series.
- MDS-UPDRS Instruction Criteria: Subject is sitting, Subject is in a straight-backed chair with arms, Subject has both feet comfortably on the floor, Subject places right foot on the ground in a comfortable position, Subject raises right foot off the ground, Subject stomps right foot on the ground, Subject stomps (raises) right foot as high as possible, Subject stomps right foot as fast as possible, Subject stomps right foot 10 times, Subject does not stomp left foot
- MDS-UPDRS Rating Criteria: Speed, Slowing, Amplitude, Decrementing Amplitude, Number/timing of Hesitations, Number/timing of Halts, Freezes

Stomping, Left Foot – Subject is Sitting with their left foot on the ground; Subject then lifts their left foot off the ground and stomps it back onto the ground in rapid succession.
- Initiation Frame: First visible movement directly related to lifting the left foot, including flexion of the left thigh, flexion of the left leg, movement of the left foot, or any other movement clearly connected to the preparation and/or execution of the first foot stomp of the series.
- Termination Frame: Last visible movement of the left lower limb as part of the last foot stomp of the series.
- MDS-UPDRS Instruction Criteria: Subject is sitting, Subject is in a straight-backed chair with arms, Subject has both feet comfortably on the floor, Subject places left foot on the ground in a comfortable position, Subject raises left foot off the ground, Subject stomps left foot on the ground, Subject stomps (raises) left foot as high as possible, Subject stomps left foot as fast as possible, Subject stomps left foot 10 times, Subject does not stomp right foot
- MDS-UPDRS Rating Criteria: Speed, Slowing, Amplitude, Decrementing Amplitude, Number/timing of Hesitations, Number/timing of Halts, Freezes

Postural Tremor, Right and Left Hands – Subject flexes their arm with fingers extended and abducted and with forearm extended and pronated, then maintains this position.
- Initiation Frame: First frame where Subject meets all criteria and is not intentionally moving their upper limb; this does not include unintentional motion (e.g. tremor, sway, shaking, etc.) or minor intentional movements performed to maintain this position (e.g. flexing the arm to compensate for drop, etc.).
- Termination Frame: Last frame Subject meets all criteria, or the last frame before Subject makes an intentional movement of the upper limb not related to maintaining its position.

- MDS-UPDRS Instruction Criteria: Subject has arm stretched in front of their body, Subject's arm is palm down, Subject's wrist is straight, Subject's fingers are comfortably separated without touching, Subject maintains behavior for 10 seconds
- MDS-UPDRS Rating Criteria: Presence of Tremor (including Re-Emergent Rest Tremor), Amplitude of Tremor

Kinetic Tremor, Right Hand – The Clinician stands in front of Subject with a single raised finger within Subject's reaching distance; Subject then alternates between touching the Clinician's finger and their own nose using a finger from their right hand. The Clinician may use an object instead of their finger.

- Initiation Frame: First frame with visible movement of Subject's right upper limb directly related to and continuous with the action of reaching to touch their nose or the Clinician's finger.
- Termination Frame: Last frame where Subject is touching their nose or the Clinician's finger during the last nose-touch or finger-touch of the series.
- MDS-UPDRS Instruction Criteria: Subject has right arm outstretched, Subject performs the finger-to-nose maneuver, [Subject touches Clinician's finger with their right finger], [Subject touches their nose with their right finger], Subject's right arm is as outstretched as possible when touching Clinician's finger, Subject performs finger-to-nose maneuver slowly enough to not hide tremor, Subject repeats finger-to-nose maneuver at least three times, Subject does not perform finger-to-nose maneuver with their left arm
- MDS-UPDRS Rating Criteria: Presence of Tremor, Amplitude of Tremor

Kinetic Tremor, Left Hand – The Clinician stands in front of Subject with a single raised finger within Subject's reaching distance; Subject then alternates between touching the Clinician's finger and their own nose using a finger from their left hand. The Clinician may use an object instead of their finger.

- Initiation Frame: First frame with visible movement of Subject's left upper limb directly related to and continuous with the action of reaching to touch their nose or the Clinician's finger.
- Termination Frame: Last frame where Subject is touching their nose or the Clinician's finger during the last nose-touch or finger-touch of the series.
- MDS-UPDRS Instruction Criteria: Subject has left arm outstretched, Subject performs the finger-to-nose maneuver, [Subject touches Clinician's finger with their left finger], [Subject touches their nose with their left finger], Subject's left arm is as outstretched as possible when touching Clinician's finger, Subject performs finger-to-nose maneuver slowly enough to not hide tremor, Subject repeats finger-to-nose maneuver at least three times, Subject does not perform finger-to-nose maneuver with their right arm
- MDS-UPDRS Rating Criteria: Presence of Tremor, Amplitude of Tremor

Postural Transitions

Sit-to-Stand – Subject starts Sitting and attempts to Stand in one continuous action.

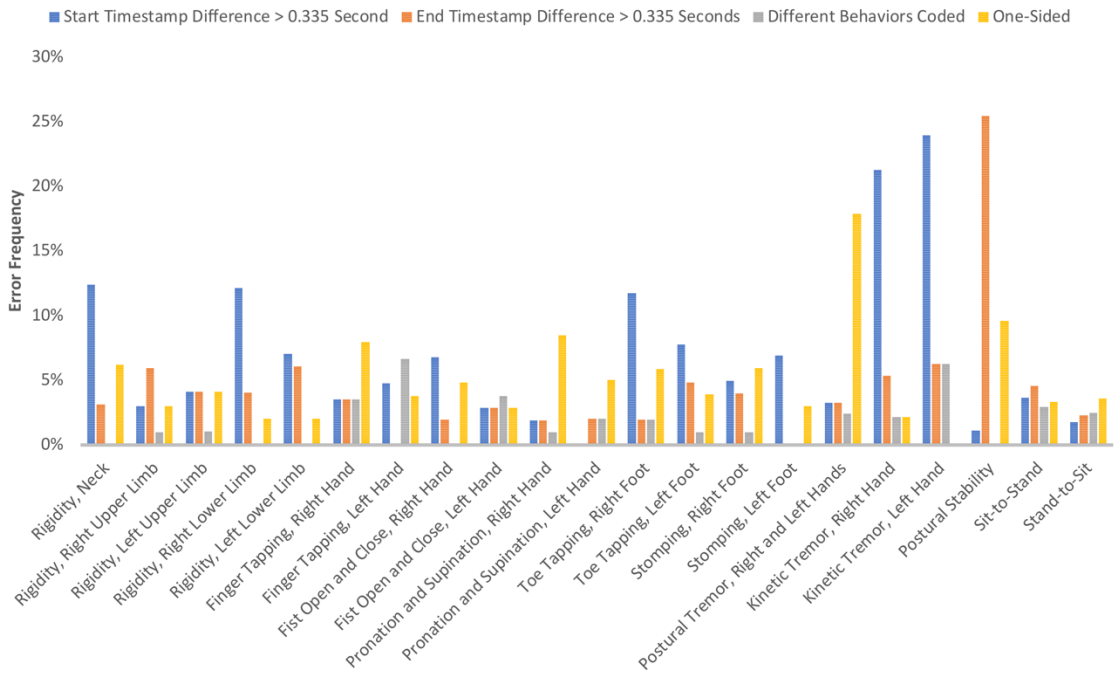
- Initiation Frame: Subject makes an intentional movement related to the Transition, including extension of the legs, repositioning of the hands and/or feet, flexion or extension of the torso, extension of the hip, or any other movement clearly connected to the preparation and/or execution of the Transition.

- Termination Frame: Last frame before Subject meets criteria for a PGT behavior, or last visible movement continuous with the Transition, whichever occurs first.

Stand-to-Sit – Subject starts Standing and attempts to Sit in one continuous action.

- Initiation Frame: Subject makes an intentional movement related to the Transition, including flexion of the legs, repositioning of the hands and/or feet, flexion of the torso, flexion of the hip, or any other movement clearly connected to the preparation and/or execution of the Transition.
- Termination Frame: Last frame before Subject meets criteria for a PGT behavior, or last visible movement continuous with the Transition, whichever occurs first.

Figure A.2: Frequency of errors of commission and errors of omission made by pairs of coders for each task across all videos.



Chapter 4 Supplementary Information

Table A.1: Number (%) of valid participant-days with less than 15% missing data* by H&Y Stage and by day of the week.**

	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	All
H&Y Stage 1/2	2 (100%)	0 (0%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	12 (85.71%)
H&Y Stage 2	6 (50%)	2 (16.67%)	10 (83.33%)	10 (83.33%)	11 (91.67%)	9 (75%)	7 (58.33%)	55 (65.48%)
H&Y Stage 2/3	5 (83.33%)	0 (0%)	6 (100%)	6 (100%)	6 (100%)	5 (83.33%)	4 (66.67%)	32 (76.19%)
H&Y Stage 3	4 (66.67%)	0 (0%)	4 (66.67%)	5 (83.33%)	5 (83.33%)	4 (66.67%)	3 (50%)	25 (59.52%)
All	17 (65.38%)	2 (7.69%)	22 (84.62%)	23 (88.46%)	24 (92.31%)	20 (76.92%)	16 (61.54%)	124 (68.13%)

*Participant-days with greater than 15% of the activity data missing were not modelled with cosinors.
**Note that the day of the week specifies the start day of the model (e.g. Sunday tabulates the cosinor models for Sunday 18:00:00 – Monday 17:59:45).

Table A.2: Cosinor parameters of the final analytical cohort and their associations*** with baseline characteristics.**

		Age †	BMI †	MMSE †	ESS †	Levodopa †	Sex ◊	Handedness ◊
MESOR	95% CI	[-2.43, -1.24]	[-2.71, -1.05]	[-5.52, -1.30]	[-1.70, 0.26]	[0.01, 0.03]	[0.93, 098]	[0.91, 0.97]
	Coefficient/Odds Ratio	-1.83	-1.88	-3.41	-0.72	0.02	0.95	0.94
	p-value	< 0.01*	< 0.01*	< 0.01*	0.15	< 0.01*	< 0.01*	< 0.01*
Amplitude	95% CI	[-2.28, -1.14]	[-2.48, -0.86]	[-6.08, -2.15]	[-1.89, -0.03]	[0.01, 0.03]	[0.92, 0.98]	[0.91, 0.97]
	Coefficient/Odds Ratio	-1.71	-1.67	-4.11	-0.96	0.02	0.95	0.94
	p-value	< 0.01*	< 0.01*	< 0.01*	0.04*	< 0.01*	< 0.01*	< 0.01*
Acrophase	95% CI	[-1:48, 6:22]	[-2:48, 8:03]	[-29:04, -3:09]	[-8:43, 2:59]	[0:02, 0:09]	--	--
	Coefficient/Odds Ratio	2:17	2:37	-16:07	2:52	00:05		
	p-value	0.27	0.34	0.02*	0.33	< 0.01*		

**Note that MESOR and Amplitude are reported in AC, and Acrophase in time (minute:second).

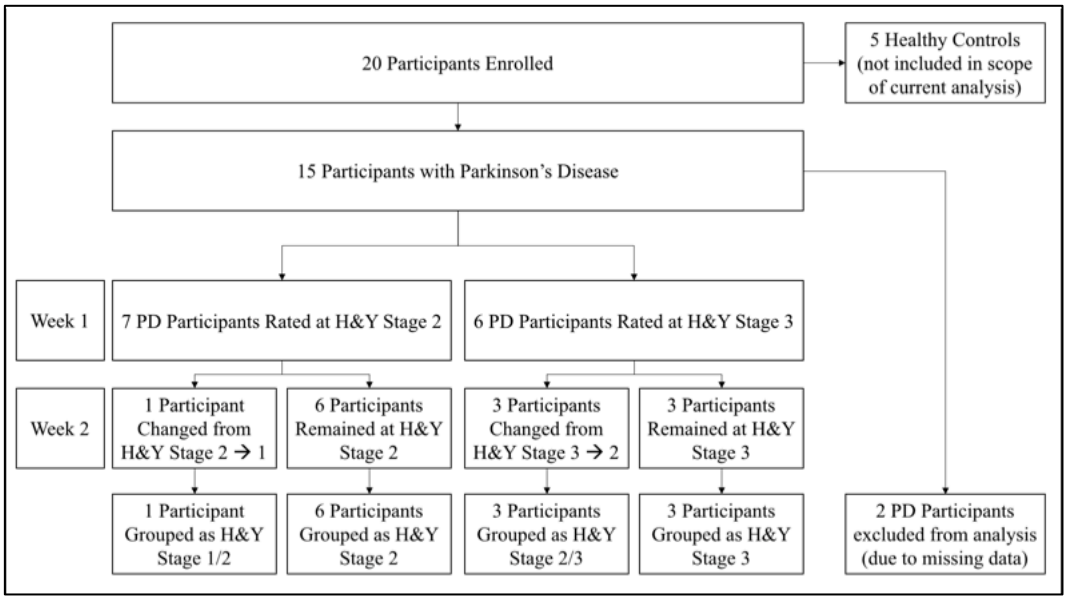
***For all regressions, the sample analyzed contained both weeks had a total n = 124, and degrees of freedom of F(1, 122). Coefficients are reported as change in Cosinor Parameter per 1 MDS-UPDRS score.

Abbreviations: AC (Activity Count), CI (Confidence Interval), MESOR (Midline Estimating Statistic Of Rhythm), MDS-UPDRS (Movement Disorder Society's Unified Parkinson's Disease Rating Scale). * = $p < 0.05$

† Simple Linear Regression, reporting coefficient

◊ Simple Logistic Regression, reporting odds ratio

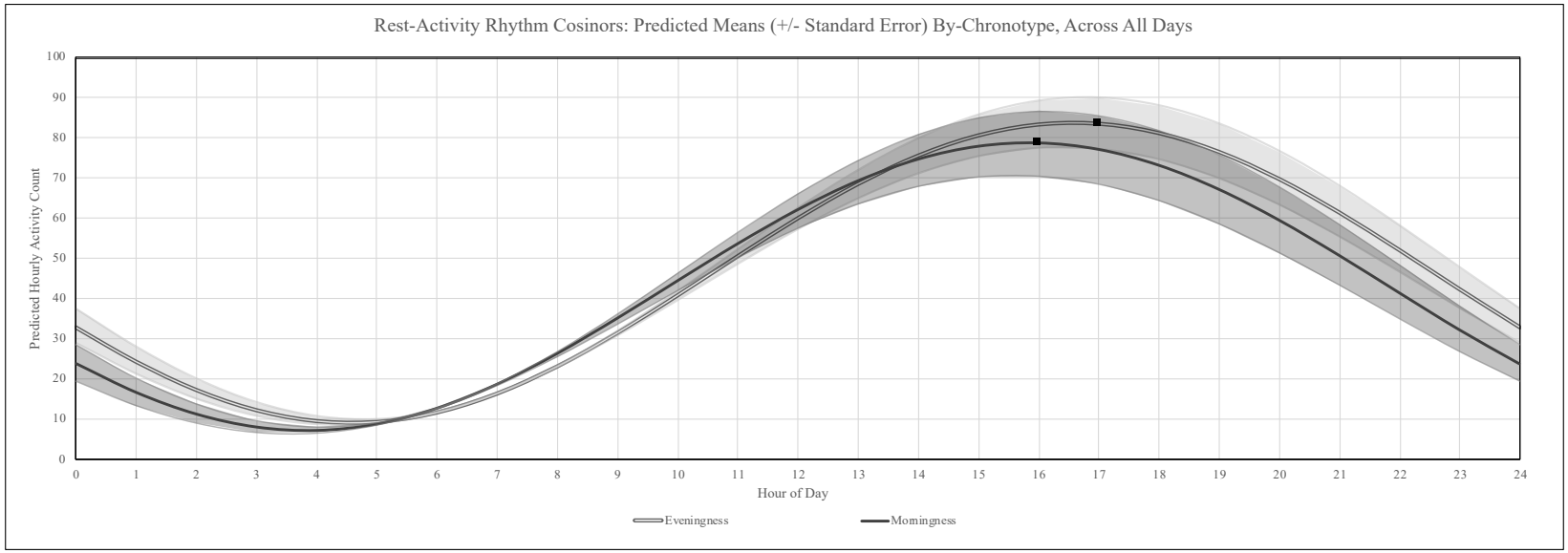
Figure A.3: Flow chart of participant inclusion and assignment to sub-groups based on Hoehn and Yahr (H&Y) Stage. Participants were rated by clinicians during an in-lab visit following each week of in-home recording. The two in-lab visits were an average of 36.31 (standard deviation: 4.80, range: [28 – 49]) days apart for the final analytical cohort (n = 13).

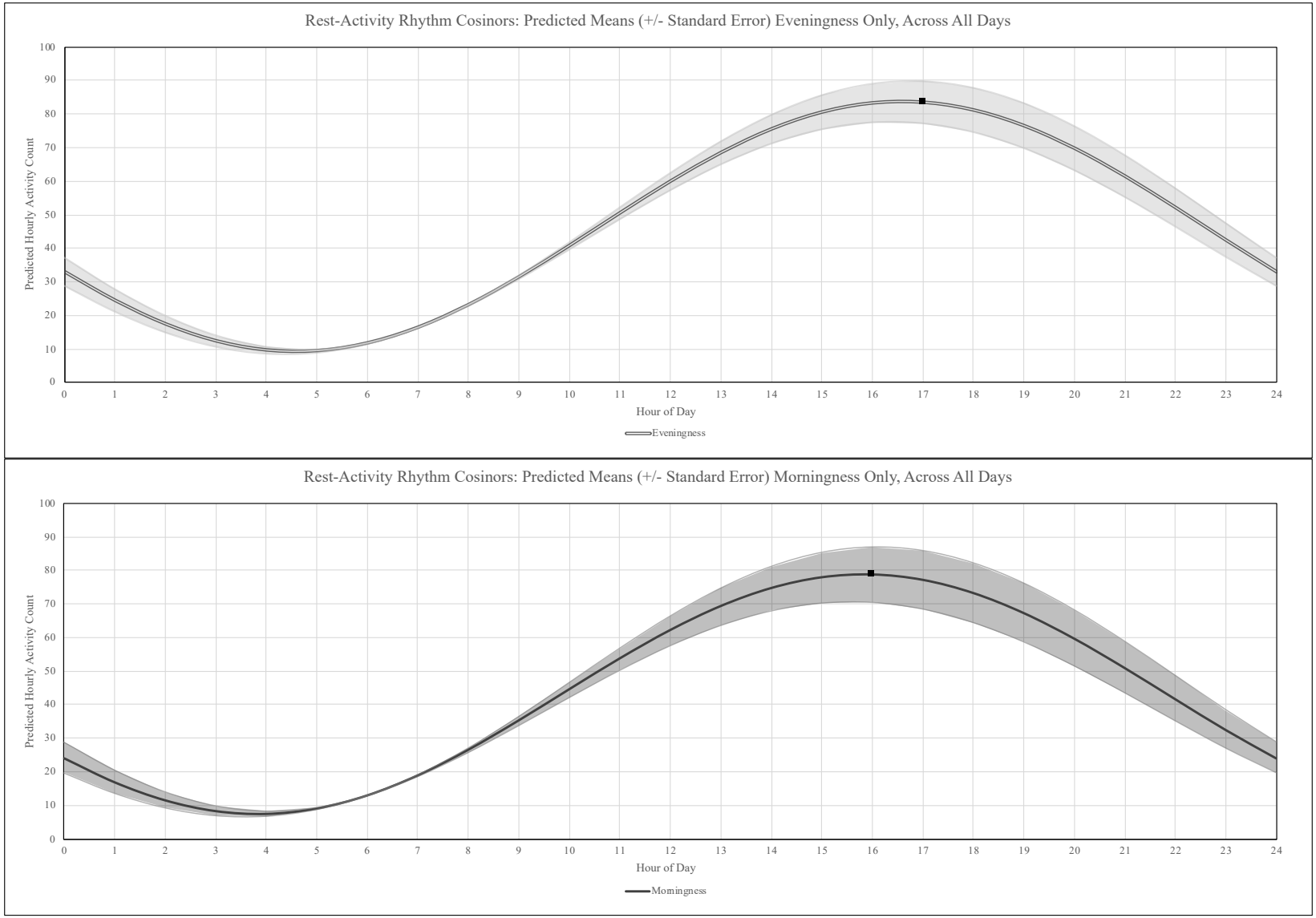


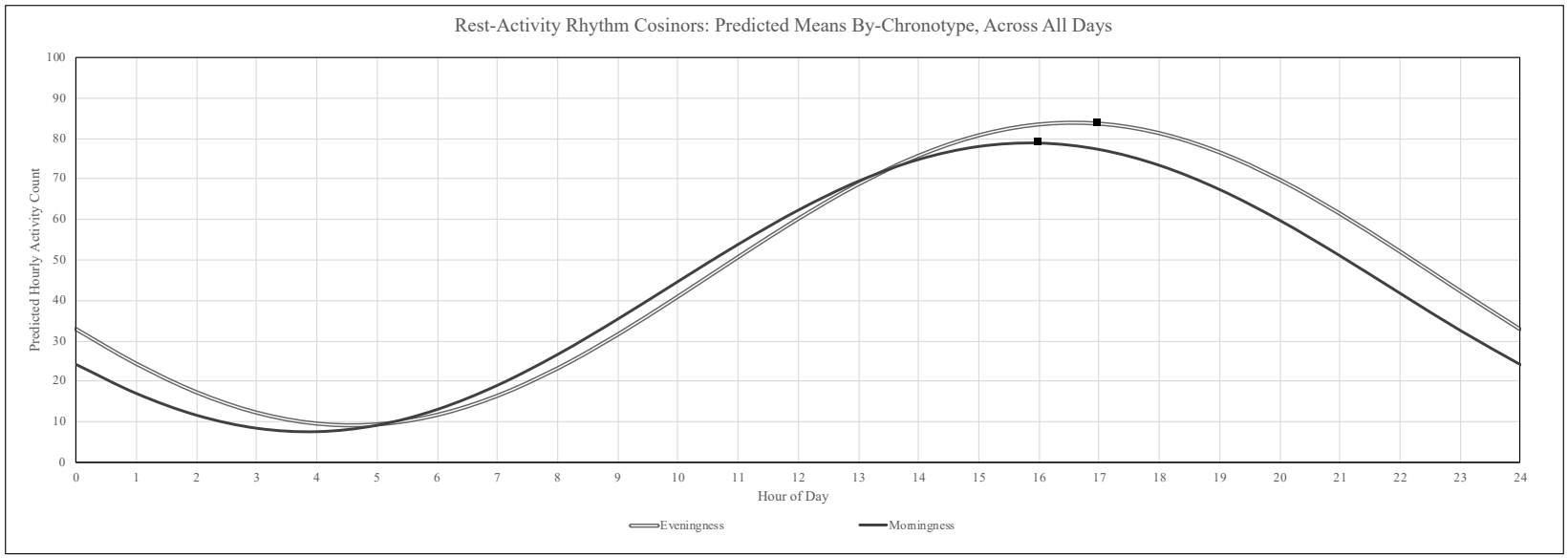
Chapter 5 Supplementary Information

Figure A.4: Predicted marginal means for rest-activity rhythm parameters (MESOR, Amplitude, and Acrophase) and sleep timings (Sleep Onset, Sleep Mid, and Sleep Offset) derived from the by-Chronotype across-Day one-way linear mixed model.

[A.4A] Rest-activity rhythms visualized by-Chronotype across-Days using cosinor models. Shaded areas represents the range of the standard error for that model's base parameters. Black squares denote the hour of peak activity (i.e. Acrophase).




Rest-Activity Rhythm Cosinors: Predicted Means (+/- Standard Error) Eveningness Only, Across All Days
Predicted Hourly Activity Count
Hour of Day
Eveningness
Rest-Activity Rhythm Cosinors: Predicted Means (+/- Standard Error) Morningness Only, Across All Days
Predicted Hourly Activity Count
Hour of Day
Morningness


Rest-Activity Rhythm Cosinors: Predicted Means By-Chronotype, Across All Days
Predicted Hourly Activity Count
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Hour of Day
Eveningness
Morningness

[A.4B] Sleep timings by-Chronotype, across-Days. Error bars represent +/- standard error. ** indicates between-Chronotype Wald tests with p-value < 0.05

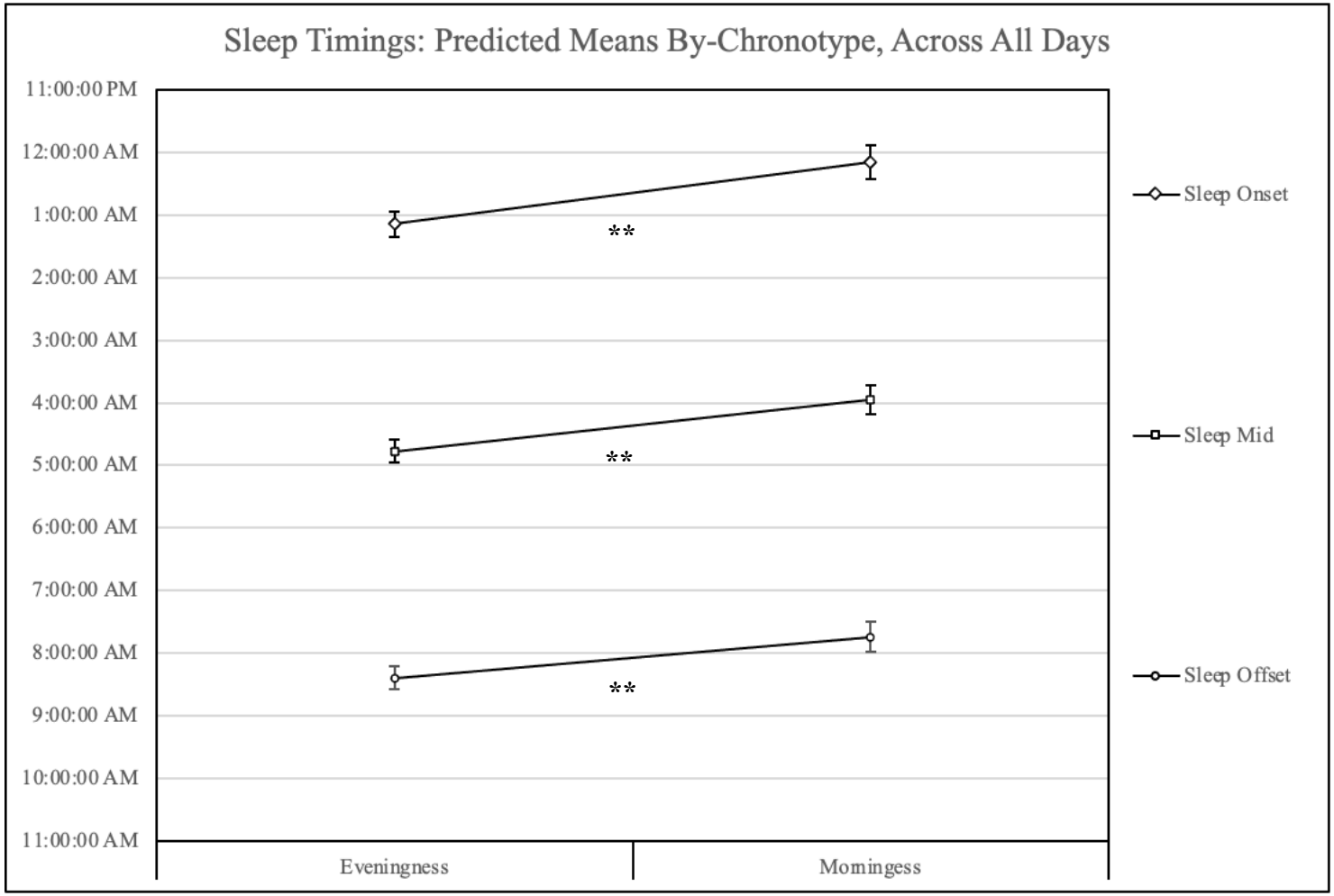
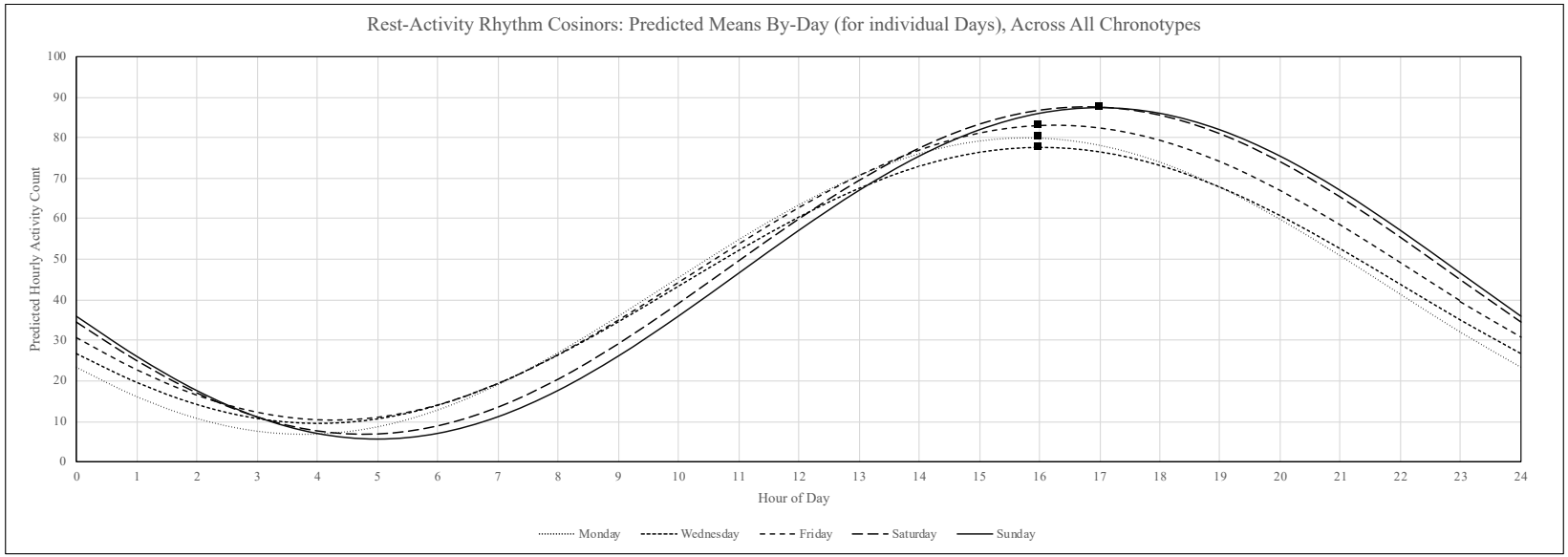
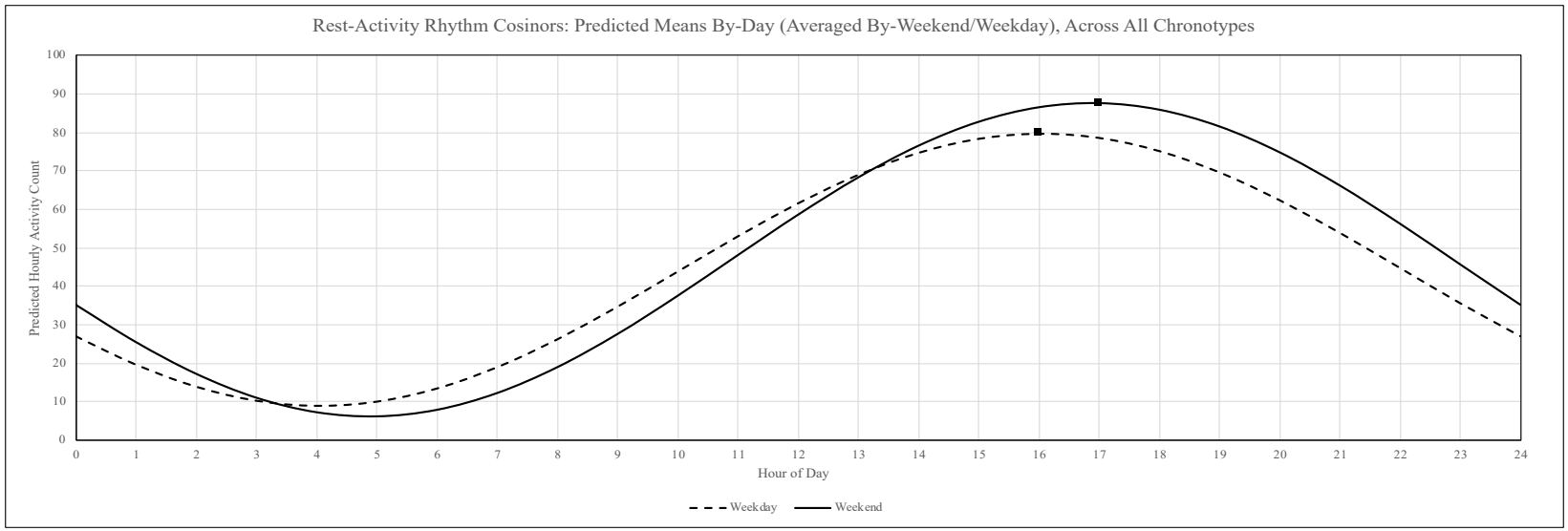


Figure A.5: Predicted marginal means for rest-activity rhythm parameters (MESOR, Amplitude, and Acrophase) and sleep timings (Sleep Onset, Sleep Mid, and Sleep Offset) derived from the by-Day across-Chronotype one-way linear mixed model.

[A.5A] Rest-activity rhythms visualized by-Day across-Chronotypes using cosinor models, both for individual days and for weekends/weekdays. Black squares denote the hour of peak activity (i.e. Acrophase). Monday, Tuesday, Wednesday, Thursday, and Friday were considered weekdays; Saturday and Sunday were considered weekends. Note that Tuesday/Thursday were included in weekday average, but were excluded from the individual days figure to aid interpretation.




Rest-Activity Rhythm Cosinors: Predicted Means By-Day (Averaged By-Weekend/Weekday), Across All Chronotypes
Predicted Hourly Activity Count
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Hour of Day
Weekday
Weekend

[A.5B] Sleep timings by-Day, across-Chronotype. Error bars represent +/- standard error. Wald tests were conducted between individual Days and Sunday (reference day) for all sleep timings; ** indicates p-value < 0.05, * indicates p-value ≥ 0.05 and < 0.10.

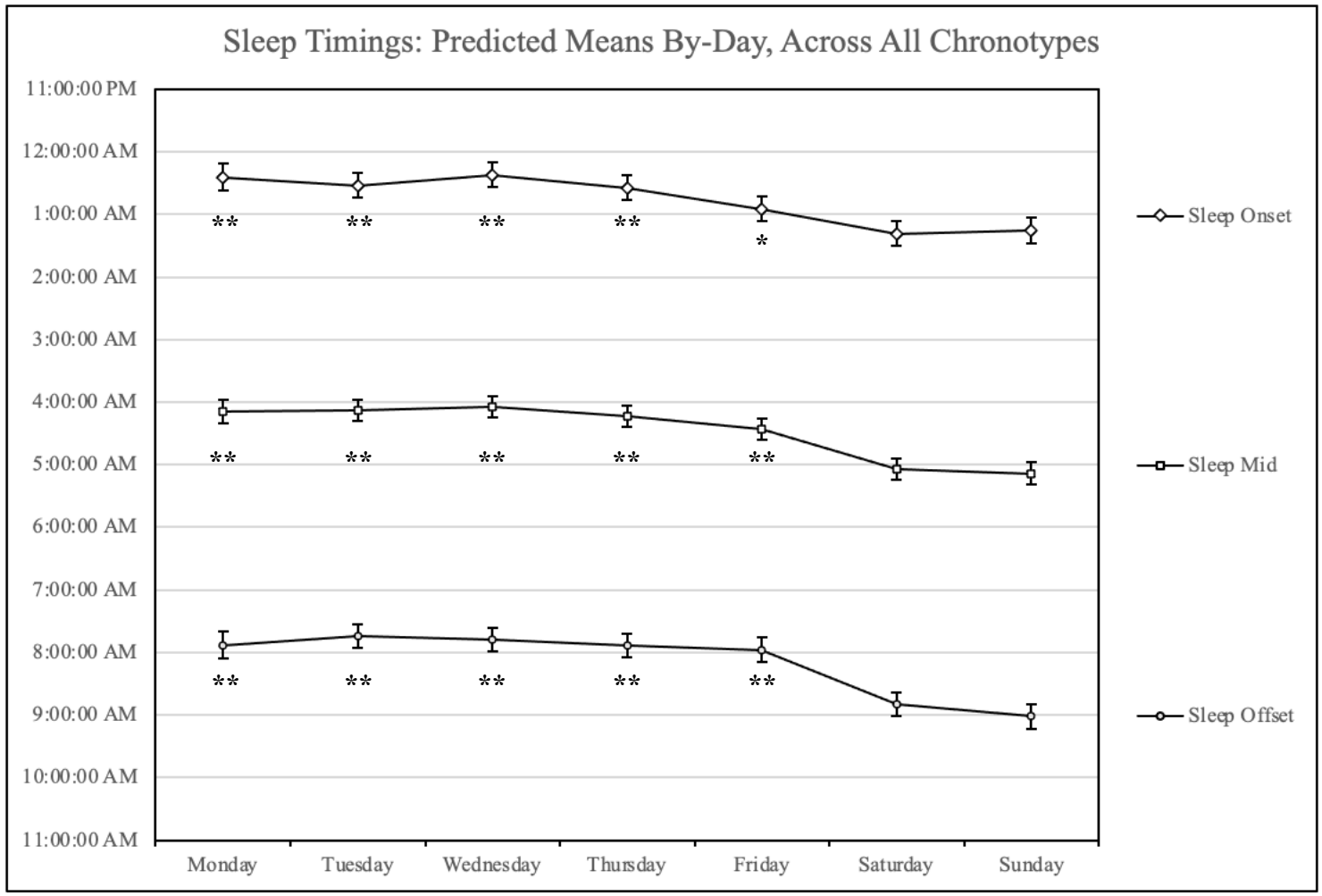


Table A.3: Number (%) of valid participant-days analyzed in this paper by day of the week, across weeks of the study, divided by Chronotype. Only participant-days with both a cosinor model and an overnight sleep period were considered valid.

Evening Chrono-type	Saturday	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	All Days
Week 1	8 (53.33%)	8 (53.33%)	8 (53.33%)	8 (53.33%)	8 (53.33%)	7 (46.67%)	9 (60.00%)	56 (53.33%)
Week 2	11 (73.33%)	8 (53.33%)	11 (73.33%)	10 (66.67%)	12 (80.00%)	13 (86.67%)	10 (66.67%)	75 (71.43%)
Week 3	*Sleep Clinic*	*Sleep Clinic*	*Sleep Clinic*	15 (100.00%)	15 (100.00%)	15 (100.00%)	13 (86.67%)	58 (96.67%)
Week 4	15 (100.00%)	15 (100.00%)	13 (86.67%)	14 (93.33%)	15 (100.00%)	13 (86.67%)	12 (80.00%)	97 (92.38%)
Week 5	12 (80.00%)	8 (53.33%)	2 (13.33%)	--	--	--	--	22 (48.89%)
All Weeks	46 (76.67%)	39 (65.00%)	34 (56.67%)	47 (78.33%)	50 (83.33%)	48 (80.00%)	44 (73.33%)	308 (73.33%)

Morning Chrono-type	Saturday	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	All Days
Week 1	6 (66.67%)	6 (66.67%)	6 (66.67%)	6 (66.67%)	6 (66.67%)	6 (66.67%)	6 (66.67%)	42 (66.67%)
Week 2	6 (66.67%)	6 (66.67%)	5 (55.56%)	6 (66.67%)	8 (88.89%)	8 (88.89%)	8 (88.89%)	47 (74.60%)
Week 3	*Sleep Clinic*	*Sleep Clinic*	*Sleep Clinic*	9 (100.00%)	9 (100.00%)	9 (100.00%)	9 (100.00%)	36 (100.00%)
Week 4	7 (77.78%)	7 (77.78%)	9 (100.00%)	8 (88.89%)	9 (100.00%)	8 (88.89%)	8 (88.89%)	56 (88.89%)
Week 5	8 (88.89%)	7 (77.78%)	1 (11.11%)	--	--	--	--	16 (59.26%)
All Weeks	27 (75.00%)	26 (72.22%)	21 (58.33%)	29 (80.56%)	32 (88.89%)	31 (86.11%)	31 (86.11%)	197 (78.17%)

Sleep Clinic: Participant-day includes time spent in the scheduled mid-study sleep clinic visit; these participant-days were excluded from all analyses due to the controlled nature of the sleep clinic's environment.
--: Day occurs after the scheduled last visit of the study; no data collected.

Table A.4: : Estimated variance components for each variable at each nested level in a two-way (Chronotype x Day of the Week) Linear Mixed Model (LMM); components are presented as *% of Total Variance* for their respective variables.

Variable	Participant	Study Week	Day of the Week	Residual	Total
MESOR	55%	4%	35%	6%	100%
Amplitude	32%	3%	58%	6%	100%
Acrophase	7%	0%	86%	7%	100%
Sleep Onset	44%	6%	41%	8%	100%
Sleep Mid	20%	15%	57%	8%	100%
Sleep Offset	18%	23%	51%	9%	100%
Time in Bed	26%	11%	54%	9%	100%
Average Activity during Sleep	10%	24%	58%	9%	100%
Peak Activity during Rest	36%	8%	47%	10%	100%
Sleep Onset Latency	16%	10%	64%	10%	100%
Sleep Offset Latency	8%	10%	70%	11%	100%
Sleep Efficiency	16%	3%	69%	13%	100%
Wake After Sleep Onset	29%	0%	54%	17%	100%
Total Sleep Time	7%	8%	62%	23%	100%
Percent Sleep Time	22%	5%	48%	24%	100%
Fragmentation Index	19%	5%	37%	39%	100%
Average Across all Variables	23%	8%	56%	13%	100%

Table A.5: Descriptive statistics of raw cosinor and sleep data for each Chronotype across Days of the Week, and the p-value of between-Chronotype t-tests.

Variable	Evening Chronotype		Morning Chronotype		All Participants		Between-Group Comparison	
	Average (Standard Deviation)	Skewness-Kurtosis Test p-value	Average (Standard Deviation)	Skewness-Kurtosis Test p-value	Average (Standard Deviation)	Skewness-Kurtosis Test p-value	Equal Variances Test p-value	Two-Sample Test p-value
MESOR (AC)	46.50 (17.22)	0.0001 **	41.90 (13.96)	< 0.0001 **	44.72 (16.18)	< 0.0001 **	0.0015 **	0.0090 **
Amplitude (AC)	38.51 (18.20)	< 0.0001 **	33.20 (14.47)	< 0.0001 **	36.46 (17.04)	< 0.0001 **	0.0005 **	0.0040 **
Acrophase (Time)	16:46 (2:03)	0.8230	15:41 (2:02)	0.0082 **	16:21 (2:06)	0.0915 *	0.8774	< 0.0001 **
Sleep Onset (Time)	01:22 (1:39)	0.0001 **	00:03 (1:31)	0.4431	00:48 (1:43)	0.1682	0.1821	< 0.0001 **
Sleep Mid (Time)	04:59 (1:38)	0.8102	03:46 (1:17)	0.1354	04:27 (1:36)	0.0150 **	0.0001 **	< 0.0001 **
Sleep Offset (Time)	08:37 (1:58)	0.1251	07:28 (1:26)	0.0306 **	08:07 (1:51)	0.0001 **	< 0.0001 **	< 0.0001 **
Time in Bed (Hours)	7.25 (1.61)	< 0.0001 **	7.42 (1.50)	0.0128 **	7.32 (1.56)	< 0.0001 **	0.2420	0.0867 *
Average Activity during Sleep (AC per Minute)	12.51 (11.05)	< 0.0001 **	12.07 (7.39)	< 0.0001 **	12.31 (9.62)	< 0.0001 **	< 0.0001 **	0.1230
Peak Activity during Rest (AC per 15 seconds)	277.31 (150.84)	< 0.0001 **	269.43 (116.33)	< 0.0001 **	273.87 (136.81)	< 0.0001 **	< 0.0001 **	0.9420
Sleep Onset Latency (Minutes)	41.83 (59.86)	< 0.0001 **	36.25 (57.25)	< 0.0001 **	39.40 (58.75)	< 0.0001 **	0.4710	0.2545
Sleep Offset Latency (Minutes)	30.59 (36.91)	< 0.0001 **	32.68 (44.41)	< 0.0001 **	31.50 (40.33)	< 0.0001 **	0.0023 **	0.7160
Sleep Efficiency (%)	76.77 (10.79)	0.0001 **	77.16 (10.80)	< 0.0001 **	76.94 (10.78)	< 0.0001 **	0.9802	0.3747
Wake After Sleep Onset (Hours)	0.84 (0.52)	< 0.0001 **	0.89 (0.48)	< 0.0001 **	0.86 (0.50)	< 0.0001 **	0.3024	0.1196
Total Sleep Time (Hours)	6.41 (1.45)	0.0024 **	6.53 (1.33)	0.7675	6.46 (1.40)	0.0165 **	0.1764	0.0878 *

Percent Sleep Time (%)	88.55 (6.15)	< 0.0001 **	88.13 (5.53)	< 0.0001 **	88.37 (5.89)	< 0.0001 **	0.0869 *	0.2440
Fragmentation Index (%)	10.35 (5.51)	0.0001 **	11.14 (4.62)	< 0.0001 **	10.70 (5.15)	< 0.0001 **	0.0044 **	0.0070 **

* p-value 0.05 < 0.10
** p-value < 0.05

Table A.6: Predicted marginal means and Wald test p-values derived from one-way LMMs.

[A.6A] Predicted marginal means (standard error) for each Chronotype across all Days of the Week derived from the by-Chronotype across-Day one-way linear mixed model, and the p-values of between-Chronotype Wald tests.

Variable	Eveningness	Morningness	p-value
	Marginal Mean (Standard Error)		
MESOR (AC)	46.47 (3.38)	43.05 (4.45)	0.5609
Amplitude (AC)	37.30 (2.76)	35.69 (3.63)	0.7368
Acrophase (Time)	16:35 (0:12)	15:50 (0:16)	0.0329 **
Sleep Onset (Time)	01:09 (0:12)	00:10 (0:16)	0.0062 **
Sleep Mid (Time)	04:46 (0:11)	03:57 (0:14)	0.0084 **
Sleep Offset (Time)	08:24 (0:11)	07:44 (0:14)	0.0370 **
Time in Bed (Hours)	7.26 (0.15)	7.57 (0.20)	0.2455
Average Activity during Sleep (AC per Minute)	13.59 (1.42)	11.16 (1.86)	0.3250
Peak Activity during Rest (AC per 15 seconds)	291.21 (25.07)	270.30 (33.00)	0.6323
Sleep Onset Latency (Minutes)	39.40 (7.26)	38.82 (9.53)	0.9635
Sleep Offset Latency (Minutes)	30.31 (3.67)	34.61 (4.79)	0.5032
Sleep Efficiency (%)	76.74 (1.32)	77.57 (1.74)	0.7186
Wake After Sleep Onset (Hours)	0.88 (0.07)	0.87 (0.09)	0.8916
Total Sleep Time (Hours)	6.38 (0.17)	6.71 (0.22)	0.2502
Percent Sleep Time (%)	88.01 (1.00)	88.51 (1.31)	0.7750
Fragmentation Index (%)	10.29 (0.76)	11.21 (0.99)	0.4843

[A.6B] Predicted marginal means (standard error) for each Day of the Week across all Chronotypes derived from the by-Day across-Chronotype one-way linear mixed model, the p-values of between-Day across-Chronotype Wald tests (each individual Day was compared to Sunday, the designated reference Day), and the p-values of the joint Wald tests.

Variable	Monday	Tuesday	Wednes-day	Thursday	Friday	Saturday	Sunday	Joint
MESOR (AC)	43.42 (2.88) 0.0917 *	45.58 (2.78) 0.5481	43.64 (2.76) 0.0913 *	42.70 (2.77) 0.0260 **	46.73 (2.79) 0.9727	47.28 (2.79) 0.7322	46.67 (2.83) Base	0.0356 **
Amplitude (AC)	36.53 (2.67) 0.0742 *	37.17 (2.50) 0.1039	34.04 (2.47) 0.0023 **	32.48 (2.48) 0.0002 **	36.30 (2.51) 0.0432 **	40.43 (2.51) 0.8534	40.85 (2.58) Base	0.0007 **
Acrophase (Time)	15:47 (0:16) 0.0001 **	16:03 (0:14) 0.0013 **	16:02 (0:14) 0.0008 **	16:08 (0:14) 0.0029 **	16:15 (0:14) 0.0110 **	16:47 (0:14) 0.4405	17:00 (0:15) Base	0.0003 **
Sleep Onset (Time)	00:25 (0:13) 0.0001 **	00:32 (0:12) 0.0003 **	00:22 (0:12) < 0.0001 **	00:34 (0:12) 0.0006 **	00:55 (0:12) 0.0848 *	01:19 (0:12) 0.8117	01:16 (0:12) Base	< 0.0001 **
Sleep Mid (Time)	04:09 (0:11) < 0.0001 **	04:08 (0:10) < 0.0001 **	04:05 (0:10) < 0.0001 **	04:14 (0:10) < 0.0001 **	04:26 (0:10) 0.0001 **	05:04 (0:10) 0.6775	05:08 (0:11) Base	< 0.0001 **
Sleep Offset (Time)	07:53 (0:13) < 0.0001 **	07:44 (0:11) < 0.0001 **	07:48 (0:11) < 0.0001 **	07:53 (0:11) < 0.0001 **	07:57 (0:11) < 0.0001 **	08:50 (0:11) 0.3655	09:01 (0:12) Base	< 0.0001 **
Time in Bed (Hours)	7.48 (0.21) 0.2860	7.21 (0.18) 0.0240 **	7.44 (0.18) 0.1899	7.33 (0.18) 0.0766 *	7.05 (0.18) 0.0033 **	7.50 (0.19) 0.2991	7.74 (0.20) Base	0.0979 *

Variable	Monday	Tuesday	Wednes-day	Thursday	Friday	Saturday	Sunday	Joint
Average Activity during Sleep (AC per Minute)	13.52 (1.42) 0.8151	12.31 (1.32) 0.4832	11.65 (1.30) 0.2163	13.81 (1.30) 0.6286	13.28 (1.32) 0.9518	11.06 (1.32) 0.0852 *	13.20 (1.37) Base	0.1869
Peak Activity during Rest (AC per 15 seconds)	294.65 (23.55) 0.7437	276.37 (22.15) 0.5365	284.92 (21.91) 0.8666	291.93 (21.97) 0.8363	282.83 (22.22) 0.7814	265.30 (22.23) 0.2214	288.08 (22.81) Base	0.7424
Sleep Onset Latency (Minutes)	40.89 (8.67) 0.4807	33.77 (7.81) 0.1232	48.32 (7.63) 0.9448	37.30 (7.67) 0.2419	39.47 (7.82) 0.3603	27.34 (7.87) 0.0234 **	47.70 (8.21) Base	0.1793
Sleep Offset Latency (Minutes)	23.18 (5.58) 0.0025 **	31.48 (4.89) 0.0486 **	25.98 (4.74) 0.0043 **	35.12 (4.77) 0.1508	31.88 (4.89) 0.0548 *	31.65 (4.93) 0.0514 *	44.32 (5.21) Base	0.0578 *
Sleep Efficiency (%)	77.17 (1.49) 0.2341	77.56 (1.35) 0.1251	76.90 (1.33) 0.2706	76.42 (1.33) 0.4351	76.31 (1.36) 0.4849	79.69 (1.36) 0.0028 **	75.27 (1.42) Base	0.0957 *
Wake After Sleep Onset (Hours)	0.95 (0.07) 0.5923	0.86 (0.07) 0.4315	0.87 (0.07) 0.5577	0.92 (0.07) 0.8876	0.86 (0.07) 0.4464	0.78 (0.07) 0.0553 *	0.91 (0.07) Base	0.2471
Total Sleep Time (Hours)	6.53 (0.19) 0.1247	6.35 (0.17) 0.0111 **	6.57 (0.17) 0.1459	6.41 (0.17) 0.0225 **	6.19 (0.17) 0.0007 **	6.72 (0.17) 0.5253	6.84 (0.18) Base	0.0140 **
Percent Sleep Time (%)	87.45 (0.89) 0.3981	88.33 (0.85) 0.6476	88.28 (0.84) 0.7011	87.62 (0.84) 0.5193	88.05 (0.85) 0.9721	89.52 (0.85) 0.0189 **	88.03 (0.87) Base	0.0348 **
Fragmentation Index (%)	10.95 (0.77) 0.9381	10.03 (0.71) 0.1611	10.53 (0.70) 0.4873	11.25 (0.71) 0.7184	10.54 (0.72) 0.5056	10.33 (0.72) 0.3337	11.01 (0.74) Base	0.5703

* p-value 0.05 < 0.10
** p-value < 0.05

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