Sleep and Circadian Phenotypes in Seasonal Depression

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Background: Sleep and circadian rhythm disruptions have long been considered important symptoms and theorized underlying mechanisms in seasonal depression. However, discrepant observational findings and mixed treatment responses suggest heterogenous sleep and circadian disruptions in this population. This study aimed to elucidate distinct sleep and circadian profiles in seasonal depression to 1) clarify mixed findings of prior work and 2) identify modifiable treatment targets for future interventions.

Methods: Biobehavioral, prospective self-report, and retrospective self-report measures of sleep and circadian rhythms were assessed during the winter in individuals meeting diagnostic criteria for Seasonal Affective Disorder (SAD), subsyndromal-SAD (S-SAD), or nonseasonal, never depressed controls (*N*=196). Sleep and circadian measures included: circadian phase/chronotype, sleep timing, total sleep time, sleep efficiency, regularity, and daytime sleepiness. Three *k*-means cluster analyses were conducted for each measurement modality. Resulting cluster solutions were compared on demographics, depression severity, and sleep and circadian dimensions.

Results: There were two consistent sleep and circadian profiles across all three cluster analyses, an 'Insomnia' cluster, characterized by short total sleep times (<6.5 hours), irregular and fragmented sleep and an 'Advanced' cluster, characterized by early sleep and circadian timing and longer total sleep times (> 7.5 hours). A smaller cluster, 'Nappers with long sleep' cluster, was also identified in the biobehavioral cluster. Clusters did not differ on depression severity or stratify by diagnostic group. Despite marked differences between clusters, there were few sleep and

circadian differences between diagnostic groups (controls, SAD, S-SAD). Retrospective clusters did not differ on chronotype or sleep timing.

Conclusion: The heterogeneity in seasonal depression is characterized by three sleep and circadian profiles with similar depression severity. Rather than assuming a homogenous sleep and circadian profile in seasonal depression, assessing sleep and circadian rhythms prior to treatment may reduce treatment failures. More broadly, this work highlights the utility of a precision medicine approach to treat sleep and circadian disruptions in individuals with dysregulated mood.

Table of Contents

List of Tables

List of Figures

Preface

Sleep is one of the most conserved features of evolution. We all sleep, some of us better than others. The nuances of how we sleep can be overlooked, and I hope this work contributes to the growing understanding how important sleep is for our well-being. I'd like to thank my family and fabulous cohort for their immense support during this process. Thank you to my parents for letting me practice my presentation many (many) times. Thank you to my amazing partner, Josh, for your patience and kindness during this process. A huge thank you to my mentor, Dr. Kathryn Roecklein, for encouraging me to ask hard questions and communicate my findings effectively – scientific writing is an art! Thank you to my committee members, Drs. Meredith Wallace and Martica Hall, for your support and perspective during the thesis process.

1.0 Specific Aims

Over 16 million Americans with Seasonal Affective Disorder (SAD) spend 40% of the year with clinically significant depressive symptoms (Modell et al., 2005). Empirically-supported treatments in SAD, in particular light therapy, cognitive-behavioral therapy for SAD (CBT-SAD), and antidepressant medications, are not effective for all patients (Roecklein, Wong, et al., 2013). In nonseasonal depression, treatments targeting sleep and circadian disruptions have been shown to alleviate depressive symptoms (Manber et al., 2008). Given the prevalence of sleep and circadian disturbances in SAD, sleep and circadian treatments could be effective. However, marked heterogeneity of sleep and circadian disturbances in SAD hinder implementation of effective treatments. Patients with SAD typically present with delayed sleep timing and hypersomnolence; however, one third of individuals with SAD are phase-advanced (Lewy et al., 2006), and a quarter to one half have circadian timing similar to controls (Burgess et al., 2004; Eastman et al., 1993). While self-reported hypersomnolence is a cardinal symptom of SAD (Kaplan & Harvey, 2009), actigraphic findings do not uniformly support hypersomnolence (Winkler et al., 2005; Wescott et al., in prep). Additionally, insomnia symptoms (Borisenkov et al., 2015) and combined insomnia and hypersomnolence (Roecklein, Carney et al., 2013) are prevalent, suggesting multiple sleep presentations in SAD, each with distinct treatment approaches. Past studies using a group means approach may have obscured these presentations.

This marked heterogeneity in symptom presentation obscures etiologically different sleep subgroups and hinders reliable assessment and effective sleep treatment of individuals with SAD. Cluster-analytic techniques have been implemented in other disorders to identify treatment targets by capturing homogenous subgroups. Although these analyses have been used in

insomnia (van de Laar et al., 2017), hypersomnolence (Cooke et al., 2019), and circadian rhythm abnormalities (Robillard et al., 2018) as related to nonseasonal depression, clustering techniques have yet to be employed in SAD. We aim to elucidate the heterogeneity of sleep and circadian disturbances within SAD by empirically determining sleep and circadian phenotypes.

Aim 1: Examine heterogeneity of biobehavioral sleep and circadian markers in SAD. We hypothesize distinct biobehavioral sleep and circadian phenotypes in SAD that differ by depressive severity in winter.

Aim 2: Examine self-reported sleep and circadian heterogeneity in SAD. We hypothesize distinct self-reported sleep and circadian phenotypes in SAD will emerge using both prospective and retrospective reports that differ by depressive severity in winter.

Aim 3. Examine whether individuals change clusters. We will compare the resulting clusters in Aims 1 & 2 above on biobehavioral and self-reported sleep & circadian variables.

Ancillary Aim 4. **Compare resulting clusters to controls.** We hypothesize that distinct biobehavioral and self-reported sleep and circadian clusters will differ from nonseasonal, never depressed controls. Using a cluster analytic technique to identify distinct sleep and circadian phenotypes will identify variables that associate together and predict depression symptomology in SAD. By implementing this novel statistical technique, we hope to better characterize sleep and circadian presentations in SAD and possibly identify modifiable treatment targets. In time, these findings could contribute to personalized treatment of SAD based on sleep and circadian phenotype.

2.0 Introduction

2.1 Brief Overview and Rationale

Seasonal Affective Disorder is characterized by seasonal variations in depressive and/or manic/hypomanic mood states where episodes recur and remit at specific times of the year (Rosenthal, 1984). This seasonal pattern of episodes can characterize major depressive disorder or bipolar I or II disorder depending on bipolar or unipolar pattern of episodes (APA, 2013). Major Depressive Disorder With a Seasonal Pattern (Seasonal Affective Disorder; SAD; APA, 2013) is a unipolar mood disorder characterized by recurrent seasonal depressive episodes. These depressive episodes typically occur during the fall/winter months with spontaneous summer remission during the spring/summer. Individuals with SAD experience on average over 14 depressive episodes which last for about 40% of the year (Modell et al., 2005). While empirically-supported treatments have been implemented in SAD, in particular light therapy, cognitive-behavioral therapy for SAD (CBT-SAD), and antidepressant medications, these treatments are not effective for all patients (Roecklein, Wong, et al., 2013). Treatments focusing primarily on sleep have not yet been empirically tested in SAD, but treatments targeting sleep and circadian disruptions in nonseasonal depression have been found to be effective in alleviating depressive symptoms (Manber et al., 2008). Sleep and circadian disruptions are modifiable acute and residual symptoms of seasonal and nonseasonal depression that confer risk for relapse of depressive episodes (Baglioni, Battagliese, et al., 2011). Given the highly recurrent nature of SAD and the prevalence of sleep and circadian disturbances in SAD, treating sleep and circadian disturbances in SAD could be effective. However, there is marked heterogeneity of sleep and circadian

disturbances in SAD, which hinder implementation of effective treatments. For instance, cognitive-behavioral therapy for insomnia (CBT-I) may be effective in SAD patients with insomnia or distorted cognitions about their sleep, but it might be relatively ineffective for those with hypersomnolence. Bright light therapy might be more beneficial for SAD patients with circadian misalignment. Characterizing distinct sleep and circadian phenotypes in SAD must precede sleep and circadian interventions (Wescott et al., 2020).

Cluster analyses are a key method for examining heterogeneous subpopulations in psychiatric disorders and have been at the forefront of the Research Domain Criteria (RDoC) framework implemented by the National Institutes of Mental Health (NIMH) in 2009. The current nosology of psychological diagnostic criteria has made heterogeneity the norm, not the exception, in psychiatric disorders. Symptom presentation, disease course, and biological underpinnings vary substantially within diagnoses, which hinder a mechanistic understanding of disease progression (Marquand et al., 2016). As transdiagnostic symptoms, pathophysiological mechanisms, and modifiable treatment targets in psychiatric disorders, sleep and circadian disturbances are candidate markers for stratifying heterogeneity by more than symptom severity. Sleep and circadian subgroups could elucidate shared depressive pathophysiology, as well as identify modifiable treatment targets in SAD. Currently, treatment for SAD does not typically involve assessment of sleep with actigraphy, nor does treatment for SAD typically include sleep-focused interventions. To identify clinically meaningful subgroups in SAD, we aim to empirically determine sleep and circadian phenotypes using a cluster-analytic approach and compare the resulting subgroups on depressive severity. The substantial heterogeneity of sleep and circadian disturbances of SAD is described below.

2.2 Circadian Rhythms in SAD

The seasonal pattern of depressive episodes in SAD parallels seasonal changes in environmental light levels (Cassidy & Carroll, 2002). Reduced winter light levels are thought to be an environmental trigger of depressive episodes (Rosenthal, 1984), and abnormal responses, perhaps in the retina itself, to low environmental light are hypothesized etiological theories of SAD (Wehr et al., 2001). Light entrains and synchronizes the internal circadian clock to the external environment through retinal projections to the body's central oscillator, the suprachiasmatic nucleus (SCN) via melanopsin containing intrinsically photosensitive retinal ganglion cells (ipRGCs; LeGates, Fernandez, & Hattar, 2014). Light has downstream effects on sleep regulation (Hattar et al., 2006), alertness (Schmidt et al., 2011), and mood (Fernandez et al., 2018) through SCN mediated pathways. Light's effect on mood also operates through a direct pathway independent of the circadian system (Fernandez et al., 2018; Knapen et al., 2016). The retinal subsensitivity hypothesis posits that seasonal changes in environmental light levels coupled with subthreshold retinal responses to light are implicated in circadian misalignment, disturbed sleep patterns, and mood changes in SAD (Hebert et al., 2002). Circadian misalignment is one way of phenotyping sleep in SAD, and occurs when there is a mismatch between the timing of circadian phase and either the external environment or an endogenous cycle, such as the sleep/wake cycle. Circadian misalignment can negatively impact sleep quality and daytime alertness. The prevailing circadian misalignment theory in SAD is the phase-shift hypothesis, which postulates that SAD occurs from a circadian delay relative to the sleep/wake cycle during the winter (Lewy et al., 2006). Circadian misalignment in SAD is often measured as the phase angle difference between internal circadian timing and the sleep/wake cycle, using a marker of circadian phase (i.e., melatonin secretion, core body temperature, etc.) and the

timing of mid-sleep respectively. The typical misalignment between delayed circadian timing and the sleep/wake cycle resembles early-onset insomnia and morning sleep inertia (i.e., difficulty falling asleep and difficulty waking up the following morning; Lewy et al., 2006; Roecklein, Wong, et al., 2013). However, advanced rather than delayed circadian misalignment has also been observed in 29% of individuals with SAD (N = 68; Lewy et al., 2006). The antidepressant effects of light treatment and melatonin administration in SAD (Terman, Terman, & Ross, 1998) could potentially be from advancing delayed circadian rhythms, providing evidence for circadian misalignment in SAD. In a constant routine protocol, bright light treatment advanced both melatonin release (as measured by dim-light melatonin onset; DLMO) and rectal temperature in SAD patients (n = 6) who were initially phase-delayed compared to controls (n = 6; Avery et al., 1997; Dahl et al., 1993). Using DLMO as a marker for circadian phase and self-reported sleep time, Lewy et al. (2006) found that 71% of SAD patients were phase-delayed and 29% were phase-advanced, as indicated by a phase angle difference greater or smaller than 6 hours. Treatments aimed at normalizing the phase angle difference towards the optimal 6-hour window was moderately correlated (r^2 = .35) with decreases in depressive symptoms. This finding indicates the role of circadian misalignment in depressive symptomology in SAD (Lewy et al., 2006). However, individuals were only classified as either delayed or advanced even if they deviated from the 6-hour PAD by a few minutes. Other studies have shown that circadian misalignment is not a ubiquitous etiological phenotype in SAD. In a 120-hr forced desynchrony protocol, Koorengevel et al. (2002) found no difference in the period or phase of the circadian pacemaker between SAD patients and controls (N = 14) when measuring core body temperature and melatonin secretion. Similarly, Checkley et al. (1993) found no differences in melatonin rhythms in SAD patients and controls (N = 40). Using core body temperature as a marker for circadian phase, Burgess et al.

(2004) and Eastman et al. (1993) found that 46% (N = 26) and 22% (n = 22) of SAD patients respectively had circadian timing indistinguishable from controls determined by baseline phase angles, indicating marked heterogeneity in circadian typology in SAD.

While light therapy is still considered the gold standard treatment in SAD (Golden et al., 2005; Menculini et al., 2018), and is effective in about ½ of individuals with SAD (Terman et al., 1998), the effects of light therapy on mood cannot be fully explained by circadian mechanisms (Dimitrova et al., 2017), challenging the etiological circadian misalignment dogma in SAD. If the antidepressant effects of light therapy were mediated by circadian changes, the degree of phase angle improvement following light therapy should align with symptom improvement (Lewy et al., 2006). However, phase advancing accounts for only some, but not all, of the antidepressant effects of light therapy (Burgess et al., 2004) and subsequent work has shown no relationship between light therapy and phase angle improvements (N = 61; Murray et al., 2005). Circadian misalignment may be an epiphenomenon of effective treatment and not actually mechanistic (Fernandez et al., 2018). These discrepant findings suggest multiple subgroups within SAD with different phase shifts, degrees of alignment (Roecklein, Wong, et al., 2013) or even lack of any circadian disruptions. Alternative theories invoking the direct (i.e., non-circadian) effects of light on mood could explain both the relatively high response rate to light therapy in SAD (50%), as well as the inconsistencies in studies testing circadian mediation of that light therapy response (Roecklein, Wong, et al., 2013). For our purposes of phenotyping sleep in SAD, circadian timing remains a critical metric, but measures of retinal sensitivity could be used in future studies to directly test questions related to the retinal subsensitivity hypothesis.

Sleep timing is another way to phenotype sleep in SAD. Seasonality of depressive symptoms has been associated with later self-reported sleep timing preference in large community

samples (Putilov, 2018; Sandman et al., 2016), and adults with delayed sleep phase syndrome (DSPS) are 3.3 times more likely to meet criteria for SAD than those without DSPS (Lee et al., 2011). Adolescents with SAD also self-report later sleep and wake times during the winter (Borisenkov et al., 2014). Behavioral measures of sleep estimation, such as actigraphy, infer sleep and circadian parameters using accelerometer-based devices (Sadeh, Hauri, Kripke, & Lavie, 1995). Using actigraphic rest activity rhythms (RARs), 24-hour periods of activity and rest, individuals with SAD showed delayed activity timing and reduced interdaily stability (Teicher, 1997), yet this study also found advanced timing in a significant minority of SAD patients (29%). That advanced minority group is consistent with the heterogeneity reported above for circadian timing in SAD. More recent work found an increase in early evening settling (down-mesor) during the winter months in SAD participants (Smagula et al., 2018), which could be related to feelings of fatigue, lethargy, and/or behavioral disengagement during the winter, but did not examine sleep onset times. In addition, work from our lab showed earlier sleep timing on average measured by actigrahic midpoint in SAD participants compared to controls during the winter months that was not present in summer (n = 66; Wescott et al., in preparation). This earlier sleep midpoint contradicts earlier findings of delayed sleep timing during the winter in SAD compared to controls (n = 17; Winkler et al., 2005). These discrepancies in sleep timing in SAD might be explained by methodological difference between existing work (e.g., small samples, self-report vs. behavioral assessments, lack of multi-season measurements), or it could be because not all individuals with SAD have delayed sleep timing. If present, delayed sleep timing could be indicative of either circadian or behavioral delays, which have significantly different treatment implications (Murray et al., 2017). Chronotherapies (e.g., light therapy, melatonin, blue light blockers) would likely be more effective for participants with delayed circadian timing whereas behavioral delays might

benefit from behavioral interventions. To accurately differentiate circadian treatment targets in SAD, physiological, behavioral measures, and self-report measures were required. We included measures of circadian timing (e.g., DLMO), sleep timing from actigraphy, prospective sleep diaries, and self-reported sleep timing from the Munich Chronotype Questionnaire (MCTQ; Roenneberg, Wirz-Justice, & Merrow, 2003) to capture circadian phenotypes in SAD participants. We compared the PAD between DLMO and actigraphic mid-sleep across clusters to determine if circadian misalignment differentiates clusters.

2.3 Sleep Disruptions in SAD

Insomnia, defined as difficulty initiating or maintaining sleep (American Psychology Association, 2013), has been associated with the onset and recurrence of depressive episodes (Baglioni, Spiegelhalder, et al., 2011). In comparison, hypersomnolence is defined as excessive quantity of nighttime sleep, daytime sleepiness, and/or sleep inertia (i.e., diminished sensory, motor, and cognitive function upon waking; APA, 2013). Relative to insomnia, the relationship between depression and hypersomnolence has been relatively unstudied, hindered by changes in the definition and measurement (Dauvilliers, Lopez, Ohayon, & Bayard, 2013; Plante, 2017). Despite this, hypersomnolence has been found to be a treatment-resistant symptom of depression (Zimmerman et al., 2005) and increases the likelihood of depressive relapse (Breslau, Roth, Rosenthal, & Andreski, 1996; Jaussent et al., 2011; Kaplan, Gruber, Eidelman, Talbot, & Harvey, 2011; Kaplan & Harvey, 2009).

Self-reported hypersomnolence is a distinguishing feature of SAD (Rosenthal, 1984). Hypersomnolence in SAD typically presents as a self-reported winter increase in sleep compared

to summer, which can vary from 30 minutes (Anderson et al., 1994) to over two hours (Hardin et al., 1991). Previous studies have found that 64-80% of SAD participants report hypersomnolence in winter (Kaplan & Harvey, 2009), but these reports have relied primarily on self-reported changes in sleep duration, typically assessed with retrospective questionnaires or semi-structured clinical interviews. Most frequently, hypersomnolence is assessed in SAD with the Seasonal Pattern Assessment Questionnaire (SPAQ; Magnusson, 1996), a retrospective questionnaire that asks participants to report the extent to which their sleep varies across the year, endorsing from "no change" to 'extremely marked change" across the seasons. Hardin et al. (1991) assessed retrospective self-reported seasonal variation in weight (in lbs.) and sleep duration (in hrs.) and found significantly lengthened sleep during the winter in SAD patients (N = 149), compared to controls. These SAD patients reported sleeping on average 2.5 hours longer in the winter compared to the summer. The validity of the SPAQ for diagnosing or categorizing SAD respondents has been called into question (Shapiro et al., 1994), and the self-reported sleep duration change across the seasons is limited by being a retrospectively assessed, self-report item. The SPAQ has low specificity for SAD diagnosis, which leads to an overestimation of the prevalence of SAD (Thompson, Thompson, & Smith, 2004). In one study, winter sleep diaries (N = 10) were consistent with seasonal sleep increases reported using the SPAQ (N = 1571; Anderson et al., 1994). However, in another study Shapiro et al. (1994) found that the 2.5-hour winter sleep increase in SAD patients from the SPAQ was not supported by daily diary findings in a much larger sample (N = 115).

Hypersomnolence has also been assessed using retrospective self-report with the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder Version (SIGH-SAD; Williams et al., 1992). The hypersomnolence question on the

SIGH-SAD assesses current excessive sleep duration (e.g., "Have you been sleeping more than usual this past month? How much more?" with responses selected from (0) no increase in sleep length, (1) at least one hour longer, (2) at least two hours longer, (3) at least three hours longer, or (4) four or more hours longer). Using the SIGH-SAD, between 64% (N = 51; Roecklein et al., 2013) and 73% (N = 86; Terman et al., 1996) of SAD participants have endorsed lengthened sleep time during the winter. Using diagnostic criteria for seasonal depression from the DSM-IV, Winkler et al. (2002) found 87% of patients with SAD (N = 610) endorsed lengthened sleep time during the winter; however, the criteria for lengthened sleep time was unspecified. Finally, when using the atypical depression diagnostic scale, individuals with SAD reported hypersomnolence, defined here as sleeping more than 10 hours a day for at least 3 days a week in SAD (36%, n =53) more than nonseasonal depression (24%, n = 54; Tam et al., 1997). Most of the self-report findings support hypersomnolence in some fraction of SAD participants, although daily diary findings are not consistent. These assessment methods are likely vulnerable to negative mood effects on symptom reporting and self-report bias, as well as retrospective recall bias, making prospective self-report measures (e.g., daily diaries) and behavioral measures of sleep duration an important element of the present study.

Actigraphy has been used to assess circadian timing as described above, but has also been used to measure sleep in SAD. Actigraphic measurements have not corroborated SAD patients' retrospective self-reports of substantially longer sleep duration in winter. Using actigraphy, Winkler et al. (2005) found that individuals with SAD (n = 17) slept 1.35 hours less than controls in winter and showed more fragmented sleep. In a larger sample of SAD participants (n = 66), we found that there was a group by season interaction of total sleep time, with SAD participants sleeping longer than controls during the winter (Wescott et al., in prep). However, the average

sleep duration (7.2 hours) was well below the clinical cut-off for hypersomnolence (9-10 hours; APA, 2013). The upper quartile in this study slept between 8.2 and 12.6 hours in winter, indicating substantial heterogeneity in behaviorally-assessed sleep duration within SAD participants.

These discrepancies between self-reported and actigraphic sleep duration in SAD could reflect the challenge of accurately measuring hypersomnolence in mood disorders (Plante, 2017). Self-reported hypersomnolence could reflect depressive symptoms including anhedonia and fatigue (Dauvilliers et al., 2013; Kaplan & Harvey, 2009), distorted cognitions about sleep (Harvey, 2011), or a perceived need for longer sleep duration in the presence of excessive daytime sleepiness (Kaplan & Harvey, 2009). Individuals reporting hypersomnolence could also be spending increased time in bed and/or experiencing fragmented sleep leading them to report sleeping for longer durations (Kaplan, Gruber, Eidelman, Talbot, & Harvey, 2011). Thus, it is pertinent to include both self-report and behavioral measures of hypersomnolence in our clustering analysis. Our recent attempt to measure self-reported hypersomnolence in SAD showed that actigraphic total sleep time, actigraphic time in bed, later sleep midpoint, naps, and fatigue were all statistically significant predictors of self-reported hypersomnolence (Wescott et al., in prep). Sleepiness (e.g., daytime naps) and lengthened sleep duration have been shown to be distinct components of hypersomnolence (Kaplan et al., 2015), thus there might be separate subgroups of hypersomnolent presentations represented in SAD. We aim to accurately distinguish between long sleep duration and excessive daytime sleepiness presentations of hypersomnolence in SAD and to capture potential clustering discrepancies between actigraphic and self-reported sleep. We included actigraphic and prospective and retrospective self-reported total sleep time, self-reported sleepiness, and actigraphic/self-reported naps as a behavioral proxy for sleepiness.

Findings of insomnia and co-occurring insomnia and hypersomnolence in SAD suggests additional heterogeneity in sleep presentations in SAD. Previous self-reports of combined insomnia and hypersomnolence (47%, n = 51) in a seasonal sample might reflect oscillating nights of insomnia and hypersomnolence (Roecklein, Carney, et al., 2013). After a night of difficulty initiating sleep (early-onset insomnia), individuals might compensate by sleeping in the next morning or taking daytime naps (Bond & Wooten, 1996). This sleep extension could lead to reports of morning hypersomnolence and may precipitate future nights of insomnia. Notably, this combined presentation of early-onset insomnia and morning hypersomnolence could be a behavioral reflection of delayed sleep phase. To capture this potential oscillation in sleep duration, we included the standard deviation of actigraphic midpoint and sleep diary midpoint measures of sleep regularity. Insomnia symptoms have also been reported in children and adolescents with SAD including shorter sleep durations, delayed sleep times, lower sleep efficiencies, and longer sleep latencies than controls (Borisenkov et al., 2015). In this study, Borisenkov and colleagues found prominent social jetlag (the difference in midsleep from school days and weekends) in female adolescents with SAD but not males. While future studies should replicate these findings, we did not incorporate measures of social jetlag in our cluster analyses based on only one study testing this variable. Sleep duration deficiency, a combination of higher sleep need and shorter sleep duration, was associated with increased seasonality in Norwegian adults along with complaints of insomnia and daytime sleepiness/fatigue (Øyane et al., 2008). However, this large epidemiological study (N = 8860) also found an association between high seasonality and long sleep durations in women, suggesting that the high seasonality group was actually comprised different clinical subgroups based on self-report sleep (e.g., hypersomnolence or insomnia; Øyane, Bjelland, Pallesen, Holsten, & Bjorvatn, 2008). To distinguish presentations of insomnia

symptoms in SAD (short sleep duration, difficulty initiating/maintaining sleep), we included self-report and actigraphic total sleep time and sleep maintenance efficiency.

To investigate the anticipated heterogeneity of sleep presentations in SAD, it is pertinent to incorporate multiple levels of sleep measurement to accurately identify modifiable treatment targets. Self-report measures show poor agreement with actigraphy (Berg et al., 2008; Girschik et al., 2012), and it has been suggested that self-reported and behaviorally-assessed measures capture different aspects of sleep (Aili, Åström-Paulsson, Stoetzer, Svartengren, & Hillert, 2017; Tryon et al., 2007). For example, psychosocial factors such as low social support and depressed mood explain under-reporting of sleep efficiency compared to actigraphically-measured efficiency (Jackowska et al., 2016). Additionally, two commonly used self-reported sleep metrics, the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) and the Epworth Sleepiness Scale (ESS; Johns, 1991), are not related to and do not differentiate actigraphic or polysomnographic sleep (Buysse & Reis, 2008), indicating that these self-reported sleep metrics capture a different dimension of sleep. In fact, the PSQI was found to correlate with self-reported psychological factors, sleep disturbances, and stress. Therefore, it is advised to include actigraphy and both prospective and retrospective self-reported measures of sleep to capture distinct sleep perceptions and dimensions, including individual's perception of their sleep (Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006). Discrepancies between different sleep measurements (behavioral vs. self-report) are prevalent in SAD and can hinder accurate assessment and treatment. Therefore, understanding how sleep variables group together at different levels of measurement in SAD can inform treatment selection. Due to large discrepancies across sleep modalities, it is clinically meaningful to understand the nature of clusters when assessing sleep from a subjective or behavioral perspective. However, it can be difficult to account for

various sleep variables (e.g., sleep duration, efficiency, timing, variability, etc.) across physiological, behavioral, and subjective metrics. Cluster analyses can capture homogenous subgroups across multiple levels of sleep measurement and aid in the variable selection process (Wallace et al., 2018), allowing identification of sleep and circadian phenotypes.

2.4 Cluster Analyses Describing Heterogeneity in Patient Populations

Data-driven cluster analytic approaches have been implemented across a range of psychiatric disorders to parse heterogeneous presentations into homogenous clinical subgroups with the hope of developing more effective, targeted treatments. While clustering approaches are often used within diagnoses to partition distinct clinical phenotypes, previous work has yielded inconsistent findings. These inconsistencies are largely due to variations in the input information used to stratify resulting phenotypes, ranging from neuropsychological scores and neuroimaging methods to symptom measures. An overwhelming majority of previous work has used symptom profiles to classify subgroups. Interestingly, nonseasonal depression shows the most consistent symptom clustering, with many studies finding "typical" and "atypical" subgroups (Lamers et al., 2010; Milaneschi et al., 2016); however, this is not an unequivocal finding across studies (Hybels et al., 2009; Loo et al., 2014). In many cases, using self-report symptom presentation yields clusters based on severity and not etiologically distinct subgroups. In fact, a systematic review on subtypes in nonseasonal depression concluded that the majority of clustering studies reflect subgroups differing by depressive severity and not symptomatic subtypes (van Loo et al., 2012). To overcome this issue, Marquand and colleagues (2016) recommend including multiple measurement

modalities to stratify psychiatric disorders and to ensure external validation of the clusters to clinically meaningful variables.

Sleep and circadian disturbances can be measured using self-report, behavioral, and physiological methods allowing for identification of clinically meaningful clusters (Wallace et al., 2018). Due to this variety of sleep and circadian variables to choose from, variables are selected based on the population of interest. Many sleep and circadian cluster analyses have been conducted within specific sleep and circadian disorders based on diagnostic criteria with resulting clusters reflecting symptom profiles. Often, the resulting clusters differ by depression severity. Using self-reported diagnostic symptoms of hypersomnolence disorder, Cook et al. (2019) found two distinct clusters using a hierarchical approach (N = 62). When comparing these clusters across other hypersomnolence metrics, the more severe hypersomnolence phenotype also had elevated depressive symptoms compared to the less severe phenotype. Šonka, Šusta, and Billiard, (2015) used a hierarchical clustering approach to test to diagnostic divisions of hypersomnias (N = 96) and confirmed independent divisions of narcolepsy type 1 and hypersomnia and showed evidence for the overlap between monosymptomatic hypersomnia and narcolepsy type 2. A hierarchical cluster analysis in obstructive sleep apnea (N = 18,263) found that the most severe apneic phenotype also had comorbid diagnosis of depression (Bailly et al., 2016). Nguyen and colleagues (2019) identified four circadian clusters in a college population (N = 303; intermediate phase, advanced phase, delayed phase, and misaligned). The delayed and misalignment cluster showed greater depressive severity than the advanced or the intermediate. While understanding homogenous sleep clusters within sleep disorders is informative, work has also been done identifying sleep and circadian subgroups outside of sleep disorders.

The multifaceted nature of sleep and circadian rhythm disturbances in psychiatric disorders presents an opportunity to stratify homogenous subgroups in a clinically meaningful and intervenable way without partitioning participants by their psychiatric symptoms. In individuals with low-functioning Autism, sleep phenotypes have been shown to differentiate on symptom severity and adaptive functioning (Cohen et al., 2017). Two distinct sleep clusters, 'stable' sleepers and 'unstable' sleepers were found using a hierarchical cluster analysis (N = 106), the later characterized by shorter sleep duration, earlier sleep offset, and variability in sleep timing. The 'unstable' sleep phenotype showed greater functioning impairments. These findings suggest that profiling and targeting sleep in Autism could be a potential avenue for interventions. Sleep specific phenotypes have been identified in chronic fatigue syndrome (CFS; Gotts et al., 2013), highlighting the need to screen for sleep disturbances in CFS and tailor sleep-specific interventions based on patient's phenotype. Sleep and circadian markers have also been used to cluster patients with mood disorders. Using latent profile analysis, Kaplan et et al. (2015) found four distinct sleep phenotypes of individuals with bipolar disorder during the euthymic period: long sleep, excessive sleepiness, short sleep, and normal sleep, each with distinct proposed etiologies. Of note, the 'long sleep' cluster was best described by longer time in bed by actigraphy, again demonstrating the need for multiple sleep measurements when conducting cluster analyses. Additionally, these authors showed that belonging in the 'excessive sleepiness' cluster predicted relapse into hypomania/mania, underscoring the utility of distinct sleep phenotypes for treatment prevention. In a sample of young adults (N = 50) with either unipolar depression (n = 35) or controls (n = 15), Robillard et al. (2018) identified pathophysiological subgroups using circadian markers of DLMO and core body temperature and compared resulting subgroups to psychopathological symptomatology. The inclusion of nondepressed controls in this cluster analysis differs from the

studies described above. Despite including controls, the resulting clusters did not cluster by diagnostic group. Using a *k*-means approach, described in detail below, Robillard et al. (2018) found a two-cluster solution characterized by delayed circadian markers and conventional circadian markers. The delayed cluster, which included participants from both the depression and control group, showed higher depressive symptom severity. Identifying this clinically relevant subgroup of delayed individuals could inform effective treatment interventions. While the authors did not provide potential reasons for control participants being included, it is possible that the controls clustering in the delayed cluster characterized by greater depression might have been at high risk for a subsequent first onset depressive episode. In contrast to the work above, Carpenter et al. (2017) found three distinct sleep phenotypes (delayed sleep, disrupted sleep, and long sleep) using a *k*-means approach in young adults with affective disorders ($N = 50$) that did not differ on depressive symptoms or overall functioning. However, the authors concluded that the presence of distinct sleep phenotypes could affect treatment response, and properly treating sleep and circadian disturbances based on phenotype could potentially improve mood symptoms. To accurately describe the resulting subgroups in our cluster analysis and to avoid potential stratification based on diagnosis, we identified sleep and circadian clusters within the SAD continuum including SAD and subsyndromal SAD (S-SAD) and compare the resulting clusters on demographics, depression severity, diagnostic group, and sleep and circadian characteristics. A brief overview of cluster analytic techniques is described below.

2.5 Overview of Cluster Analyses

Clustering techniques divide a sample into homogenous subgroups using selected variables of interest. Individuals in a given subgroup are more similar to one another than they are to individuals in other subgroups. Common methodological approaches to elucidate subgroups include model-based finite-mixture models (Fraley & Raftrey, 1998) and data-driven heuristic clustering analyses (Han, Kamber, & Pei, 2011). Both analytic techniques are considered unsupervised in the sense that they use the structure of the data to identify homogenous subgroups (i.e., the algorithms are not provided information about the group each observation belongs to). Choosing the appropriate cluster analytic method ultimately depends on the research question of interest, the number of variables used to stratify subgroups, the hypothesized distribution of clusters, and the sample size. The current study utilized a data-driven heuristic clustering analysis, but we will briefly discuss model-based finite-mixture models for completeness. Finite-mixture models assume that a mixture of probability distributions underlie the data. Each subgroup is presumed to have a unique distribution that forms the overall mixture distribution. This probabilistic approach allows for a softer clustering segmentation where each observation is given a probability of belonging to a given subgroup. By fitting a model to the data, statistical inferences can be made for each cluster (Titterington, Smith, & Makov, 1985), and these model-based approaches can accommodate different underlying cluster distributions. Standard fit indices such as the Bayesian information criterion (BIC; Kass & Raftery, 1995) and bootstrap likelihood ratio test (BLR; McLachlan, 1987) can be used to determine the optimal cluster distribution in finite-mixture models and allow a more straightforward assessment of the number of clusters than data-driven approaches. While finite-mixture models offer immense flexibility, they require moderate to large samples sizes: $N \geq 500$ for skewed (Wallace et al., 2018) or normal distributions (Tein et

al., 2013) or $N \geq 1000$ when there is not a clear separation of clusters (Jaki et al., 2018). In contrast, data-driven clustering analyses can accommodate smaller sample sizes but with less flexibility in the resulting clustering solution (e.g., observations assigned to only one cluster). One commonly followed sample size estimate for data-driven heuristic approaches is a minimum sample size of 2^m where m is the number of variables to cluster on (Formann, 1984).

Due to the sample size constraints and number of variables to cluster on, this study used a data-driven heuristic clustering analysis. Data-driven approaches include both hierarchical and partitional methods (e.g., *k*-means) to divide the data into 'hard' clusters such that each observation is placed into one cluster or another (Hastie, Tibshirani, & Friedman, 2009), which differs from the probabilistic model-based approach of finite-mixture models. If there is a presumed nested structure of the data, hierarchical cluster analyses are used. Hierarchical methods form a hierarchy of clusters using either top-down ("divisive clustering") or bottom-up ("agglomerative clustering") approaches. Divisive clustering recursively splits the initial cluster (i.e., entire data set) into smaller groups whereas agglomerative clustering considers each observation to be its own cluster and combines clusters using the proximity of observations. Hierarchical methods require pre-selecting both a distance metric, the distance between two datapoints and a linkage method, a measure of dissimilarity between clusters. For example, a commonly used agglomerative hierarchical method uses the squared Euclidean distance metric and Ward's linkage method (Ward, 1963). Hierarchical clusters are visualized using a dendrogram, a tree-like diagram that shows each merge or split. In contrast to hierarchical clusters, partitional clustering techniques divide the sample into a pre-specified number (k) of non-overlapping clusters by the similarity of observations. This similarity metric is quantified using various distance functions (i.e., how close observations are to one another). The overarching goal of partitioning clustering methods is to define clusters by

minimizing the within-cluster sum of squares (WCSS), a measure of the compactness of a cluster. One of the most widely used clustering approaches is *k*-means clustering, which uses an iterative approach to assign observations to clusters (MacQueen, 1967). *k*-means clustering minimizes WCSS by using a distance metric (i.e., the squared Euclidean distance) to segregate clusters.

Determining the optimal number of clusters *k* in *k*-means is somewhat subjective and depends on the method used. Common methods include but not limited to: the elbow method, silhouette method, gap statistic, the information theoretic approach (the "jump method"), and/or a general rule of thumb (k = square root(n) / 2). The elbow method chooses *k* number of clusters with the smallest WCSS (Ng, 2012). To determine the optimal *k,* the elbow method compares WCSS at different values of *k*. This involves visual inspection of WCSS plotted at different values of *k*. True to its name, the bend in the plot (the elbow) is considered the optimal number of clusters with each additional cluster adding little value in minimizing WCSS. The silhouette method measures the quality of a cluster, or how well each observation fits within each cluster (Kaufman & Rousseeuw, 1990). Similar to the elbow method, the silhouette method determines the degree of separation between clusters using a graphical representation of how well each observation is classified into a given cluster. The corresponding silhouette index reflects the within-cluster compactness and between-cluster separation of each cluster, with a higher index indicating a better clustering. The gap statistic (Tibshirani, Walther & Hastie, 2001) compares the WCSS for different values of *k* to their expected values using the null distribution. The number of optimal clusters will have the largest gap statistic. The jump method (Sugar & James, 2003) uses measures of distortion (measure of within-cluster dispersion, defined as the squared Mahalanobis distance between an observation and its cluster center) at different values of *k*. These measures of distortion are then transformed into a "jump" value and plotted against *k*. The value of *k* where the line "jumps" is

considered the optimal value of *k.* Due to the subjective nature of choosing the optimal *k,* comparing across different methods and reporting any discrepancies between methods is advised. One preferred method is the Nbclust package in R, which simultaneously uses information from 30 different indices to determine the optimal number of clusters (Charrad et al., 2014).

While *k*-means clustering is a useful analytic technique, it has its limitations. Considering that *k*-means evaluates the contribution of each variable equally, careful variable selection is important. This can be problematic when there are many clinically meaningful variables to cluster on and no *a priori* hypotheses of each variable's utility for clustering (Witten & Tibshirani, 2010). If using a *k*-means approach, the clusters will be determined using every variable entered even if only a small fraction of the variables are meaningful for identifying the true underlying clusters, which can lead to a misidentification of clusters. This methodological challenge is amplified when homologous variables measured at different levels are used (e.g., self-report vs. behavioral metrics), which increases the total number of variables to be entered (Wallace et al., 2018). Further, variables at various levels of measurement often have different ranges. For example, sleep duration from actigraphy is calculated to the fraction of a minute (e.g., 433.78 min) whereas self-reported sleep duration is reported to fraction of an hour (e.g., 7.5 hr). While scaling self-reported sleep duration to minutes would be more comparable (e.g., 450 min), it would not include the full range of sleep durations that would have been measured by actigraphy (i.e., it would not be as specific). Variables with larger ranges and greater variances may have a greater impact on the clustering results (i.e., actigraphic sleep duration; Henry et al., 2005; Mohamad & Usman, 2013). However, standardizing variables to have equal variances can also eliminate any of the variance to cluster the data on (Milligan, 1996). As a compromise, dividing variables by their ranges has been proposed as a way to ensure each variable is on the same scale while maintaining the intrinsic

difference between the variances (Milligan & Cooper, 1988). To avoid potential pitfalls in our clustering technique we: 1) chose our variables *a priori* based on the sleep in SAD literature reviewed above, 2) separated homologous behavioral and prospective and retrospective self-report variables into three separate cluster analyses to avoid variables with large variances driving the clustering, and 3) scaled our variables by dividing by their ranges. Separating our clustering analyses by measurement type also allowed for a unique comparison of behavioral, prospective self-report, and retrospective self-report clusters.

Implementing a *k*-means cluster analysis will always identify clusters, even in homogenous data. Therefore, the stability (internal validation) and validity (external validation) of the clustering solution needs to be evaluated. Cluster validation includes internal measures of goodness-of-fit and external criteria based on classification information. Internal measures of cluster analyses focus on cohesion within clusters and separation between clusters using WCSS and between-cluster sum of squares (BCSS) respectively. Common internal metrics include the Jaccard index (Milligan, 1996), which assesses the stability of the clustering solution, the Separation index (Qiu & Joe, 2006), which measures the degree of separation between the clusters, and the Dunn index, which evaluates the proportion of separation between clusters to compactness within clusters. These internal validation metrics assess how well the clustering solution minimizes WCSS. External measures evaluate the clusters with external classification indices. Common external measures include the Rand index (Rand, 1972), and the Fowlkes and Mallows index (Fowlkes & Mallows, 1983) but require an additional sample or the true clustering solution to compare. Clusters can be compared and/or characterized by variables used in the clustering analysis or an additional set of clinically meaningful variables (Marquand et al., 2016). In the current study, we did not use a separate sample to compare our clustering solution to; however, we did compare

resulting clusters by depression severity, diagnostic group, demographic information, and sleep and circadian variables as a means of external validation.

2.6 Current Study

Previous work has demonstrated the utility of using sleep and circadian disturbances to uncover clinically meaningful subgroups. A sleep and circadian focused cluster analysis has not yet been conducted in SAD despite heterogeneity of sleep and circadian disturbances in SAD. Previous sleep and circadian cluster analyses in depression have stratified clusters by diagnostic symptoms (Bailly et al., 2016; Cook et al., 2019) or by using variables of interest for the diagnostic population (Kaplan et al., 2015; Robillard et al., 2018). We used three *k*-means cluster analyses to capture sleep and circadian phenotypes by either behavioral, prospective self-report, or retrospective self-report variables. We aimed to identify sleep and circadian phenotypes during the winter in individuals with SAD and subsyndromal-SAD and compare the resulting subgroups on measures of depression severity and diagnostic assignment. We also aimed to examine the nature of clusters across different levels of measurement. Using a cluster analytic technique should identify sleep disturbances that associate together and predict depression symptomology in SAD. By implementing this novel statistical technique, we hoped to better characterize sleep and circadian presentations in SAD, and possibly identify modifiable treatment targets.

Hypothesis 1*:* We predicted that subgroups of individuals would be characterized by biobehavioral sleep and circadian variables and differ by depression severity.

Hypothesis 2: We predicted that subgroups would also be characterized by prospective and retrospective self-reported sleep and circadian variables and differ by depression severity.

Hypothesis 3: We predicted that participants might change clusters depending on measurement modality.

Ancillary Hypothesis 4: We predicted that the subgroups would be significantly different from control participants on biobehavioral and retrospective self-report sleep and circadian variables.

3.0 Methods

3.1 Participants

We recruited participants aged 18-65 through the Pitt+Me® Research Participant Registry, an institutional research participant registry in Pittsburgh, Pennsylvania (latitude 40°26′N). This registry identifies and recruits hospital patients, volunteers, and community residents who may be eligible to participate in ongoing University of Pittsburgh clinical research studies. All study procedures are explained to participants prior to obtaining and documenting informed consent. The University of Pittsburgh Institutional Review Board approved all study procedures prior to participant recruitment, and the research was conducted in accordance with the Helsinki Declaration as revised in 1989. We excluded individuals with psychotic disorders, bipolar disorder, sleep disordered breathing, narcolepsy, substance induced mood disorder, or shift-workers. Participants completed assessments during the winter months (December 21st – March 21st). The following assessments were used to assess inclusion and exclusion criteria for SAD and S-SAD group participants.

3.2 Clinical Assessments

3.2.1 SCID

The Structured Clinical Interview for DSM-V, Research Version, Patient Edition With Psychotic Screen was used to assess for a lifetime mood disorder diagnoses and to screen for select comorbid Axis I disorders (SCID-I/P; First, 2015). The SCID includes a seasonal pattern specifier to apply to recurrent depression and bipolar presentations. Only unipolar presentations on SAD were included in this study.

3.2.2 SIGH-SAD

The Structured Interview Guide for the Hamilton Rating Scale for Depression—Seasonal Affective Disorder Version (SIGH-SAD) is the most commonly used clinical assessment for measuring changes in SAD symptoms in SAD research (Williams, Link, Rosenthal, Amira, & Terman, 1992) and has been shown to have high inter-rater reliability (.923-.967; Rohan et al., 2016). The SIGH-SAD is a 29-item semi-structured interview that includes the 21-item Hamilton Rating Scale for Depression (HAM-D) and an additional eight items to assess atypical symptoms of depression. The SIGH-SAD was used to determine whether or not individuals met criteria for a SAD episode during winter. For inclusion in the SAD group, individuals were required to meet previously established SIGH-SAD-based SAD episode criteria (Michael Terman et al., 1990). The total score on the SIGH-SAD was used as a measure of depression severity.

3.2.3 M-SPAQ

The Modified Seasonal Pattern Assessment Questionnaire was used to measure the degree of individual variation in mood and behavior across the seasons. Previously established criteria were used as inclusion criteria (Kasper et al., 1989). The global seasonality scale (GSS), an M-SPAQ subscale, is calculated by summing 6 self-reported items (i.e., sleep, appetite, mood, energy level, weight and social behavior), rated on a 5-point Likert scale ranging from 0- "no change", to 4-"extremely marked change."

3.3 Diagnostic Criteria

3.3.1 Seasonal Affective Disorder (SAD)

Individuals diagnosed with SAD had a GSS > 11 and endorsed at least a moderate problem in their seasonal changes. In addition, the participant must endorse "feeling worst" during January and/or February, with or without other affected months, excluding July and/or August. Individuals with SAD had a history of SAD on the SCID, and a current Major Depressive Episode (MDE). SAD participants met the Structured Interview Guide for the Hamilton Rating Scale for Depression—Seasonal Affective Disorder Version (SIGH-SAD) criteria for a current SAD episode, which is a score of ≥ 20 with ≥ 5 on the atypical depressive symptom subscale.

3.3.2 Subsyndromal Seasonal Affective Disorder (S-SAD)

Individuals diagnosed with S-SAD had have a GSS of 8 or 9 and endorse at least mild problems with the seasons or a GSS > 10 with no or only mild problem severity endorsed. In addition, these participants must have a winter pattern of feeling worst as described above. Finally, they did not meet criteria for SAD or MDD on the SCID, nor meet the Structured Interview Guide for the Hamilton Rating Scale for Depression—Seasonal Affective Disorder Version (SIGH-SAD) criteria for a current SAD episode.

3.3.3 Nonseasonal, Never Depressed Controls

Controls did not have a current or past major depressive episode and did not met the SIGH-SAD criteria for a current SAD episode.

3.4 Self-report Questionnaires

3.4.1 Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a self-report measure of sleep characteristics and quality (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). It distinguishes "good sleepers" from "poor sleepers" with high specificity and has a high internal consistency (Cronbach α=0.85; Buysse et al., 1989). To capture a more granular depiction of self-reported sleep in our sample, we extracted self-reported measures of total sleep time, sleep onset, and sleep efficiency from the PSQI instead of using the global

score. Since we are interested in the quantification of insomnia symptoms, we chose not to use other self-report metrics of insomnia that focus on the diagnostic criteria of Insomnia Disorder, namely the frequency and severity of insomnia symptoms (e.g., Insomnia Severity Index (ISI; Bastien, Vallières, & Morin, 2001) or the Insomnia Symptom Questionnaire (ISQ; Okun et al., 2009)).

3.4.2 Epworth Sleepiness Scale (ESS)

The ESS is a self-report scale in which participants rate their likelihood of dozing off under various circumstances from 0 (no chance) to 3 (high chance; Johns, 1991). Scores range from 0 to 24, with higher scores indicating greater daytime sleepiness. A score of 10 or higher is used as the clinical cut-off for excessive daytime sleepiness (Johns, 1991). The ESS has a high test-retest reliability in healthy individuals over a 5-month period (r = .82) as well as a high internal consistency (Cronbach's α = .88; Johns, 1991). The total ESS score was used for the analysis.

3.4.3 Munich Chronotype Questionnaire (MCTQ)

The MCTQ is a self-report measure of habitual sleep timing on work and free days (Roenneberg et al., 2003). The MCTQ comprises 14 questions and assesses the regularity of one's work schedule, the number of workdays per week, sleep timing on workdays and work-free days, and alarm clock use on workdays and work-free days. The MCTQ estimates circadian timing as the midpoint of sleep on free days and controls for sleep debt by subtracting sleep midpoint minus half of the difference between sleep duration on work-free days and average sleep duration of the week (MSFsc). We included the MSFsc in our analysis as a self-reported measure of circadian

timing. In contrast to other self-reported measures of chronotype (e.g., Morningness-Eveningness Questionnaire (MEQ); Horne & Ostberg, 1976), the MSFsc provides a quantification of sleep timing (Roenneberg, 2015). Further, the MSFsc has been shown to be a stronger predictor of DLMO timing than the MEQ (Kantermann et al., 2015).

3.5 Sleep Diaries

Participants completed daily Pittsburgh sleep diaries (Monk et al., 1994) for 5-14 days. As a prospective self-report measure, including sleep diaries allowed us to distinguish between retrospectively assessed sleep and circadian variables. The sleep variables includes: *1) Total Sleep Time* (TST) the amount of time between sleep start and end time minus any nighttime awakenings, *2) Sleep efficiency* the proportion of sleep time relative to time in bed, *3) Variability* the standard deviation of sleep midpoint, *4) Timing* sleep onset and, *5) Naps* the duration of naps as a proxy for daytime sleepiness.

3.6 Actigraphy

Participants wore an Actiwatch spectrum (Philips Respironics, Bend, OR, USA) on their non-dominant wrist for 5-14 days. Actigraphy data was sampled in 30 second epochs. The actigraphy-based sleep-wake variables were determined using the Actiware software program (Philips Respironics) using a threshold sensitivity value of 40 counts/per epoch. Rest intervals are

manually set using sleep diary information, event markers, and/or a cutoff of activity below 40 counts. The Actiware algorithm distinguishes sleep from wake within the defined rest interval.

The actigraphy variables include: *1) Total Sleep Time* (TST) the number of minutes scored as sleep during the primary sleep period, *2) Sleep efficiency* the proportion of minutes scored as sleep to wake during the primary sleep period, *3) Variability* the standard deviation of sleep midpoint, *4) Timing* the sleep onset for the primary sleep period and, *5) Naps* the duration of daytime sleep (naps or minor rest intervals) as a proxy for daytime sleepiness. While sleep midpoint is the most parsimonious measure of sleep timing that is the least confounded by sleep duration (Hasler et al., 2012), it is strongly correlated with the timing of DLMO (Burgess et al., 2003). In contrast, sleep onset does not correlate with DLMO (Burgess et al., 2003) and is a modifiable behavioral factor of sleep (Huang & Redline, 2019). Since we are interested in segregating circadian timing from behavioral timing and included DLMO as a measure of circadian timing, we included sleep onset to capture the behavioral aspect of sleep timing. We did not include sleep offset due to the societal influences on waketimes (e.g., work or school start times; Roenneberg et al., 2019).

3.7 Dim Light Melatonin Onset (DLMO)

DLMO is the most widely used measure of circadian phase and was collected here via saliva. Participants stayed in a dimly lit conference room for a 6-hour period during the evening. Saliva samples were collected from participants every 30 minutes starting 5 hours before and ending 1 hour after their habitual bedtime utilizing salivettes.

Saliva samples were assayed for melatonin by SolidPhase, Inc. (Portland, ME) using an analytical sensitivity of 0.2 pg/mL. DLMO was determined by linear interpolation between saliva samples using both a fixed and a relative threshold. The fixed threshold was 3 pg/mL, and the relative threshold was the value at which the level exceeded 2 standard deviations of the average of 3 baseline values (Benloucif et al., 2008). Comparisons between the fixed and relative thresholds have yielded mixed findings; the fixed threshold was shown to be more consistent but less precise than the relative threshold (Burgess et al., 2010), however the relative threshold has produced spurious results in other work (Crowley et al., 2015). There was no difference in sample size between both measures. Therefore, to improve the precision of our estimate, we included the relative threshold as our primary analysis and ran a post-hoc cluster analysis using the fixed threshold for comparison.

3.8 Analytic Plan

All statistical procedures were conducted using R Studio 1.1.463 (R Core Team, 2017). We separated our homologous biobehavioral, retrospective, and prospective self-report variables into three separate cluster analyses to compare clustering results across different measurement modalities. The biobehavioral cluster included DLMO and actigraphic total sleep time, sleep efficiency, standard deviation of sleep midpoint (variability), duration of naps, and timing of sleep onset (m=6). The prospective self-report cluster included the following variables from sleep diaries: sleep duration, sleep efficiency, standard deviation of sleep midpoint (variability), duration of naps, and timing of sleep onset (m=5). The retrospective self-report cluster included the MSFsc value from the MCTQ as a measure of circadian timing, average sleep duration, sleep efficiency,

and the timing of sleep onset from the PSQI, and the ESS as a measure of daytime sleepiness (m=6). An ancillary analysis for the biobehavioral cluster included PAD between DLMO and actigraphic midsleep as a clustering variable.

All clustering variables were assessed for correlations within each data set (Figure 3). We also examined the distribution of age and sex in our sample between SAD and S-SAD groups. Prior to performing cluster analyses, we assessed the clustering tendency of each data set using the Hopkins statistic (Lawson & Jurs, 1990), which tests the null hypothesis that the data is uniformly distributed (i.e., no underlying clusters). If the Hopkins statistic is > .5, we rejected the null hypothesis and concluded that there was an underlying cluster structure to our data. We also used a visual assessment of cluster tendency (VAT; Bezdek & Hathaway, 2002) to visually assess the dissimilarity matrix of the data (Figure 4). Underlying clustering tendency was evident for all three clustering analyses.

Cluster analyses were conducted using a *k*-means approach with the Euclidean distance metric as a measure of similarity. Due to the sensitivity of this approach to large ranges and variances, we scaled each indicator by their range, which still allowed for enough variation within each indicator for an accurate clustering solution (Henry et al., 2005; Milligan & Cooper, 1988). The number of clusters (*k*) was determined using the Nbclust package in R (Charrad et al., 2014), which simultaneously uses information from 30 different indices to determine the optimal number of clusters. Observations were randomly sorted prior to clustering. Resulting clusters were compared on demographics, sleep and circadian variables, depression severity, and diagnostic group. Post-hoc we compared clusters to a sample of nonseasonal, never depressed controls. A Bonferroni correction was applied to cluster contrasts to control for type 1 error. If normality and homogeneity of variance assumptions were met, clusters were compared use one-way analysis of

variance with student's t-tests for post-hoc contrasts. If these assumptions were not met, the Krustal-Wallis chi-square test or Fisher's Exact test was used with Dunn's test for post-hoc contrasts.

Aim 1*:* We conducted a *k*-means cluster analysis on *a priori* selected biobehavioral sleep and circadian variables and compared clusters on depression severity.

Aim 2: We conducted two *k*-means cluster analyses on *a priori* selected prospective and retrospective self-reported sleep and circadian variables and compared clusters on depression severity.

Aim 3: To determine the stability of the resulting cluster assignments, we examined how the resulting clusters compared to one another.

Ancillary Aim 4**:** We compared each cluster to control participants with no history of depression, and no seasonal variation in mood and behavior.

4.0 Results

4.1 Sample Description

There were 74 individuals with SAD, 44 individuals with S-SAD, and 78 nonseasonal controls with no history of depression (*N*=196). Neither age nor sex differed between the diagnostic groups in the full sample (Table 1). As expected, depression severity measured by the SIGH-SAD was significantly higher in the SAD group compared to S-SAD and controls, and higher in S-SAD compared to controls (Table 1). Notably, sleep diary efficiency and onset differed between the groups; individuals with both SAD and S-SAD reported ~3% less sleep efficiency than controls, and individuals with SAD reported 36 minutes earlier sleep onset than controls. Individuals with SAD reported higher levels of daytime sleepiness than controls, although not higher than the cut-off of 10 (Johns et al., 1991).

4.2 Aim 1: Biobehavioral Clusters

There were 60 SAD and S-SAD participants (51%) and 46 controls (59%) with complete actigraphy and DLMO data. Preliminary examination demonstrated neither age ($F_{(1, 51)}$= 1.1, p>.05) nor gender (FE; p>.05) differed by diagnostic group in this subsample. Some clustering variables were significantly correlated (Figure 3), although correlations were small to medium (r's < 0.6). Based on the results from Nbclust, the best number of clusters was three: one was characterized by long total sleep times and naps ("Nappers with long sleep"; n=6); one

characterized by short total sleep times and low sleep efficiencies ("Insomnia"; *n*=23); and one characterized by early DLMOs and early sleep onset times ("Advanced"; *n*=31). Clusters did not differ by diagnostic group or depression severity. Table 2 shows mean values for demographic, clinical, sleep, and circadian variables across biobehavioral cluster groups and controls.

4.2.1 Ancillary Aim 4

When the three biobehavioral clusters were compared to a sample of nonseasonal, never depressed controls, the controls were younger than the "Advanced" cluster. Both the "Nappers with long sleep" cluster (8.4 hours) and the "Advanced" cluster (7.6 hours) had significantly longer average total sleep times than controls (7 hours). The "Insomnia" cluster (6.4 hours) had significantly shorter total sleep time compared to controls and the other clusters. The "Nappers with long sleep" cluster had significantly more naps than all other groups. The "Advanced" cluster had significantly earlier DLMOs than all other groups and a significantly longer PAD (7.3 hours) compared to controls (6.6 hours). The "Insomnia" cluster had significantly lower sleep efficiencies compared to controls and later sleep onset times compared to the "Advanced" cluster.

4.2.2 Additional Biobehavioral Analyses

Including the fixed DLMO instead of the relative DLMO yielded similar results (Table 2), except the "Insomnia" cluster had significantly shorter PAD compared to the "Advanced" cluster. There were only two participants who changed their cluster assignments compared to the relative DLMO clustering, one from "Insomnia" to "Advanced" and one from "Advanced" to "Insomnia".

Including PAD as a clustering variable resulted in only two clusters akin to the "Insomnia" and "Advanced" clusters (Table 3).

4.3 Aim 2: Prospective Self-report Clusters

There were 88 SAD and S-SAD participants (75%) and 67 controls (86%) with complete sleep diary data. Preliminary examination demonstrated neither age ($F_{(1, 80)}$= .7, p>.05) nor gender (FE; p>.05) differed by diagnostic group in this subsample. Some clustering variables were significantly correlated (Figure 3), although r's<.45. Based on the results of Nbclust, the best number of clusters was two: one characterized by shorter total sleep times, lower sleep efficiencies, and irregular sleep ("Insomnia"; n=27); and one characterized by longer total sleep times and earlier sleep onset ("Advanced"; n=61). Clusters did not differ on depression severity. Table 4 shows mean values for demographic, clinical, sleep, and circadian variables across the two prospective self-report clusters and controls.

4.3.1 Ancillary Aim 4

The "Insomnia" cluster (6.6 hours) reported significantly shorter total sleep times and the "Advanced" cluster (7.9 hours) reported significantly longer total sleep times than controls (7.3 hours). The "Insomnia" cluster reported significantly lower sleep efficiency and greater sleep irregularity than both the "Advanced" cluster and controls. The "Advanced" cluster reported significantly earlier sleep onset times than the "Insomnia" cluster and controls.

4.4 Aim 2: Retrospective Self-report Clusters

There were 72 SAD and S-SAD participants (61%) and 28 controls (36%) with complete retrospective self-report data. In order to accurately interpret MSF_{sc} from the MCTQ, participants could not have any alarm use on 'free days,' which lead to missing MSF_{sc} for 28 participants (14%) who had completed the MCTQ. Neither age ($F_{(1, 70)}$= .02, p>.05) nor gender (FE; p>.05) differed by diagnostic group in this subsample. No clustering variables were significantly correlated (Figure 3). Based on the results from Nbclust, the best number of clusters were two: one characterized by shorter total sleep times and lower sleep efficiencies ("Insomnia"; n=21); and one characterized by longer total sleep times ("Advanced"; n=51). Depression severity did not differ between clusters. Table 5 reports demographic, clinical, sleep, and circadian variables across retrospective self-report clusters and controls.

4.4.1 Ancillary Aim 4

Consistent with the biobehavioral and prospective self-report clusters, average total sleep time for the "Insomnia" cluster (5.4 hours) and the "Advanced" cluster (8.2 hours) significantly differed from controls (7 hours). The "Insomnia" cluster reported significantly lower sleep efficiencies than both groups. The "Advanced" cluster reported significantly higher daytime sleepiness than controls. Notably, the "Advanced" did not differ on sleep onset compared to either group.

4.5 Aim 3: Clustering Across Modalities

Descriptive examinations of clusters across measurement modalities indicated that every participant in the biobehavioral "Nappers with long sleep" cluster was grouped in the "Advanced" cluster for both prospective and retrospective self-report. The majority (76%) of the biobehavioral "Insomnia" cluster was grouped in the prospective "Insomnia" cluster; however, only 25% of the biobehavioral "Insomnia" cluster was in the retrospective "Insomnia" cluster. From the biobehavioral "Advanced" cluster, the majority were captured as "Advanced" by prospective (94%) and retrospective self-report (83%). See Figure 2.

5.0 Discussion

Sleep and circadian characteristics in SAD include expected hypersomnolence and circadian misalignment, but not exclusively and not for the majority. Three distinct sleep and circadian profiles were identified, each with unique and modifiable treatment targets. This is significant considering the few sleep and circadian differences between diagnostic groups (controls, SAD, S-SAD) in the largest sleep and circadian analysis in seasonal depression. Each clustering analysis identified both an 'Insomnia' cluster, characterized by short total sleep times and low sleep efficiencies, and an 'Advanced' cluster, characterized by longer total sleep times and early sleep onsets. The biobehavioral sleep and circadian cluster analysis split the 'Advanced' cluster into a 'Nappers with long sleep' cluster, characterized by long total sleep times and daytime naps and an 'Advanced' cluster, characterized by early circadian phase and sleep onset. Clusters did not differ on depression severity or stratify by SAD vs. S-SAD. Despite few differences between Controls, SAD, and S-SAD groups on sleep and circadian variables, our cluster analyses revealed distinct sleep and circadian profiles in within seasonal depression, potentially explaining mixed findings in previous work.

Each cluster comprises a unique constellation of sleep and circadian characteristics with associated clinical implications. The 'Advanced' cluster highlights early sleep and circadian timing as a prominent phenotype in seasonal depression, despite being previously considered a minority (30%; Lewy et al., 2006). The 'Advanced' cluster was defined by significantly early circadian timing, with average DLMOs (7:42pm) over an hour earlier than both controls (8:54pm) and other clusters (~9:00pm). This cluster had a significantly longer PAD between DLMO and actigraphic midsleep (7.3 hours) than controls (6.6 hours) but did not differ from controls on sleep

onset time, which indicates substantial phase-advance. While most individuals with seasonal depression are typecast as delayed circadian phase, previous work has demonstrated advanced circadian timing in a subset of participants (Lewy et al., 2006). It has been proposed that these 'Advanced' participants are the 50% non-responders to morning light (Burgess et al., 2004), who might benefit from evening light or morning melatonin administration (Lewy et al., 2006). Future research should examine other factors that could contribute to earlier circadian profiles, including retinal sensitivity (e.g., the post-illumination pupil response; PIPR), light exposure, and other circadian entrainers (e.g., meals times).

In the 'Advanced' cluster, early diary sleep onset times suggest early settling, which could lead to longer total sleep times. Early self-reported sleep onset is consistent with previous work in this sample using RARs, which identified early settling, or an earlier decrease in physical activity at the end of the active period (Smagula et al., 2018). Early settling may be a function of feelings of fatigue, lethargy, and/or behavioral disengagement. Individuals experiencing fatigue or disengagement might discontinue physical activity in the evening and retire to bed early, which could contribute to longer total sleep times. While the mean actigraphic total sleep time in the 'Advanced' cluster (7.6 hours) is below the duration threshold for hypersomnolence (>9-10 hours; APA, 2013), this cluster slept 35 min longer than controls (7 hours), a statistically and clinically significant difference. Participants in the 'Advanced' cluster reported significantly longer total sleep times than controls on both sleep diaries (7.9 hours vs. 7.3 hours) and retrospective self-report (8.2 hours vs. 6.9 hours). Further, the retrospective self-report 'Advanced' cluster reported greater daytime sleepiness than controls, which is a component of hypersomnolence. This combination of early settling and longer than average sleep times in over half of this sample might

encapsulate how hypersomnolence typically presents in seasonal depression (Wescott et al., in prep).

Insomnia is an overlooked presentation in seasonal depression. The 'Insomnia' cluster consistently had average total sleep times less than 6.5 hours in all analyses and evidenced fragmented and irregular sleep. These findings support insomnia symptoms reported in seasonal samples (Borisenkov et al., 2015; Roecklein, Carney, et al., 2013) and findings of shorter and fragmented winter actigraphic sleep in SAD (Winkler et al., 2005). The presence of an 'Insomnia' subgroup in seasonal depression could explain the variation in winter total sleep time findings (Anderson et al., 1994; Shapiro et al., 1994; Winkler et al., 2005; Wescott et al., in prep). While the 'Insomnia' cluster had later sleep onset times than the 'Advanced' cluster, this did not significantly differ from controls, suggesting that this 'Insomnia' cluster does not have behavioral delays in sleep timing.

Despite no differences in behavioral sleep timing, the 'Insomnia' cluster had significantly shorter PAD (5.8 hours) than the 'Advanced' cluster (6.6. hours) when using the Fixed DLMO threshold (crossing 3pg/mL) to calculate PAD, which could be indicative of internal desynchrony between the timing of sleep and circadian rhythms (PAD <6 hours; Lewy et al., 2006). While it is possible insomnia symptoms are associated with a phase delay, prior studies reporting a phase delay in SAD did not evaluate sleep duration or continuity and often standardized the sleep/wake cycle of participants to isolate any circadian effects of light therapy (Avery et al., 1997; Burgess et al., 2004; Dahl et al., 1993; Lewy et al., 2006). However, this finding was not present when using the relative DLMO threshold, a more sensitive method that is thought to more accurately capture the initial rise of melatonin secretion (Molina & Burgess, 2011).

The ‘Nappers with long sleep’ cluster in the biobehavioral clustering analysis highlights the combination of daytime naps and longer nighttime sleep in seasonal depression. This supports our previous work showing a winter increase in total sleep time in SAD compared to controls when including naps (Wescott et al., in prep). In the present study, participants in the ‘Nappers with long sleep’ cluster had an average total sleep time of 9 hours when including nap duration, close to the cut-off of hypersomnolence (>9-10 hours; APA, 2013). This cluster also evidenced irregular sleep patterns, which could reflect oscillating nights of self-onset insomnia and hypersomnolence (Roecklein, Carney, et al., 2013). These oscillations might occur as a result of daytime napping, which can fragment the 24-hour sleep/wake cycle (Wallace et al., 2020). Daytime naps can reduce homeostatic sleep pressure, making it difficult to fall asleep at night and shortening the night’s sleep, which can lead to increased sleep pressure the following day. Notably, this is the smallest subgroup with only six participants (9.7%), suggesting that the majority of participants with seasonal depression are not characterized by daytime naps. All participants in the ‘Nappers with long sleep’ cluster revealed in the biobehavioral cluster analysis were lumped into the ‘Advanced’ cluster in both the prospective and retrospective clustering analyses, suggesting that the ‘Nappers with long sleep’ subgroup most closely resembles the ‘Advanced’ cluster, likely due to longer total sleep times. Assessing daytime naps could discern these clinical presentations.

Comparing biobehavioral, prospective and retrospective self-report clusters suggests solely relying on retrospective self-report measures may not discriminate sleep and circadian phenotypes in seasonal depression. While retrospective self-report revealed both an ‘Insomnia’ and ‘Advanced’ cluster, the ‘Advanced’ cluster was not distinguished by early sleep onset times. Further, there were no differences between clusters on chronotype (MSF_{sc}; phase of entrainment), suggesting that self-reported measures of chronotype cannot distinguish circadian phase in

seasonal depression. This supports prior work showing that although the MSF_{sc} correlates with DLMO, one MSF_{sc} time point was associated with a four hour range of DLMO times (Kantermann et al., 2015). Due to the lack of specificity for the MSF_{sc}, the authors advised against using the MSF_{sc} to determine timing of chronotherapy. In contrast, sleep diaries were the most similar to biobehavioral measures with the exception of distinguishing participants with daytime naps. In the absence of biobehavioral measurements in clinical settings, prospective sleep diaries could be an inexpensive option that are more reliable than retrospective self-report measures.

While resulting sleep and circadian subgroups did not differ on depression severity, each distinct subgroup was characterized by modifiable treatment targets. Participants in the 'Insomnia' cluster might benefit from Cognitive-behavioral therapy for insomnia (CBT-I), which could improve sleep efficiency and lengthen total sleep time. Participants in the 'Advanced' cluster might respond better to behavioral activation, a component of CBT-SAD (Rohan et al., 2016), which may increase physical and social activity in the evening to reverse early settling. Either CBT-I or CBT-SAD could be effective for reducing daytime naps for participants in the 'Nappers with long sleep' cluster. While morning bright light therapy is considered the gold standard treatment in SAD (Terman et al., 1989), it might be most effective for participants in the 'Insomnia' cluster and less effective for participants in the 'Advanced' cluster. Morning bright light therapy has been shown to consolidate the sleep-wake cycle in SAD for participants with short sleep durations and fragmented sleep (Winkler et al., 2005), and bright light therapy improves symptoms of insomnia in otherwise healthy individuals (hedge's $g = .47$; van Maanen et al., 2016). In contrast, 'Advanced' participants would likely not respond to morning light (Burgess et al., 2004) and might benefit from evening light or morning melatonin administration (Lewy et al., 2006).

The heterogenous presentation of sleep and circadian disruptions in seasonal depression might be optimally treated with a broader approach such as the Transdiagnostic sleep and circadian intervention (TranS-C; Harvey et al., 2016). The standard TranS-C intervention includes four core modules and seven optional modules that can be included depending on a participant's primary sleep and/or circadian problem. Based on the nature of sleep and circadian disturbances in seasonal depression, a TranS-C intervention would like include the following three "optional" modules: 1) 'Improving sleep efficiency' to address the sleep fragmentation seen in the 'Insomnia' cluster; 2) 'Reducing time in bed' to improve hypersomnolent presentations with excessive naps; and 3) 'Dealing with delayed or advanced phase' to target any circadian disruption. Since treatment for SAD does not currently include sleep-focused interventions, future work should employ sleep and circadian interventions in seasonal depression and test clusters of initial symptoms as moderators of treatment outcomes.

5.1 Strengths & Limitations

This study benefitted from multiple measures of sleep and circadian disruptions across three measurement modalities to elucidate data-driven subgroups, a greater variety of measures than has been used in SAD studies previously. The focus on sleep and circadian disruptions helped identify constellations of symptoms in the first quantitatively sophisticated approach to characterize subgroups in SAD. The *k*-means approach was well-matched to the sample size, which was the largest to report sleep outcomes in SAD, and the first to include measures of both actigraphy measures of sleep and biomarkers of circadian rhythms in SAD.

There are a few important limitations. The cross-sectional design limits any causal interpretations of whether these sleep and circadian disruptions are symptoms of winter depressive episodes or potential contributors to onset and recurrence of winter depression. Due to the data-driven nature of cluster analyses, these findings would be bolstered by verification in a separate dataset. Additionally, there were uneven sample sizes across each clustering analyses, which hindered comparisons across measurements. A quarter of the sample had unusable DLMOs due to super secretion (high baselines), low secretion (low baselines that never rose), or because onset did not occur during the testing window. Low melatonin secretions could reflect an extremely delayed circadian phase that was not captured by our protocol (last DLMO collected at 1am) or was acutely suppressed by light in the 10 – 25 lux range (Phillips et al., 2019). Additionally, our use of salivary melatonin as a marker of circadian phase differs from previous work in SAD using plasma melatonin (Lewy et al., 2006) or core body temperature (Avery et al., 1997; Burgess et al., 2004; Dahl et al., 1993; Eastman et al., 1993).

5.2 Conclusion

5.2.1 Main Findings

The use of a data-driven clustering analysis unveiled distinct presentations of sleep and circadian disruptions in seasonal depression. Two consistent sleep and circadian profiles were described: ‘Insomnia’ – short total sleep times (<6.5 hours), irregular and fragmented sleep and ‘Advanced’ – early sleep and circadian timing and longer total sleep times (> 7.5 hours). The presence of distinct sleep and circadian clusters in seasonal depression could affect treatment

response, and properly treating sleep and circadian disturbances based on phenotype could potentially improve mood symptoms.

5.2.2 Clinical Implications

Treating sleep and circadian disruptions in seasonal depression would benefit from an individually-tailored, precision medicine approach. Changing the perspective of sleep in SAD from uniformly hypersomnolence and phase delay, to heterogenous presentations will be more effective when identifying the most promising interventions. Identifying the key drivers of sleep-related pathophysiology in seasonal depression may even minimize time to remission and reduce recurrence rates. For example, if the 50% of individuals with SAD who do not respond to morning light therapy are better treated with CBT-SAD or CBT-I, then starting with those psychotherapies rather than light therapy may forestall a treatment failure experience.

5.2.3 Future Directions

Implementing a precision medicine approach to sleep and circadian disruptions in individuals with dysregulated mood could uncover pathophysiological mechanisms underlying distinct phenotypes. While the current study focused on seasonal depression, sleep and circadian disruptions are transdiagnostic. Targeting specific sleep-wake and biological rhythm profiles could aid our understanding the etiology of mood dysregulation and improve treatment response.

Table 1. Demographic, sleep, and circadian measures across diagnostic groups.

	Controls	SAD	S-SAD	Test statistics	Significant pair-wise comparisons
N	78	74	44		
Age	37.1 *(13.5)*	40.3 *(13.2)*	42.2 *(13.6)*	$F_{(2, 185)}=2.2$	
Sex (%female)	58 *(74%)*	64 *(86%)*	35 *(80%)*	$\chi^2=4.3$	
SIGH-SAD[1]	3.8 *(4.7)*	26.8 *(8.3)*	14.0 *(6.3)*	$\chi^2=124.6^{***}$	C < S-SAD < SAD
Relative DLMO[2]	20.4 *(3.1)*	20.2 *(1.2)*	20.3 *(1.0)*	$F_{(2, 103)}=.1$	
Fixed DLMO[2]	21.6 *(1.4)*	20.9 *(1.5)*	21.4 *(1.2)*	$F_{(2, 100)}=2.5$	
MSF_{sc}[3]	3.6 *(.5)*	3.8 *(.9)*	3.9 *(.6)*	$F_{(2, 97)}=2.1$	
Duration $_{actigraphy}$	420 *(55.6)*	439 *(60.1)*	421 *(56.8)*	$F_{(2, 103)}=1.2$	
Duration $_{diary}$	436 *(57.4)*	455 *(58.9)*	441 *(54.7)*	$F_{(2, 152)}=1.6$	
Duration $_{PSQI}$	417 *(72.6)*	445.8 *(127.8)*	436.8 *(76.2)*	$F_{(2, 97)}=.7$	
Efficiency $_{actigraphy}$	88.6 *(4.2)*	87.0 *(5.4)*	86.1 *(7.2)*	$\chi^2=3.6$	
Efficiency $_{diary}$	91.7 *(6.1)*	89.0 *(8.7)*	88.3 *(6.0)*	$\chi^2=8.8^{**}$	S-SAD, SAD < C
Efficiency $_{PSQI}$	93.0 *(7.5)*	89.3 *(17.0)*	90.5 *(11.3)*	$\chi^2=5.4$	
Regularity $_{actigraphy}$	58.4 *(32.8)*	63.6 *(23.2)*	52.6 *(20.9)*	$F_{(2, 103)}=1.1$	
Regularity $_{diary}$	51.4 *(28.6)*	55.4 *(31.6)*	49.6 *28.4)*	$F_{(2, 151)}=.5$	
Onset $_{actigraphy}$	23.7 *(1.7)*	23.3 *(1.1)*	23.7 *(1.4)*	$F_{(2, 103)}=.9$	
Onset $_{diary}$	23.9 *(1.4)*	23.3 *(1.2)*	23.7 *(1.1)*	$\chi^2=8.8^{*}$	SAD < C
Onset $_{PSQI}$	22.8 *(1.1)*	22.9 *(1.5)*	23.0 *(1.0)*	$F_{(2, 97)}=.4$	
Naps $_{actigraphy}$	2.5 *(6.0)*	6.5 *(13.2)*	1.9 *(6.3)*	$\chi^2=24.7$	
Naps $_{diary}$	9.1 *(13.1)*	18.5 *(30.0)*	7.3 *(17.1)*	$\chi^2=4.2$	
Epworth[4]	6.4 *(3.9)*	9.1 *(4.2)*	7.9 *(4.3)*	$F_{(2, 97)}=3.7^{*}$	C < SAD

[1] Structured Interview Guide for the Hamilton Rating Scale for Depression—Seasonal Affective Disorder Version total score. [2] Dim light melatonin onset. [3] Midsleep on free days corrected for sleep debt calculated from the Munich Chronotype Questionnaire. [4] Epworth Sleepiness Scale. *Note*: * = $p<.05$, ** = $p<.01$, *** = $p<.001$.

Table 2. Comparisons on demographic, clinical, sleep-wake, and circadian variables across biobehavioral cluster groups and controls.

	Cluster 1 'Nappers with long sleep'	Cluster 2 'Insomnia'	Cluster 3 'Advanced'	Test statistics	Significant pair-wise comparisons	Controls	Test statistics	Significant pair-wise comparisons
N	6	23	31			46		
Age	33.3 *(12.7)*	39.9 *(13.9)*	43.3 *(12.4)*	$F_{(2, 50)}$= 1.5		34.9 (*12.8)*	$F_{(3, 95)}$= 2.8*	C < 3
Sex (%F)	6 *(100%)*	19 *(83%)*	27 *(87%)*	FE[4]		34 *(74%)*	FE[4]	
Group (%SAD)	6 *(100%)*	15 *(65%)*	17 *(63%)*	FE[4]				
SIGH-SAD[1]	29.2 *(6.7)*	22.3 *(8.3)*	20.7 *(9.0)*	$F_{(2, 52)}$= 2.4		3.5 *(4.7)*	χ^2=62.7***	C < 1, 2, 3
Relative DLMO[2]	21.0 *(1.1)*	20.8 *(1.0)*	19.7 (.9)	χ^2=16.1***	3 < 1, 2	20.9 *(1.2)*	$F_{(3, 102)}$= 9.0***	3 < C, 2
Duration	505 *(37.3)*	382 *(40.3)*	455 *(43.8)*	$F_{(2, 57)}$= 30.1***	2 < 3 < 1	420 *(55.6)*	$F_{(3, 102)}$= 15.5***	2 < C < 1, 3
Efficiency	89.3 *(3.9)*	84.0 *(7.5)*	88.1 *(4.5)*	χ^2=7.8*	2 < 3	88.6 *(4.2)*	χ^2=10.9*	2 < C
Regularity	81 *(24)*	74 *(20)*	45 *(12)*	χ^2=29.8***	3 < 1, 2	54 *(36)*	χ^2=26.8***	3 < 1, 2; C < 2
Onset	23.2 *(.7)*	0.2 *(112)*	22.8 *(.9)*	$F_{(2, 57)}$= 12.3***	3 < 1, 2	23.7 *(1.7)*	χ^2=17.1***	3 < 2
Naps	31.8 *(15.9)*	1.7 *(4.6)*	1.9 *(5.7)*	χ^2=25.9***	2, 3, < 1	2.7 *(6.0)*	χ^2=29.0***	C, 2, 3 < 1
PAD[3]	6.9 *(.8)*	6.9 *(.9)*	7.3 *(.9)*	χ^2= 2.3		6.6 *(1.0)*	$F_{(3, 102)}$= 2.8*	C < 3
N	5	22	33			45		
Age	28.4 *(4.2)*	41.6 *(14.9)*	42.4 *(12.2)*	$F_{(2, 50)}$= 2.6		33.5 (*12.0)*	$F_{(3, 94)}$= 4.6**	C < 3
Sex (%F)	5 *(100%)*	18 *(82%)*	28 *(85%)*	FE[4]		34 *(74%)*	FE[4]	
Group (%SAD)	5 *(100%)*	15 *(68%)*	19 *(58%)*	FE[4]				
SIGH-SAD[1]	30.8 *(5.9)*	22.4 *(8.5)*	21.7 *(9.0)*	$F_{(2, 52)}$= 2.4		3.7 *(4.9)*	χ^2=63.4***	C < 1, 2, 3
Fixed DLMO[2]	21.6 *(1.3)*	22.2 *(1.0)*	20.2 (1.2)	$F_{(2, 57)}$= 20.0***	3 < 1, 2	21.6 *(1.4)*	$F_{(3, 101)}$= 12.3***	3 < C, 2
Duration	497 *(35.7)*	395 *(41.9)*	451 *(48.1)*	$F_{(2, 57)}$= 15.7***	2 < 1, 3	420 *(55.5)*	$F_{(3, 101)}$= 9.2***	C, 2 < 1, 3
Efficiency	88.7 *(4.0)*	84.2 *(7.4)*	88.2 *(4.4)*	χ^2=7.9*	2 < 3	89.0 *(3.8)*	χ^2=12.8**	2 < C
Regularity	84 *(26)*	73 *(20)*	44 *(12)*	χ^2=30.7***	3 < 2	56 *(26)*	χ^2=27.0***	3 < 2
Onset	23.2 *(.7)*	0.3 *(1.2)*	22.8 *(.9)*	$F_{(2, 57)}$= 15.8***	3 < 2	23.6 *(1.6)*	χ^2=20.9***	3 < 2
Naps	32.5 *(17.7)*	1.4 *(4.6)*	2.5 *(5.9)*	χ^2=22.1***	2, 3, < 1	2.9 *(6.2)*	χ^2=23.8***	C, 2, 3 < 1
PAD[3]	6.2 *(.9)*	5.8 *(1.2)*	6.6 *(1.1)*	$F_{(2, 57)}$= 3.5*	2 < 3	5.9 *(1.3)*	$F_{(3, 101)}$= 3.3*	C < 3

[1] Structured Interview Guide for the Hamilton Rating Scale for Depression—Seasonal Affective Disorder Version total score. [2] Dim light melatonin onset. [3] Phase angle difference between DLMO and average midsleep from actigraphy. [4] Fisher's Exact Test. *Note*: * = p<.05, ** = p<.01, *** = p<.001

Table 3. Comparing biobehavioral clusters and controls including phase angle difference between DLMO and midsleep (PAD) as a clustering input variable.

	Cluster 1 'Insomnia'	Cluster 2 'Advanced'	Test statistics	Significant pair-wise comparisons	Controls	Test statistics	Significant pair-wise comparisons
N	24	36			46		
Age	39.9 *(13.9)*	43.3 *(12.4)*	$F_{(2, 50)}= 1.5$		34.9 (*12.8)*	$F_{(3, 95)}= 2.8^{*}$	C < 3
Sex (%F)	19 *(83%)*	27 *(87%)*	FE[4]		34 *(74%)*	FE[4]	
Group (%SAD)	15 *(65%)*	17 *(63%)*	FE[4]				
SIGH-SAD[1]	23.0 *(8.7)*	21.8 *(8.9)*	$F_{(1, 53)}= .2$		3.5 *(4.7)*	$\chi^2=62.7^{***}$	C < 1, 2, 3
Relative DLMO[2]	20.9 *(1.0)*	19.8 (1.0)	$F_{(1, 58)}= 16.3^{***}$	2 < 1	20.9 *(1.2)*	$F_{(2, 102)}= 10.9^{***}$	2 < C, 1
Duration	385 *(41.8)*	464 *(46.8)*	$F_{(1, 58)}= 44.2^{***}$	1 < 2	420 *(55.6)*	$F_{(2, 103)}= 18.7^{***}$	1 < C < 2
Efficiency	84.0 *(7.4)*	88.5 *(4.4)*	$\chi^2=9.0^{**}$	1 < 2	88.6 *(4.2)*	$\chi^2=12.1^{**}$	1 < C, 2
Regularity	74 *(20)*	49 *(19)*	$F_{(1, 58)}= 24.1^{***}$	2 < 1	54 *(36)*	$\chi^2=28.4^{***}$	1 < C, 2
Onset	0.2 *(112)*	22.8 *(.9)*	$F_{(1, 58)}= 27.1^{***}$	2 < 1	23.7 *(1.7)*	$\chi^2=19.0^{***}$	2 < C, 1
Naps	3.2 *(9.0)*	5.9 *(12.7)*	$\chi^2=.5$		2.7 *(6.0)*	$\chi^2=.9$	
PAD[3]	6.9 *(.9)*	7.2 *(.9)*	$F_{(1, 58)}= 1.8$		6.6 *(1.0)*	$F_{(2, 102)}= 3.8^{*}$	C < 2

[1] Structured Interview Guide for the Hamilton Rating Scale for Depression—Seasonal Affective Disorder Version total score. [2] Dim light melatonin onset. [3] Phase angle difference between DLMO and average midsleep from actigraphy. [4] Fisher's Exact Test. *Note*: * = $p<.05$, ** = $p<.01$, *** = $p<.001$

Table 4. Comparisons on demographic, clinical, sleep-wake, and circadian variables across sleep diary cluster groups and controls.

	Cluster 1 'Insomnia'	Cluster 2 'Advanced'	Test statistics	Significant pair-wise comparisons	Controls	Test statistics	Significant pair-wise comparisons
N	27	61			67		
Age	39.8 *(13.4)*	41.4 *(13.3)*	$F_{(1, 80)}$= .2		37.2 (*13.4)*	$F_{(2, 146)}$= 1.6	
Sex (%F)	20 *(74%)*	57 *(93%)*	FE*		49 *(73%)*	χ^2=8.9**	C, 1 < 2
Group (%SAD)	17 *(63%)*	38 *(62%)*	FE				
SIGH-SAD[1]	25.7 *(10.5)*	21.9 *(8.9)*	$F_{(1, 80)}$= 2.9		3.9 *(4.9)*	χ^2=86.4***	C < 1, 2
Duration	396 *(39.8)*	473 *(47.2)*	$F_{(1, 86)}$= 55.1***	1 < 2	436 *(57.4)*	$F_{(1, 152)}$= 22.9***	1 < C < 2
Efficiency	84.4 *(.1)*	90.6 *(.1)*	χ^2=12.8***	1 < 2	91.7 *(.1)*	χ^2=18.6***	1 < 2, C
Regularity	73 *(36)*	44 *(23)*	χ^2=12.8***	2 < 1	51 *(29)*	χ^2=13.3***	C, 2 < 1
Onset	0.5 *(1.1)*	22.9 *(.8)*	$F_{(1, 86)}$= 65.2***	2 < 1	23.5 *(1.4)*	χ^2=41.1***	2 < C, 1
Naps	18.2 *(31.9)*	12.5 *(23.6)*	χ^2=.02		9.2 *(13.1)*	χ^2=.01	

[1] Structured Interview Guide for the Hamilton Rating Scale for Depression—Seasonal Affective Disorder Version total score. *Note*: * = p<.05, ** = p<.01, *** = p<.001

Table 5. Comparisons on demographic, clinical, sleep-wake, and circadian variables across retrospective cluster groups and controls.

	Cluster 1 'Insomnia'	Cluster 2 'Advanced'	Test statistics	Significant pair-wise comparisons	Controls	Test statistics	Significant pair-wise comparisons
N	21	51			28		
Age	39.3 *(10.7)*	42.7 *(14.4)*	χ^2=.8		38.3 (*12.8)*	χ^2=2.3	
Sex	17 *(82%)*	45 *(88%)*	FE		22 *(79%)*	FE	
SIGH-SAD[1]	24.7 *(9.0)*	20.8 *(9.3)*	$F_{(1, 68)}$= 2.5		3.9 *(3.7)*	χ^2=51.0***	C < 1, 2
MSF_{sc}[2]	3.7 *(.7)*	3.9 *(.8)*	$F_{(1, 70)}$= .6		3.6 *(.5)*	$F_{(2, 97)}$= 1.9	
Duration	324 *(55.8)*	491 *(91.2)*	$F_{(1, 70)}$= 60.7***	1 < 2	417 *(72.6)*	$F_{(2, 97)}$= 33.4***	1 < C < 2
Efficiency %	70.6 *(9.3)*	97.6 *(8.6)*	$F_{(1, 70)}$= 139.5***	1 < 2	93.0 *(7.5)*	$F_{(2, 97)}$= 77.4***	1 < C < 2
Onset	23.1 *(1.6)*	22.8 *(1.2)*	$F_{(1, 70)}$= .7		22.8 *(1.0)*	$F_{(2, 97)}$= .5	
Epworth[3]	8.4 *(4.3)*	8.8 *(4.3)*	$F_{(1, 70)}$= .1		6.4 *(3.9)*	$F_{(2, 97)}$= 3.1	C < 2

[1] Structured Interview Guide for the Hamilton Rating Scale for Depression—Seasonal Affective Disorder Version total score. [2] Midsleep on free days corrected for sleep debt calculated from the Munich Chronotype Questionnaire. [3] Epworth Sleepiness Scale. *Note*: * = p<.05, ** = p<.01, *** = p<.001

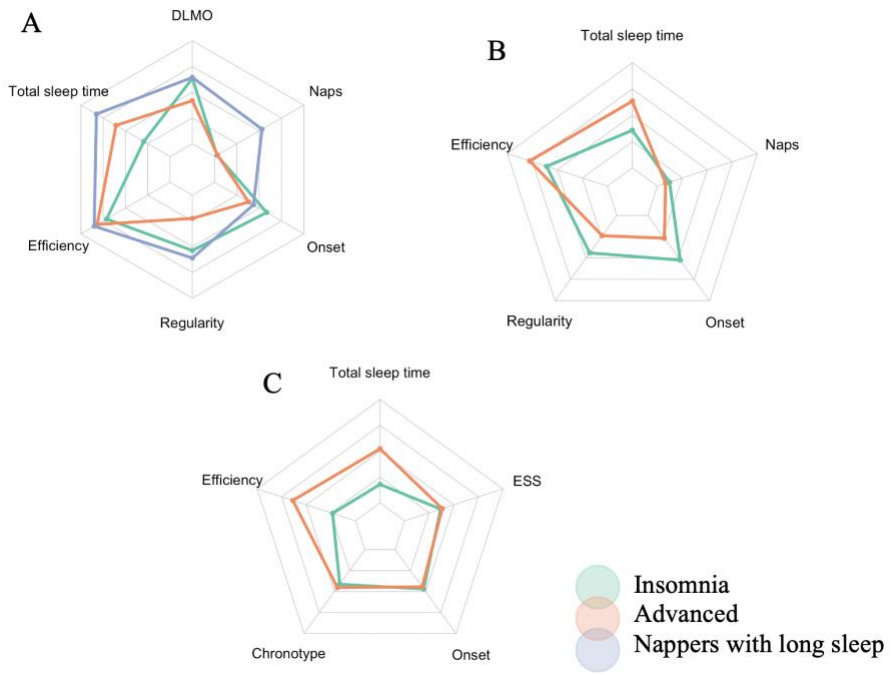

Figure 1. Spider plots of A) Biobehavioral clusters, B) Prospective self-report clusters, and C) Retrospective self-report clusters.

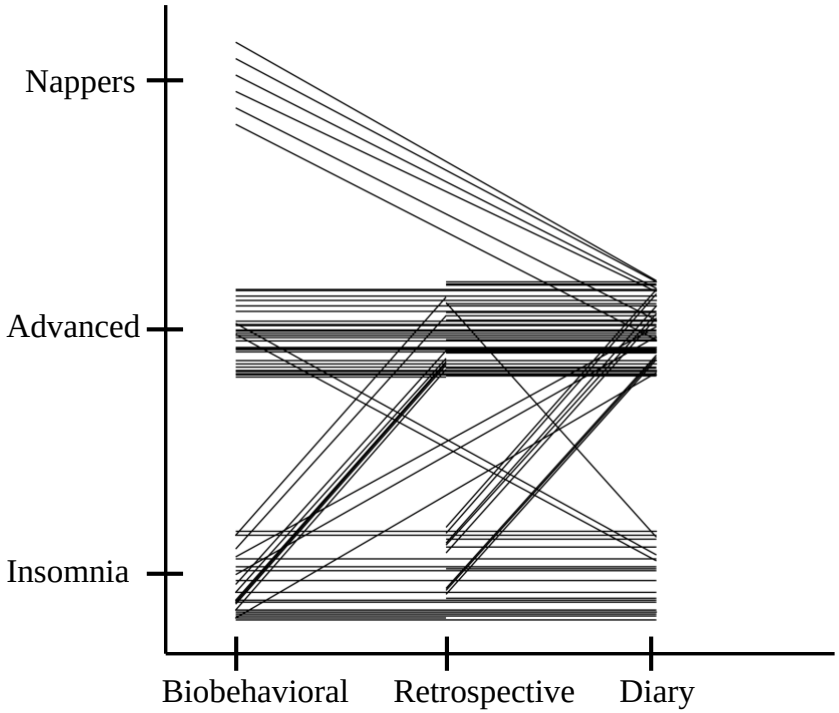

Figure 2. Descriptive examinations of clusters across Biobehavioral, Retrospective, and Prospective sleep diary measurements.

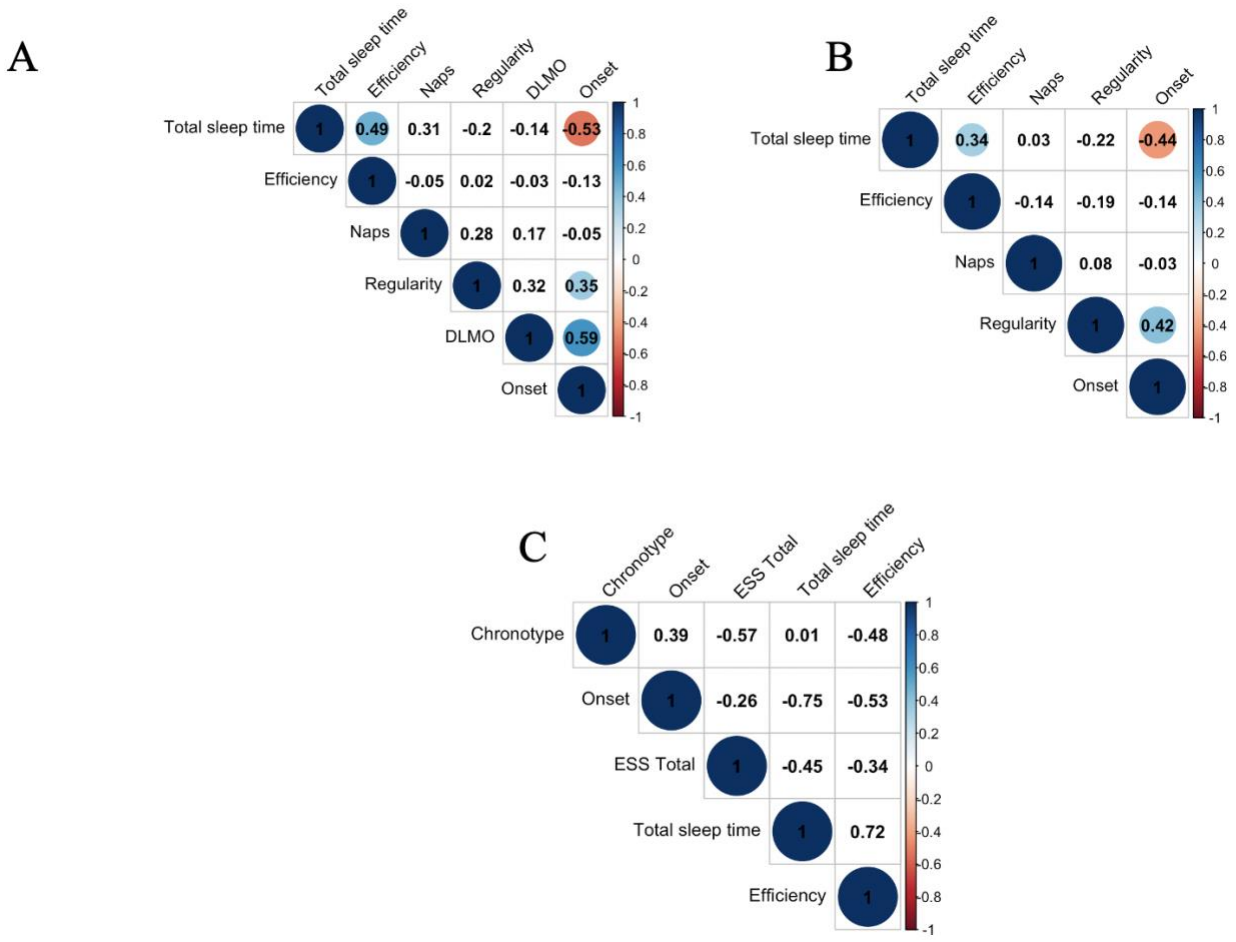

Figure 3. Correlation matrices between clustering variables for A) Biobehavioral, B) Prospective self-report, and C) Retrospective self-report.

Note: Significant correlations (p<.01) are depicted with colored circles.

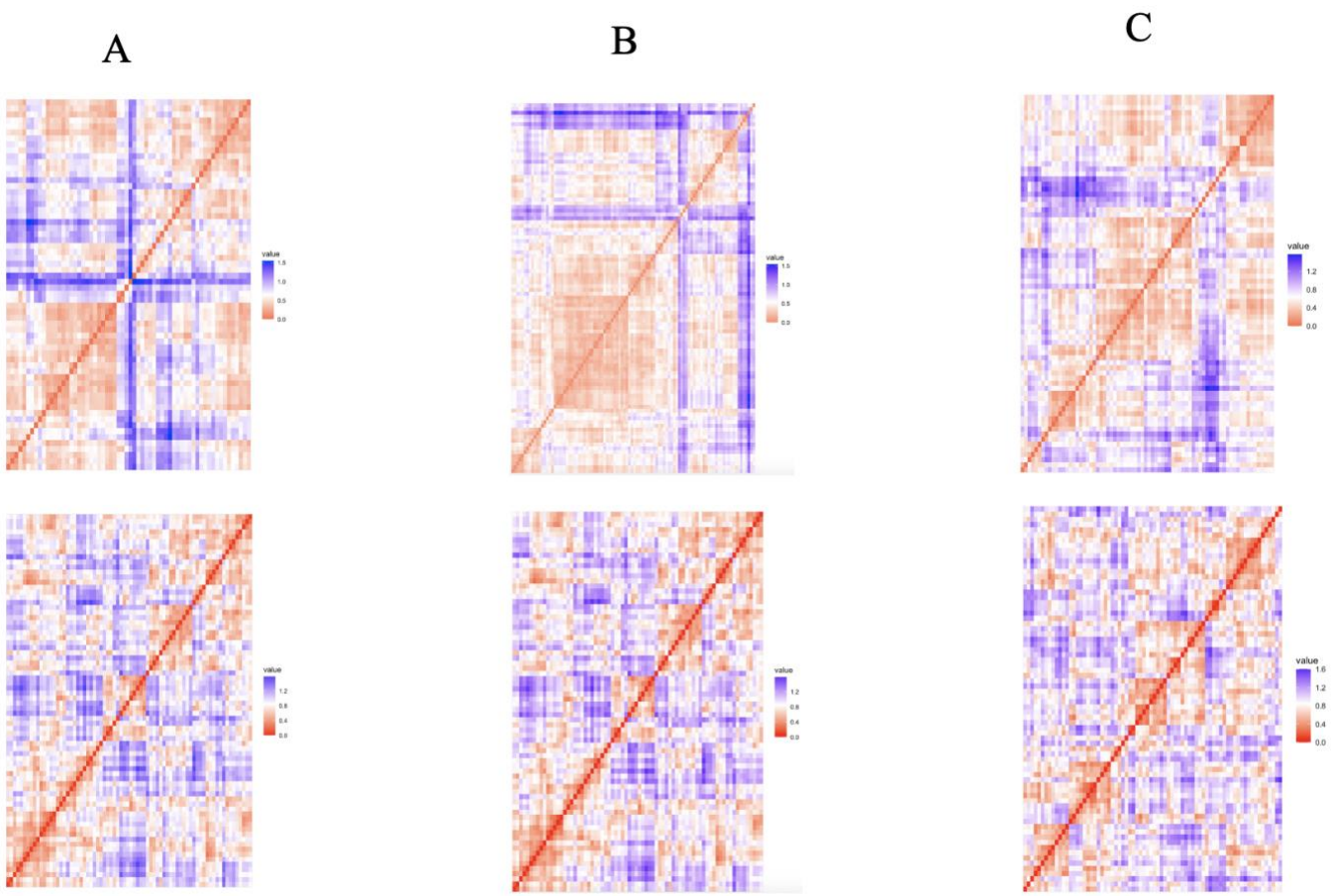

Figure 4. Visual assessment of clustering tendency of data (top row) and random data generated from the data set (bottom row). A) Biobehavioral cluster, B) Prospective cluster, C) Retrospective cluster.

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