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Sleep Challenges and Temperament Among Infants at Elevated Likelihood of Autism Spectrum Disorder

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SLEEP CHALLENGES AND TEMPERAMENT AMONG INFANTS AT ELEVATED LIKELIHOOD OF AUTISM SPECTRUM DISORDER

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ABSTRACT

The current study used parent report in a prospective longitudinal design to examine the relationship between early sleep difficulties and temperament among infants with an older sibling diagnosed with ASD (EL-ASIB, *n* = 32), those born pre-term (EL-PT, *n* = 24) and those with no familial history of ASD (LL, *n* = 28) across the first year of life. At 3, 4, 6 and 12 months, caregivers completed the Short Form of the Infant Behavior Questionnaire-Revised (IBQ-R) (Putnam et al., 2014). To understand how sleep difficulties are related to temperament, a new scale of Sleep Challenges was created with items related to falling and staying asleep as had previously been done with the Very Short Form (Macduffie et al., 2020). Trajectories of sleep difficulties between EL-ASIB, EL-PT, and LL groups were determined with the use of linear mixed-effects models. In addition, associations between early sleep difficulties and IBQ-R scales were examined. From the analyses, it was determined that EL-ASIB infants in the sample experienced greater sleep challenges towards the end of their first year. Additionally, there were several nonsignificant negative associations between surgency/regulatory capacity and sleep challenges at 12 months. Lastly, EL-ASIBs with greater surgency had less sleep challenges than other EL-ASIBs. Findings of this study point to the possibility that infant siblings of autistic children may be at greater risk for sleep challenges and early predictors of sociability are related to temperamental challenges of falling and staying asleep. Additional research is needed to examine objective measures of sleep alongside temperamental measures and its relationship to clinical outcomes.

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CHAPTER 1

INTRODUCTION

1.1 INFANT TEMPERAMENT

Temperament is defined as relatively stable and consistent dispositions that are observable early in life (Shiner et al., 2012). Multiple models have been proposed to explain infant temperament. For the purposes of this paper, Rothbart's neurobiological model of temperament will be used to explain how infants differ in their reactivity to their surroundings and regulation of self (Rothbart & Derryberry, 1981). In this framework, infant temperament is thought to be rooted in underlying biological mechanisms and serves as an early stable predictor of future psychological outcomes. Rothbart's model was also used to inform the development of the Infant Behavior Questionnaire (IBQ) in 1981 and subsequent revised versions in 1998, 2003, and 2014 (IBQ-R; Gartstein & Rothbart, 2003; Putnam et al., 2014). Three broad dimensions of infant temperament emerge from the IBQ-R: surgency, negative affect, and regulatory capacity.

Surgency, or the infant's willingness to approach new people and explore novel stimuli (Zentner & Bates, 2008), includes expressions of joy and activity level during routine activities (Gartstein & Rothbart, 2003; see Table 1.1 for detailed description). High levels of infant surgency are predictive of sociability and positive affectivity in early and middle childhood (Behrendt et al., 2020; Degnan et al., 2011; Rothbart, 2011), but also forecasts impulsivity and experience seeking in childhood (Burton et al., 2011).

Elevated approach in infancy, for example, has been linked to future difficulties with inhibitory control (Blandon et al., 2010; Rothbart et al., 2001) while higher positive emotionality is associated with reduced effortful control in young children (Kochanska et al., 2007). In contrast, infants with lower surgency are noted to be less likely to vocalize and engage with others, either as a result of reduced social motivation or developmental delays (Paterson et al., 2019). Infants and young children with lower levels of surgency are also noted to be more socially withdrawn and prefer to observe novel stimuli from a distance (Bassett et al., 2017).

Negative affectivity encapsulates emotional states like fear and anger-frustration as well as difficulty being soothed and abnormalities with falling reactivity (Zentner & Bates, 2008; see Table 1.1). Among typically developing infants, negative affectivity may contribute to higher vigilance in infancy (Vallorani et al., 2021) and moderate the relationship between infant attachment and sociability toward unfamiliar adults (Stupica et al., 2011). Additionally, negative affect in infancy is implicated in future externalizing behaviors, such that anger and frustration in infancy is predictive of ADHD symptoms (Miller et al., 2019). Severe infant fearfulness is also associated with later anxiety (Clifford et al., 2012; Pérez-Edgar et al., 2017) and social withdrawal (Buss & Kiel, 2013; Pérez-Edgar et al., 2017) in childhood and adolescence.

Regulatory Capacity, or the ability to modulate and control one's response to external stimuli, includes ease of soothing, duration of attention to a specific object, and level of enjoyment from low-intensity stimuli (Gartstein & Rothbart, 2003; see Table 1.1). Regulatory capacity in infancy typically predicts effortful control, or the ability to consciously inhibit a dominant response to focus attention on achieving goals, in

toddlerhood and early childhood (Erickson et al., 2017; Putnam et al., 2008). In turn, executive dysfunction in early childhood is linked to aggression, anti-social behaviors, and ADHD symptoms in later childhood and adolescence (Atherton et al., 2020; Macari et al., 2017; Wang et al., 2015).

1.2 THE RELATIONSHIP BETWEEN TEMPERAMENT AND INFANT SLEEP

Temperament may also be related to infant sleep challenges, though the paucity of longitudinal research examining these associations leaves many questions unanswered. Infants with high negative affectivity, for example, have been documented to experience shorter sleep duration (Mindell et al., 2017) and more frequent nighttime awakenings (Weinraub et al., 2012). Similarly, toddlers demonstrating shyness, inhibition, and separation anxiety have been shown to awake more frequently than peers without these traits (Mindell et al., 2017). Numerous theories have been posited to explain this relationship. One such theory suggests that elevated levels of cortisol may be the link between temperamental negativity and sleep challenges (Luecken et al., 2015). Specifically, lowered levels of cortisol exposure throughout the day is predictive of greater sleep duration while evening levels of cortisol is associated with ease of falling asleep at bedtime (Tuladhar et al., 2021). The proposed mediating role of cortisol adds evidence to the possible link between early sleep challenges and internalizing psychopathology in infancy and beyond.

Reduced self-regulation abilities are also associated with greater infant sleep challenges. Specifically, self-soothing behavior has been linked with the infant's ability to fall asleep at bedtime without parental assistance and then later return to sleep following

nighttime awakenings (Adams et al., 2020; Burnham et al., 2002). In one study, infants who exhibited higher levels of cuddliness on the IBQ-R at 6 months predicted more frequent nighttime awakenings accompanied with vocalizations at 12 months (Morales-Muñoz et al., 2020). This finding suggests difficulty with self-soothing and a greater need for comfort from the caregiver in order to return to sleep. Thus, the ability to self-regulate states of arousal may be key to developing optimal sleep-wake patterns in infancy.

The link between surgency and sleep challenges is less understood with some evidence suggesting that higher surgency is related to improved sleep while other researchers found the opposite (Jian & Teti, 2016). For example, infants who are highly social and demonstrate more approach behaviors have been documented to sleep longer at night than infants who exhibit negative mood and social withdrawal (Spruyt et al., 2007). In contrast, other researchers found that infants with lower surgency experienced greater sleep quality as a result of being better able to sleep alone (Morales-Muñoz et al., 2020). Additional research is needed to explore fine- grained aspects of surgency and their role in shaping infant sleep patterns.

Not all researchers, however, found evidence to support this claim. Instead of finding robust relationships between temperament and infant sleep behaviors, other researchers discovered weak or negligible associations (DeLeon & Karraker, 2007; Scher, 1998). It should be noted that this discrepancy may be the result of issues related to assessing infant temperament rather than a true insignificant association with sleep challenges. Several researchers have noted that laboratory observations, not parental report, may be more reliable in predicting sleep patterns from infant temperament (Morrell & Steele, 2003; Scher, 1998). For example, parental perceptions of infant characteristics like rhythmicity and positive mood

may not be consistent with behavioral observations of temperament (Hane et al., 2006; Scher, 1998) and instead are influenced by parental mental health factors (Gordo et al., 2018). Thus, it is possible that parental perceptions of their child's temperament mask the true relationship between sleep patterns and temperament in infancy.

As described above, there are numerous examples of associations between infant sleep patterns and temperament. The mechanisms underlying these associations, however, remain unclear and continue to elude experts. Although both temperament and sleep-wake cycle development are rooted in neurological processes, it is difficult to disentangle how these systems overlap in the developing brain. Variance in temperament, for example, is thought to arise from differences in hypothalamic–pituitary–adrenal (HPA) axis development and cortisol reactivity (Bajgarova & Bajgar, 2020) as well as vagal tone (Sullivan, 2016) and other cardiovascular activity (Torowicz et al., 2010). Meanwhile, sleep is regulated by melatonin synthesis and other biological processes centered in the suprachiasmatic nucleus in the hypothalamus (Pack et al., 2015; Pinato et al., 2019). Nevertheless, there is some overlap between these systems as the both HPA axis and sleep-wake cycle development occur in parallel during the first year of life, are regulated by circadian rhythms, and are disrupted by early life adversity (Tuladhar et al., 2021). Though the exact mechanisms have yet to be discovered, this concurrent development points to the possibility of a relationship between infant sleep patterns and temperament.

It is important to note that temporary sleep challenges are commonly reported by parents and may not be cause for much concern (Mindell et al., 2016). For some infants, however, these sleep challenges persist for much longer than expected and may indicate atypical neurodevelopment (Williamson et al., 2020). Although the relationship between sleep

problems and temperament profiles among neurotypical infants and toddlers have recently garnered interest, this line of research has been underexplored in neurodiverse samples. In particular, this question remains underexplored in infant samples at elevated likelihood (EL) of later receiving a diagnosis for autism spectrum disorder (ASD). This paucity of research is especially apparent when considering how different aspects of temperament are related to persistent sleep challenges during the first year of life. Although some have found evidence to suggest that the relationship between difficult temperament and sleep challenges is consistent between 6 and 12 months of age, data is limited prior to this age.

1.3 INFANT SIBLIBGS OF AUTISTIC CHILDREN

Autism Spectrum Disorder (ASD) has puzzled researchers and clinicians since it was first identified by Leo Kanner in 1943. Affecting 1 in 44 children in the United States, ASD is characterized by impaired social-communicative skills and restricted or repetitive interests and behaviors (Maenner et al., 2021). Autism is also unique in its heterogeneity as the diagnostic criteria encompass a wide-ranging diversity of clinical profiles (5th ed.; DSM-5; American Psychiatric Association, 2013). For example, approximately 35% of people with autism are classified as having an intellectual disability (Maenner et al., 2021) while many pursue higher education, maintain a steady job, and raise a family. The complex heterogeneity of ASD presents an exciting challenge for researchers to understand the etiology and neurodevelopmental mechanisms present in this disorder. Although a reliable diagnosis can be made before 24 months of age (Barbaro & Dissanayake, 2017; Ozonoff et al., 2015; Wu et al., 2021), the average age of diagnosis is not until 4 years old (Maenner et al., 2021). This delay has significant clinical implications as age of diagnosis has been linked to success of early intervention,

such that optimal outcomes are most commonly observed in children who begin services by the age of two years (Fein et al., 2013; Landa, 2018; Tanner & Dounavi, 2020).

As characteristic features of ASD (e.g., socio-communicative challenges and restrictive or repetitive behaviors) are typically unclear until at least 18 months of age (Tanner & Dounavi, 2020; Zwaigenbaum et al., 2021), many researchers have begun investigating the emergence of autistic traits in prospective longitudinal studies with infant siblings of autistic children. Due to the high genetic heritability of ASD, the likelihood of these infants developing ASD is estimated to be between 11.3% and 18.7% (Ozonoff et al., 2014; Xie et al., 2016) as compared to less than 3% percent of the general population (Maenner et al., 2021). Furthermore, siblings often present with subclinical autistic traits, such as delays in receptive language at 14 months on the Mullen Scales of Early Learning (MSEL, Mullen, 1995; Hudry et al., 2013) and less orientation to name at 14 months the Autism Observation Scale for Infants (AOSI, Bryson et al., 2007; Gammer et al., 2015). Thus, the use of infant siblings not only allows for better chance of detecting early traits in participants before they are diagnosed, but also allows for the identification of possible endophenotypes.

For the purposes of this study, we will focus on atypical patterns of sleep and temperament as two early indicators of neurodivergent development as described in further detail below.

1.4 TEMPERAMENT AMONG INFANT SIBLINGS OF AUTISTIC SIBLINGS

Although minimal research has been conducted to investigate temperamental profiles among EL typically developing infants, substantial research has been completed

to identify early temperamental features among EL infants and toddlers later diagnosed with ASD. Most notably, pre-diagnosed infants and autistic toddlers have been reported to exhibit reduced surgency, increased negative affect, and lowered regulatory capacity (Clifford et al., 2012; Macari et al., 2017; Paterson et al., 2019; Wall et al., 2019). These temperamental differences are described in further detail below.

To begin, several differences in surgency have been observed among infants at an elevated likelihood of developing ASD. Among infants with an older autistic sibling who later develop ASD themselves, for example, researchers have observed increased perceptual sensitivity (Clifford et al., 2012), reduced smiling (Paterson et al., 2019), and less vocal reactivity (Paterson et al., 2019) on the IBQ-R in the first year of life. These differences are especially noteworthy as they may serve as early indicators of sensory sensitivity (Macari et al., 2017), social competency (Dollar & Stifter, 2012; Garon et al., 2008), and language delay (Paterson et al., 2019). Similarly, others have found that EL infants who later received a diagnosis demonstrated lower activity levels in the first year on the Carey Temperament Scales (Carey & McDevitt, 1995; del Rosario et al., 2013) and on the IBQ (Zwaigenbaum et al., 2005) than typically developing EL infants and controls. In contrast, del Rosario et al. (2013) found that pre-diagnosed 6-month-old infants demonstrated greater approach behaviors on the Carey Temperament Scales than typically developing controls. Although lower levels of surgency are typically associated with future autistic traits, these increased approach behaviors may reflect less inhibition towards engaging non-social objects rather than greater social motivation (del Rosario et al., 2013). Such findings may present additional clues to differing patterns of temperamental development among infants who have an older sibling with autism and

may help to distinguish those who go on to receive an ASD diagnosis and those without a clinical diagnosis.

Greater negative affectivity in infancy has also repeatedly been found to be predictive of ASD outcomes in early childhood among elevated likelihood samples (Clifford et al., 2012; Garon et al., 2008; Wall et al., 2019). Specifically, parents of pre-diagnosed infants have reported increased sadness (Clifford et al., 2012) and more intense and frequent distress reactions (Zwaigenbaum et al., 2005) at 12 months on the IBQ-R and IBQ, respectively. Furthermore, greater incidence of negative emotions among infants with an autistic sibling have been observed at 8 and 14 months on the IBQ-R and at 24 months on the Early Childhood Behavior Questionnaire (ECBQ; Putnam et al., 2006), regardless of future autism diagnosis (Pijl et al., 2019). In this sample, the severity of negative affect existed on a linear gradient based on future functioning, such that those who were later diagnosed with ASD demonstrated greater levels of negative affectivity than EL typically developing infants while LL infants demonstrated the lowest levels of negative affectivity. Similar findings were also observed by Garon et al. (2015), such that infants in the elevated likelihood (EL) group demonstrated higher levels of fear and anger at 12 months on the IBQ and at 24 months on the Toddler Behavior Assessment Questionnaire – Revised (TBAQ-R; Goldsmith, 1996; Rothbart et al., 2003) than those in the low likelihood (LL) group, regardless of diagnosis. Thus, it is implied that greater negative affectivity is often observed among infant siblings of autistic children and is positively associated with future autistic trait severity.

Lastly, reduced regulatory capacity in infancy has been associated with future autistic traits in EL samples. Specifically, Garon et al. (2015) found that EL siblings

(regardless of diagnosis) demonstrated greater difficulty in regulating their emotions, attention, and behaviors than LL infants at 25 months on the TBAQ-R. In addition, diminished regulatory capacity also mediated the association between positive affect at 12 months and later autistic traits on the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000) and Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994) at 36 months in this sample. These findings were later replicated and extended by Pijl et al. (2019) who found that reduced effortful control was observed in the EL group, irrespective of diagnosis, at 14 months on the IBQ-R and at 24 months on the ECBQ. A linear risk gradient was also identified in this study, such that EL infants who later received a diagnosis displayed the lowest levels of regulatory capacity, followed by typically developing EL infants, and then LL controls.

Furthermore, reduced regulatory capacity in infancy may be predictive of future challenges in attending to and appropriately expressing emotions in early childhood, both of which are skills linked to autism severity and social adaptive functioning (Macari et al., 2017; Paterson et al., 2019). As briefly described in the previous section, the later challenges in effortful control have been linked to ADHD symptoms of impulsivity and hyperactivity (Antshel & Russo, 2019). This finding is particularly noteworthy as 40 to 80% of autistic individuals also meet diagnostic criteria for ADHD (Antshel & Russo, 2019; Joshi et al., 2017; van Steensel et al., 2013). Thus, early difficulty in self-regulating states of arousal is a possible indicator of future outcomes and comorbid conditions in ASD. These findings also have implications for the hallmark sleep problems seen in autism, such that autistic infants experience challenges in self- soothing at bedtime and during nighttime awakenings that may persist beyond the first year of life (Scher &

Cohen, 2015).

1.5 SLEEP PATTERNS AMONG INFANT SIBLINGS OF AUTISTIC CHILDREN

In recent years, there has been an increased interest in understanding the etiology and the elevated prevalence of sleep challenges in ASD. Specifically, between 50 to 80% of children with demonstrate prolonged sleep onset latency, reduced sleep duration, and frequent nocturnal awakenings in comparison to 10 to 30% of their neurotypical peers (Couturier et al., 2005; Humphreys et al., 2014; Krakowiak et al., 2012; Reynolds et al., 2019; Richdale & Schreck, 2009; Souders et al., 2009). Due to the high prevalence of sleep problems in autistic samples, some researchers suggest that ASD and disrupted sleep may result from similar underlying neurodevelopmental mechanisms (Bernier et al., 2014; MacDuffie et al., 2020; Mazzone et al., 2018).

Few studies have examined sleep challenges as a possible endophenotype in siblings of autistic children. In a sample of siblings aged 6 to 12 years, there were no significant differences in sleep profiles (e.g., sleep duration, sleep onset latency, wake after sleep onset) between autistic individuals and their siblings as measured through sleep-wake diaries (Naeem et al., 2021). In addition, both siblings and autistic children had greater risk of nightmares, early insomnia and sleep-talking than low likelihood controls. Similar findings were found in a Taiwanese sample of siblings aged 4 to 13 years on modified sleep-related items from the Sleep Habit Questionnaire (SHQ, Gau et al., 2004; Chou et al., 2012).

Among infants later diagnosed with ASD and very young autistic children, the support for early sleep differences have been mixed. For example, MacDuffie and

colleagues (2020) found that infants who were later diagnosed with ASD demonstrated greater challenges with falling asleep at 6 and 12 months on an internally developed Infant Sleep Onset Problems scale with items derived from the IBQ-R. In contrast, Nguyen et al. (2018) failed to identify significant associations between infant sleep onset latency and future autistic traits. Nguyen et al. (2018), however, did find significant predictive associations between frequency of nighttime awakenings at 12 months of age and higher scores on the Modified Checklist for Autism in Toddlers (M- CHAT) at 24 months of age. Additionally, Humphreys et al. (2014) found that pre-diagnosed 30 month old children spent significantly less time asleep after bedtime than controls, but did not observe this effect at 6 months or 18 months of age. As this work has mainly been focused on childhood, questions remain about sleep challenges in young infants at elevated likelihood of developing ASD.

1.6 INFANTS BORN PRE-TERM

It is well-documented that infants born pre-term (PT) have an increased likelihood of atypical neurodevelopment (Pierrat et al., 2017; Sharp et al., 2018). For example, approximately 7% later develop ASD (Agrawal et al., 2018; C. Wang et al., 2017) as well as being at a significantly greater risk of language delay (Nguyen et al., 2018; van Noort-van der Spek et al., 2012) and future social relationship difficulties (Mendonça et al., 2019; Ni et al., 2021; Reyes et al., 2019). Although these trends are most often seen among infants born extremely (born <28 weeks) or very (born 28 to 32 weeks) preterm, emerging evidence suggests an elevated risk of developmental disability is observable in infants born moderate (born 32 to < 34 weeks) and late (born 34 to <37 weeks) preterm

(Mahoney et al., 2013; Smyrni et al., 2021). One hypothesis proposes that inflammatory proteins in maternal, fetal, and placental blood may instigate early labor as well as impede neurodevelopment in infancy (Dammann, 2014; Favrais et al., 2011; Meldrum et al., 2013). Meanwhile, other findings suggest that cerebellar injury among pre-term birth is more common than previously considered and is linked with the development of ASD (Limperopoulos, 2010). Although additional research is needed to confirm the mechanisms of ASD in preterm infants, there is likely no single link between autism and preterm birth.

1.7 TEMPERAMENT AMONG INFANTS BORN PRE-TERM

The evidence of atypical temperament among pre-term infants is much more mixed than what is reported in pre-diagnosed autistic infants. For example, Cosentino-Rocha et al. (2014) found that PT infants tend to exhibit increased high-intensity pleasure and elevated perceptual sensitivity at 18 to 36 months of age. Additionally, a recent neuroimaging study on infants born very pre-term found that neonatal white matter abnormalities predicted blunted vocal reactivity and less high-intensity pleasure while neonatal gray matter abnormalities predicted lowered cuddliness and reduced high-intensity pleasure at 3 months of age on the IBQ-R (Tamm et al., 2020). For infants who experienced significant neonatal distress, a link has also been found between medical challenges in the NICU and later parent-reported negative affectivity at 24 months on the ECBQ (Voigt et al., 2013). It should be noted that this effect was buffered by low parental stress, such that infants who spent time in the NICU expressed less negative affectivity if they had parents who were less distressed than other parents of medically

vulnerable pre-term infants.

It is important to note that these investigations were performed on very preterm infants who are at disproportionately elevated risk of atypical development and disability (Pérez-Pereira et al., 2016). Other studies on healthy pre-term infants only found significant differences in activity level while all other areas of temperament matched with full-term controls at 6 and 12 months of age on the IBQ (Kerestes, 2005). Similarly, healthy PT infants aged 6 to 9 months did not demonstrate less positive affect or more negative affect than full-term controls during the still-face paradigm (Montirosso et al., 2010). This inconsistent evidence suggests that affectivity may not directly be impacted by pre-maturity. Instead, the relationship between preterm birth and temperament may be mediated by contextual conditions such as neonatal distress in the NICU or parental reactivity (Voigt et al., 2013). Additional research is needed to clarify the role of gestational age at birth on temperamental differences among healthy pre-term infants and those born very prematurely.

1.8 SLEEP PATTERNS AMONG INFANTS BORN PRE-TERM

Compared to infants born at term, levels of melatonin production and excretion are significantly reduced in preterm infants. While full-term infants typically show a steady increase in melatonin metabolites over the first 3 months of life, this increase is delayed until 8 to 9 months of corrected age among infants born 24 to 34 weeks premature (Biran et al., 2019). Researchers suggest that both environmental factors, such as the constant bright light exposure in the NICU (Hazelhoff et al., 2021) and premature physiology, may contribute to atypical development of brain regions responsible for

building and maintaining circadian rhythmicity in pre-term neonates (Biran et al., 2019). As a result, preterm infants often demonstrate more difficulty staying asleep through the night and maintaining wakefulness during the day as compared to their full-term peers at the same chronological age (Biran et al., 2019; Hazelhoff et al., 2021). From these findings, it is clear that although the exact mechanism may not yet be fully understood, lowered melatonin synthesis in vulnerable populations has far-reaching implications for neurodevelopment.

1.9 THE CURRENT STUDY AND STUDY AIMS

Taken all together, evidence suggests that variance in both infant temperament and sleep is rooted in biological underpinnings and is predictive of clinical outcomes. Although this understanding of sleep challenges, temperament profiles, and the relationship between these variables is decently understood in neurotypical samples, this line of questioning has not been sufficiently applied to infants at risk for developing ASD. This lack of research is especially concerning considering the lifelong concerns of insomnia in ASD, the heightened incidence of internalizing and externalizing psychopathology in autistic adolescents and adults, and the strong associations of infant temperament with future internalizing and externalizing psychopathology in childhood, adolescence, and adulthood. Furthermore, very few of these studies approach sleep challenges and differences in temperament profiles as subtle indicators of autism in the first year of life. Therefore, it is critical to refine our understanding of early autism symptomology and detect risk factors before the emergence of hallmark ASD features.

To address these gaps in the literature, the proposed study will use parent report in a prospective longitudinal design to examine the relationship between early sleep difficulties and temperament among infants with an elevated likelihood (EL) of developing ASD by being born prematurely (EL-PT) or having an older sibling diagnosed with ASD (EL-ASIB). Sleep and temperament in EL infants will be compared to those of infants at low likelihood (LL) of developing ASD, or participants who were born full-term and do not have a familial history of ASD. Primary aims and hypotheses of the study are described below.

AIM 1: Determine how trajectories of sleep challenges differ among infants in the EL-ASIB, EL-PT, and LL groups between 3 months and 12 months of age.

Hypothesis 1: Likelihood status will affect sleep challenge severity over the first year of life, such that sleep challenge scores will be higher in both EL groups than in the LL group across all timepoints.

AIM 2: Examine the relationship of infant sleep with surgency and regulatory capacity across likelihood groups between 3 months and 12 months of age.

Hypothesis 1: Infants with lower regulatory capacity scores will demonstrate more sleep challenges than infants with higher regulatory capacity scores across the study period, regardless of likelihood status.

Hypothesis 2: Sleep challenge scores will not differ between infants with higher and lower levels of surgency across the study period, regardless of likelihood status.

Table 1.1 Domains and Their Respective Subscales of the IBQ-R

SURGENCY DOMAIN	
Approach	Anticipation and swift approach towards enjoyable stimuli
Activity Level	Squirming, movement of limbs
Smiling and Laughter	Expressions of joy during routine activities and playtime
Vocal Reactivity	Amount and quality of vocalizations in response to environment and/or caregiver
Perceptual Sensitivity	Ability to detect low-intensity stimuli in surroundings
High Intensity Pleasure	Enjoyment derived from intense and complex external stimuli
NEGATIVE AFFECTIVITY DOMAIN	
Sadness	Despondency in response to disappointment or physical state
Distress to Limitations	Fussiness resulting from confinement, inability to accomplish a chosen action, or general activities
Fear	Startle response to sudden changes in the environment
Falling Reactivity/Rate of Recovery from Distress	Time needed to recover from peak arousal; ability to fall asleep with ease
REGULATORY CAPACITY DOMAIN	
Duration of Orienting	Level of focus and interaction to a specific object
Low Intensity Pleasure	Enjoyment derived from mild and simple external stimuli
Cuddliness	Expressions of pleasure and molding to body while being held
Soothability	Ability to recover from distress when caregiver attempts to soothe infant

CHAPTER 2

METHODS

2.1 PROCEDURE

The study used parent report in a prospective longitudinal design to examine the relationship between early sleep difficulties and temperament among infants with an elevated likelihood (EL) of developing ASD and lower likelihood (LL) of developing ASD. At 3, 4, 6, 9 and 12 months, caregivers will complete the Short Form of the IBQ-R. Demographic information will be collected at the start of the study. Adjusted age was used instead of chronological age for all participants who were born prematurely.

2.2 PARTICIPANTS

Participants (n = 84) are currently enrolled in a prospective longitudinal study on early autism traits. Infants who were born prematurely (EL-PT, n = 24) and infants with an older sibling diagnosed with ASD (EL-ASIB, n = 32) are classified into the EL group. All other infants with neurotypical older sibling(s) and who were born full-term were placed in the LL group (n = 28). Demographic information of gender, race, ethnicity, annual income, and maternal education were collected and are presented below (see Table 2.1).

2.3 MEASURES

Temperament

The Infant Behavior Questionnaire, Revised – Short Form (IBQ-R; Putnam et al., 2014) is a 91-item parent-report questionnaire and is among the most widely used measures of infant temperament. The IBQ-R is divided into three broad domains and their subscales, specifically 1) Surgency, including the subscales of Approach, Vocal Reactivity, High Intensity Pleasure, Smiling and Laughter, Activity Level, and Perceptual Sensitivity; 2) Negative Affectivity, including the subscales of Sadness, Distress to Limitations, Fear, and Falling Reactivity/Rate of Recovery from Distress; 3) Regulatory Capacity, including the subscales of Low Intensity Pleasure, Cuddliness, Duration of Orienting, and Soothability (see Table 1.1 for more detailed description of each subscale). Negative affectivity domain was excluded in analysis due to significant overlap of items included in the sleep challenges subscale (see Table 2.2 for list of items included in the sleep challenges subscale).

Sleep Challenges

To understand how sleep difficulties are related to temperament, a new scale of Sleep Challenges was created with items related to sleep (see Table 2.2) as had previously been done with the Very Short Form (Macduffie et al., 2020). In this previous study, the convergent validity of their subscale evaluated by comparing the score of the selected IBQ-R items with scores of the parent-report Brief Infant Sleep Questionnaire (BISQ; Sadeh, 2004)) between the ages of 6 and 12 months. The IBQ-R based score was significantly associated with sleep latency on the BISQ ($r(65) = .44$, $p < .01$), but not average duration of nocturnal wakefulness ($r(65) = 0.04$, $p = .72$). Cronbach's alpha was

used to determine the internal consistency of the items selected from the IBQ-R and was found to be acceptable at both time points of 6 months (α = .76, 95% CI [0.74, 0.78]) and 12 months (α = .76, 95% CI [.74, .78]). These findings indicate that sleep-related items on the IBQ-R likely measure challenges with falling asleep rather than difficulty staying asleep, though additional validation is needed to confirm this hypothesis.

2.4 DATA ANALYSIS

All analyses utilized SAS On-Demand for Academics (SAS Institute, Inc., Cary, NC). Datasets were cleaned by inspecting impossible values and other data entry errors. To determine the sample size needed for a medium effect size (f^2 = .15), a power analysis was conducted using G*Power 3.1 (Faul et al., 2009). To obtain a power of .80 and a medium effect size for a linear mixed regression model with two predictors, a minimum sample size of 68 participants are required to detect significance ($F(2, 65) = 3.14$). As the sample size of the present study includes 84 participants, concerns of insufficient power were minimalized. Alpha was set at .05.

Linear mixed models were used to examine how sleep challenges change across the first year of life differ between likelihood groups. In these models, the outcome was the sleep challenge score and the predictors included participant group (LL vs. EL-ASIB vs. EL-PT) and age in months (3, 4, 6, 9, and 12 months). In order to examine the relationship between sleep challenges and temperament across the first year of life, linear mixed models were employed. In these models, the outcome was the sleep challenge score and the predictors included the IBQ-R domain score (e.g., Surgency and Regulatory Capacity) and age in months. To further explore these associations, Pearson correlations

between the domain scores of Surgency/Regulatory Capacity and the sleep challenges score were used at 12 months.

Table 2.1 Sample Characteristics by Likelihood Status

	EL-ASIB N = 32	EL-PT N = 24	LL N = 28	Test Statistic*
Sex				p = .26
Female	18 (56.25%)	11 (45.83%)	13 (46.43%)	
Male	14 (43.75%)	13 (54.17%)	15 (53.57%)	
Race				p < .001
White	21 (65.63%)	13 (54.17%)	12 (42.86%)	
Black	6 (18.75%)	5 (20.83%)	9 (32.14%)	
Asian	0 (0.0%)	1 (4.17%)	2 (7.14%)	
More than one race	2 (6.25%)	3 (12.50%)	1 (3.57%)	
Unknown/Not Reported	3 (9.38%)	2 (8.33%)	4 (14.29%)	
Ethnicity				p < .001
Hispanic or Latino	2 (6.25%)	4 (16.67%)	1 (3.57%)	
Not Hispanic or Latino	26 (81.25%)	18 (75.00%)	23 (82.14%)	
Unknown/Not Reported	4 (12.50%)	2 (8.33%)	4 (14.29%)	
Household Income				p = .37
< $40k	8 (25.00%)	4 (16.67%)	3 (10.71%)	
$40k – $80k	4 (12.50%)	7 (29.17%)	11 (39.29%)	
$80k – $125k	11 (34.34%)	6 (25.00%)	9 (32.14%)	
> $125k	6 (18.75%)	5 (20.83%)	4 (14.29%)	
Unknown/Not Reported	3 (9.38%)	2 (8.33%)	1 (3.57%)	
Maternal Education				p = .01
High School Degree	1 (3.13%)	2 (8.33%)	1 (3.57%)	
Trade or Vocational	1 (3.13%)	0 (0.0%)	0 (0.0%)	
Associate or 2 Year Degree	5 (15.63%)	3 (12.50%)	3 (10.71%)	
Courses Towards College	8 (25.00%)	2 (8.33%)	5 (17.86%)	
Bachelor's Degree	10 (31.25%)	3 (12.50%)	6 (21.43%)	
Graduate Degree	5 (15.63%)	12 (50.00%)	11 (39.29%)	
Not Reported	2 (6.25%)	2 (8.33%)	2 (7.14%)	

*calculated through Chi-Square analysis

Table 2.2 IBQ-R Items Included in the Sleep Challenges Score

SUBSCALE	ITEMS INCLUDED
Distress to Limitations	**How often did the baby:** **2.** seem angry (crying and fussing) when you left her/him in the crib? **3R.** seem contented when left in the crib? **4.** cry or fuss before going to sleep for naps? **After sleeping, how often did the baby:** **62.** cry if someone doesn't come within a few minutes?
Falling Reactivity/Rate of Recovery from Distress	**When going to bed at night, how often does your baby:** **36.** fall asleep within 10 minutes? **37R.** have a hard time settling down to sleep? **38.** settle down to sleep easily? **When put down for a nap, how often did your baby:** **63.** settle down quickly?
Sadness	**When it was time for bed or a nap and your baby did not want to go, how often did s/he:** **64.** whimper or sob? **When tired, how often was your baby:** **74.** show distress?

CHAPTER 3

RESULTS

Descriptive statistics are displayed in Table 1. Overall, participant groups differed in race, ethnicity, and maternal education. Specifically, the EL-ASIB group included significantly more participants with lower maternal education and more subjects who identified as White. Additionally, the PT group comprised of more participants who identified as Hispanic or Latino.

3.1 SLEEP CHALLENGES ACROSS ASIB, PT, AND LL INFANTS

A linear mixed model was used to test the main effect of likelihood status (ASIB, PT, LL) and the age (3, 4, 6, 9, and 12 months) on sleep challenges, as well as the interaction between likelihood status and age. Neither the main effect of age (F (1, 56) = 0.07, p = .79) nor main effect of likelihood status (F (2, 72) = 0.45, p = .76) were significant. The interaction between age and likelihood status was also nonsignificant (F (2, 72) = 1.63, p = .20) (see Figure 3.1).

In order to further explore these relationships, model-based estimates of sleep challenges score within each group at each time were examined. These results show statistically significant differences between ASIBs and LL infants at 6 months (t (61) = 2.20, p = .03), 9 months (t (61) = 2.62, p = .01), and 12 months (t (61) = 2.60, p = .01). Significant differences between EL-ASIB and EL-PT infants at 4 months (t (37) = 2.16, p =.04), 6 months (t (37) =2.84 , p <.01), 9 months (t (37) = 3.21, p <.01), and 12 months

(t (37) = 3.05, p < .01) were also observed. No differences at any time point were observed between EL-PT and LL infants.

3.2 THE EFFECT OF TEMPERAMENT ON SLEEP CHALLENGES

The effect of regulatory capacity and surgency on trajectories of sleep challenges over the first year of life were examined using a linear mixed model. When combining all groups, there was no significant main effect of regulatory capacity (F (1, 70) = 0.01, p = .93). The interaction between regulatory capacity and age approached significance (F(1, 70) = 3.04, p = .09) and the main effect of age approached significance (F (1, 57) = 2.96, p = .09) (see Figure 3.2). When using surgency as a predictor instead of regulatory capacity, the main effect of surgency (F (1, 70) = 0.78, p = .38) was nonsignificant, but the main effect of age (F (1, 57) = 5.55, p = .02) and interaction between age and surgency (F (1, 70) = 5.06, p = .03) were significant (see Figure 3.3).

In order to further explore these associations across groups, Pearson correlations between temperament constructs and sleep challenges were calculated at 12 months for each group (see Table 3.1). These results show strong, but nonsignificant correlations between sleep challenges and regulatory capacity for the EL-PT group (r (2) = -.59, p = .41) and moderate, nonsignificant correlations for the EL-ASIB group (r (12) = -.41, p = .14) as well as a weak nonsignificant association for the LL group (r (14) = -.23, p = .39). Associations between sleep challenges and surgency at 12 months were strong, but not statistically significant for EL-ASIBs (r (12) = -.54, p =.05), and weak and nonsignificant for EL-PTs (r (2) = -.11, p = .89) and LLs (r (14) = -.07, p = .80).

Table 3.1 Pearson Coefficients Between Temperament and Sleep Challenges for Each Likelihood Group at 12 months

	Combined Groups (n = 34)	**EL – ASIB** (n = 14)	**EL – PT** (n = 4)	**LL** (n = 16)
Regulatory Capacity	r = -.30¥	r = -.41	r = -.59	r = -.23
Surgency	r = -.37*	r = -.54¥	r = -.11	r = -.07

¥ = p < .10
* = p < .05

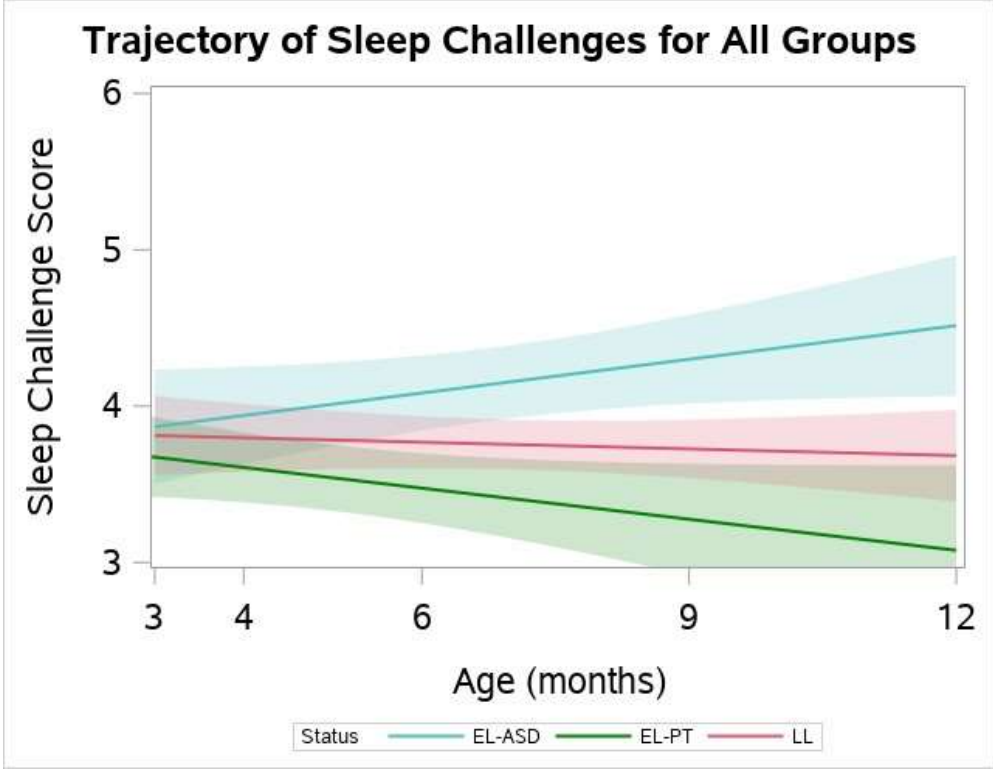

Figure 3.1 Trajectory of Sleep Challenges for All Groups Between 3 Months to 12 Months

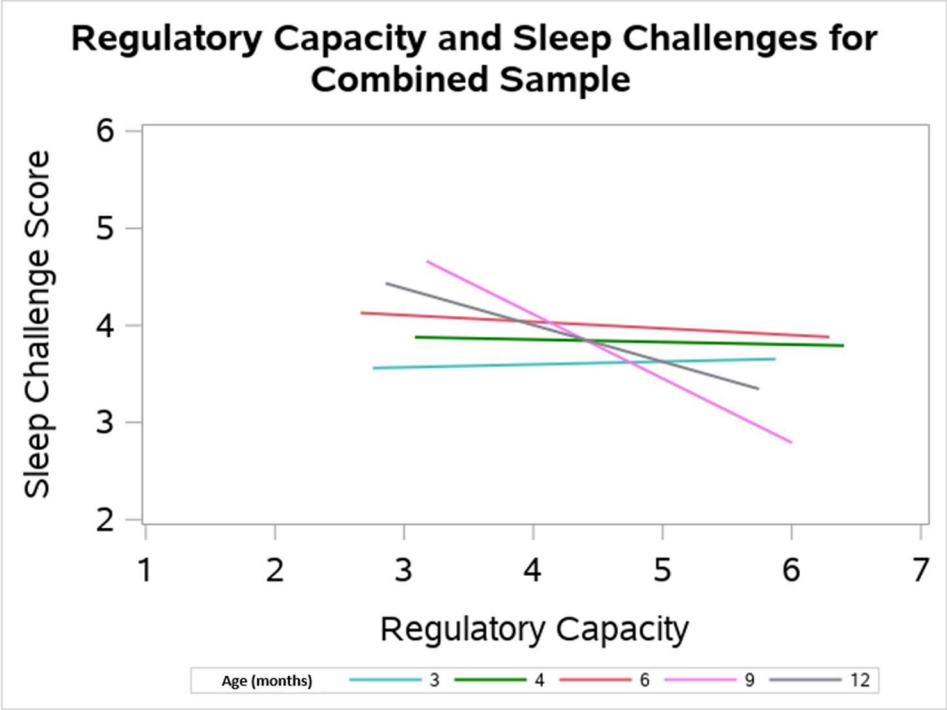

Figure 3.2 Regulatory Capacity and Sleep Challenges for Combined Sample

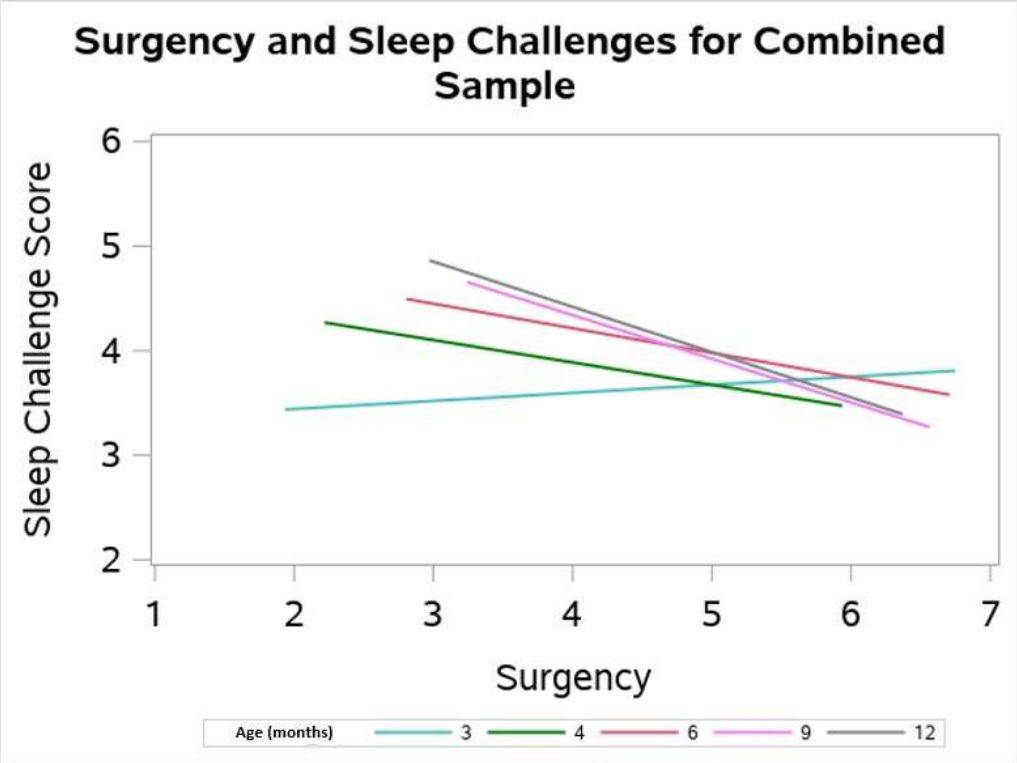

Figure 3.3 Surgency and Sleep Challenges for Combined Sample

CHAPTER 4

DISCUSSION

Results of this study present inconclusive evidence on differing trajectories in sleep challenges across the first year of life for infants with an older autistic sibling, infants born preterm, and low likelihood controls. When examining sleep challenges over time for each of the three groups, neither age, likelihood status, or the interaction between age and likelihood status affected sleep challenge severity in the sample.

Interestingly, between group differences emerged at specific time points through the calculation of least square means, or comparisons of computed means for sleep challenges in each likelihood group as estimated by the linear mixed model. Most notably, participants with an older autistic sibling demonstrated significantly more sleep challenges than controls from 6 months of age and through the end of data collection at 12 months. These findings align with previous research (Chou et al., 2012; Naeem et al., 2021) and support the hypothesis that infants with an autistic sibling demonstrate greater sleep challenges than LL infants.

In addition, participants born preterm demonstrated significantly less sleep challenges from 4 months of age through 12 months than infants in the EL-ASIB group. Meanwhile, the EL-PT group did not demonstrate significantly less sleep challenges than the LL group at any time point. Results of this study do not support the hypothesis that infants born pre-term demonstrate significantly more sleep challenges than the LL group and is contrary to previous findings (Biran et al., 2019; Hazelhoff et al., 2021). The low

scores in the EL-PT group on the sleep challenges subscale may not reflect true between-group differences, but instead point to an insufficient sample size or problems with the sleep challenges subscale in measuring sleep problems in pre-term infants.

In examining the relationship of temperament (e.g., Surgency or Regulatory Capacity) and sleeps challenges, several interesting findings emerged. When accounting for the influence of age, a relationship between sleep challenges and regulatory capacity approached significance, such that greater sleep challenges was associated with decreased regulatory capacity as infants became older. Through post-hoc comparison analysis with Pearson Correlations in each participant group at 12 months, a negative association between regulatory capacity and sleep challenges approached significance in the combined sample, but not in either the LL or EL groups. The relationship between regulatory capacity and sleep challenges partially support Hypothesis 1 in Aim 2 and corresponds with findings from previous studies (Adams et al., 2020; Burnham et al., 2002; Morales-Muñoz et al., 2020).

When the relationship between surgency and sleep challenges were examined, it was revealed that greater surgency was associated with less sleep challenges but only when accounting for the influence of age, such that greater sleep challenges was associated with decreased surgency as infants became older. Upon further inspection, it was revealed that infants with an autistic sibling demonstrated a strong, but nonsignificant, associations with sleep challenges while other associations in the LL groups were negligible. As this relationship between sleep challenges and surgency was observed only in ASIBs, it is possible that elevated surgency may uniquely protect against sleep challenges in infants with an autistic sibling.

Overall, findings from this study may point to the possibility that sleep challenges serve as an early distinction between EL-ASIB samples and other groups (e.g., LL controls and infants born pre-term), but only at specific time points towards the end of the first year of life. Furthermore, the results of this study suggest that surgency may serve as a unique protector against sleep challenges in ASIBS, such that that ASIB infants with greater surgency may not experience as many sleep challenges as ASIBs who demonstrate less surgency. Although infants born pre-term in this sample failed to demonstrate different scores on the sleep challenges subscale in comparison to LL participants or a significant relationship with between sleep challenges and temperament (e.g., Surgency and Regulatory Capacity), it is important to note that nearly all of the pre-term infants in this study were healthy. Meanwhile, most previous studies who found significant differences in temperament and sleep challenges among pre-term infants included samples comprised of infants who were born extremely or very pre-term and experienced significant medical problems (Biran et al., 2019; Dereymaeker et al., 2017; Pérez- Pereira et al., 2016; Werth et al., 2016). Thus, there may have been clearer between-group differences in temperament in this study if the EL-PT group included infants who were born prior to 32 weeks gestational age. Additional research is needed to compare the temperamental profiles and sleep challenges experienced in pre-term infants with and without significant health challenges.

4.1 STRENGTHS AND LIMITATIONS

This study is among the first to compare sleep challenges and its relationship to surgency and regulatory capacity across the first year of life in infants with an older autistic sibling,

infants born pre-term, and low likelihood controls. Although there is a large literature base dedicated to exploring temperament of infants at an elevated likelihood for ASD, the majority of this research begins after six months of age. Furthermore, much of the research on sleep challenges in infancy are focused outside of the context of ASD likelihood and instead centers around either typically developing infants or infants born pre-term (Sadeh et al., 2015). This study is therefore uniquely valuable in determining early differences in sleep challenges and its relationship to temperament across the first year of life among these three groups. Additionally, by answering these research questions in a prospective longitudinal design, the risk of recall bias associated with retrospective analysis is minimalized.

Although this study has numerous strengths, there are several limitations that must be addressed. Most notably, the results of this study relied on a measure of sleep challenges that has not been validated. While MacDuffie et al. (2020) created a similarly sleep challenges scale from the IBQ-R very short form (Putnam et al., 2014) and found strong correspondence with BISQ scores in their sample, more work is needed to validate the sleep challenges subscale used in this study. In addition, temperament was measured through a parent-report measure and may have differed from behavioral measures of temperament conducted by a trained clinician. Previous studies have identified possible influences that reduce the reliability of parent-report measures of infant temperament, such as maternal sensitivity to infant development (Tamm et al., 2020), cultural differences in perceptions of typical infant behaviors (Costa & Figueiredo, 2018), and parental insomnia (Quental et al., 2013). Although the IBQ-R offers valuable information on how infants engage with their environment on a day-to-day basis, such parent-report

measures may not be sensitive enough to detect low-level differences between the EL-PT, EL-ASIB, and LL groups (Wall et al., 2019).

Furthermore, it is unclear how generalizable the results of this study are to affected infants who do not have an older sibling with ASD. Specifically, it is unclear if the sleep challenges observed in this sample are the result of shared genetic predisposition for sleep challenges or if having an older autistic sibling with sleep challenges impacts the parents' perception of their infants sleep challenges. In addition, the PT infants in this sample were born moderate-to-late pre-term whereas much of previous research identified differences in infants born very or extremely pre-term (Dereymaeker et al., 2017; Pérez-Pereira et al., 2016; Werth et al., 2016). As a result, the role of gestational age on temperament and sleep challenges in this sample cannot be compared to previous studies investigating PT infants. Additional limitations include the failure to account for infant sleep context (e.g., co-sleeping) and parenting practices (e.g., using a bottle to soothe the infant to sleep). Thus, it remains unclear if sleep challenges observed in this sample were the result of environmental factors or biological sleep differences.

4.2 FUTURE DIRECTIONS

Future research should extend these findings by investigating the role of early sleep challenges in predicting future autistic traits. It should be noted that this manuscript used data from an ongoing study in which all participants are scheduled to undergo a gold-standard evaluation for ASD at 24 months of age. Once this outcome data is collected, analyses will be completed to determine if early sleep challenges and

temperamental differences are possible predictors of future diagnostic status.

In addition, it is imperative that investigators identify the differential influence of specific aspects of temperament on sleep challenges, such as examining subscale scores in addition to broader domain scores of surgency and regulatory capacity. As surgency emerged as a possible protective factor against sleep challenges in ASIBS, special attention should be made to identifying which aspects of surgency are driving this relationship. Similarly, additional work is needed to identify specific sleep challenges observed in EL infants and how each of these problems is influenced by temperament. By examining subscales within surgency and regulatory capacity domains and identifying specific sleep challenges, researchers will be better able to describe the mechanisms underlying the possible relationship between temperament and sleep challenges in infancy.

Lastly, additional research is needed to develop interventions designed to target sleep challenges in infancy, especially among elevated likelihood groups. Although many randomized control trials have been conducted to test the efficacy of behavioral and educational intervention programs to address sleep disturbance in early childhood, very few studies have investigated the use of these interventions during the first six months of life (Field, 2017). Thus, it is not only imperative that additional research is conducted to investigate early sleep challenges among infants who are more likely to experience neurodivergence, but also develop interventions to be used throughout the first year of life

CHAPTER 5

CONCLUSION

As far as is known, this investigation is among the first studies to examine sleep challenges and its relationship to infant temperament in the first year of life among elevated likelihood samples. The results of this study suggest ASIB infants may experience greater sleep challenges towards the end of their first year, a possible relationship between regulatory capacity/surgency and sleep challenges, and that greater surgency in ASIBs may uniquely protect against sleep challenges in infancy. If replicated, these findings could provide new insights into the cascading effects of sleep challenges in the development of ASD and the role of temperament in this effect. Further exploration is needed to examine the influence of specific aspects of temperament on infant sleep challenges, characterize the types of early sleep challenges commonly experienced by EL infants, and create tailored interventions for these infants.

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