Reduced sleep pressure in young children with autism

Ayelet Arazi (MSc) [1,2,*], Gal Meiri (MD) [3,4,*], Dor Danan (BSc) [5,4], Analya Michaelovski (MD) [6,4], Hagit Flusser (MD) [6,4], Idan Menashe (PhD) [7,4], Ariel Tarasiuk (PhD) [8,9,4], Ilan Dinstein (PhD) [10,1,4]

[1] Department of Brain and Cognitive sciences, Ben Gurion University of the Negev, Beer-Sheva, Israel

[2] Zlotowski Center for Neuroscience, Ben Gurion University of the Negev, Beer-Sheva, Israel

[3] Pre-School Psychiatry Unit, Soroka Medical Center, Beer-Sheva, Israel

[4] National Autism Research Center of Israel, Ben Gurion University of the Negev, Beer-Sheva, Israel

[5] Mental Health Center, Anxiety and Stress Research Unit, Ben Gurion University of the Negev, Beer-Sheva, Israel

[6] Zusman Child Development Center, Soroka University Medical Center, Beer-Sheva, Israel

[7] Department of Public Health, Ben Gurion University of the Negev, Beer-Sheva, Israel

[8] Sleep-Wake Disorders Unit, Soroka Medical Center, Beer-Sheva, Israel

[9] Department of Physiology and Cell Biology, Ben Gurion University of the Negev, Beer-Sheva, Israel

[10] Department of Psychology, Ben Gurion University of the Negev, Beer-Sheva, Israel

* Equal contribution as first authors

Corresponding author: Ayelet Arazi, araziay@post.bgu.ac.il

Key points

Question: Are sleep disturbances in some children with autism due to disrupted sleep homeostasis?

Findings: In this case-control study, children with Autism Spectrum Disorder (ASD) exhibited significantly weaker slow-wave-activity power and less slow-wave-sleep, indicating a reduced pressure to sleep. The reduction in sleep pressure was significantly correlated with the severity of individual children's sleep disturbances as observed in the sleep lab and as reported by parents at home.

Meaning: These findings demonstrate that disrupted sleep homeostasis manifested in reduced sleep pressure is common in children with ASD and likely to exacerbate sleep disturbances.

Abstract

Importance: Sleep disturbances and insomnia are highly prevalent in children with Autism Spectrum Disorder (ASD). Sleep homeostasis, a fundamental mechanism of sleep regulation that generates pressure to sleep as a function of wakefulness, has not been studied in children with ASD. It is not clear whether abnormalities in sleep homeostasis contribute to sleep disturbances in children with ASD.

Objective: To determine whether slow wave activity (SWA), a potent measure of homeostatic sleep pressure, is impaired in children with ASD and associated with the severity of reported sleep disturbances.

Design: Case-control comparison of overnight electroencephalogram (EEG) recordings that were performed during Polysomnography (PSG) evaluations between 2015 and 2018.

Setting: Children with autism were deeply phenotyped at the National Autism Research Center of Israel. PSG was performed at a neighboring regional sleep disorders unit that accepts children with primary care referrals.

Participants: Final analyses were performed with PSGs from 29 children with ASD, 8 females, mean age 4.6 years old (range 1.9 – 7.8), and 23 typically developing children, 8 females, mean age 5.3 years old (range 3.5-8.9).

Exposure: A single overnight PSG evaluation.

Main outcome measures: SWA power, SWA slope, and sleep architecture.

Results: Children with ASD exhibited significantly weaker SWA power, shallower SWA slopes, and a decreased proportion of slow wave sleep in comparison to controls. This difference was largest during the first two hours following sleep onset and decreased gradually during sleep. Furthermore, SWA

power of children with ASD was significantly correlated with the time of sleep onset and with parental report of latency to sleep at home.

Conclusions and relevance: These results reveal that children with ASD exhibit reduced sleep pressure, which is a dysregulation of sleep homeostasis. The extent of dysregulation in individual children is apparent in the amplitude of their SWA power, which is indicative of the severity of their sleep disturbances. These findings motivate clinical trials with specific interventions that increase homeostatic sleep pressure.

Introduction

Autism Spectrum Disorders (ASD) are a family of heterogeneous neurodevelopmental disorders characterized by impairments in social interaction and by restricted interests and repetitive behaviors [1]. Sleep disturbances appear in 40-80% of children with ASD [2–5], as compared with 20-40% of typically developing children [6,7]. Symptoms include prolonged sleep latency, shorter sleep duration, and increased wake periods during the night, as reported by both subjective parental questionnaires and actigraphy measures [8–14]. Poor sleep in children with ASD is associated with increased sensory sensitivities [15–18] and increased aberrant behaviors [18–21], which impair the quality of life of affected families [14]. PSG studies have corroborated the existence of sleep disturbances in children with ASD [22–28], but have yielded mixed results regarding potential abnormalities in sleep architecture. While some have reported that children with ASD exhibit decreased slow wave sleep (SWS, stage N3) [22–25] or rapid eye movement (REM) [11,22,28] durations, others have not [23,26–28].

It has been proposed that the sleep disturbances of children with ASD are caused by an interaction of several behavioral and physiological factors including anxiety [21], poor sleep hygiene [29], sensory hyper-sensitivities [15], abnormalities with the melatonin system (i.e., circadian rhythm) [30], and obstructive sleep apnea (OSA) [31]. To date, the potential contribution of disrupted sleep homeostasis to the emergence of insomnia in children with ASD has not been examined.

Sleep homeostasis is a critical mechanism of sleep regulation that increases the pressure to sleep as a function of time spent awake [32,33]. Larger sleep pressure generates deeper slow wave sleep, which can be quantified by the power of slow wave activity (SWA, EEG power in the Delta band, 0.75-4 Hz) [34]. Deep sleep is essential for proper cognitive function [35], stabilizing synaptic plasticity [36,37], and enabling learning and memory consolidation [38]. To our knowledge, only three studies to date have quantified the amplitude of SWA in ASD and all were performed with high-functioning adolescents and adults [39–41]. Two

of these studies reported significantly weaker SWA in the ASD group [39,40], a difference that was particularly large during the first 2-3 hours of sleep.

To evaluate potential impairments in the SWA of children with ASD, we examined PSG recordings from 29 children with ASD and 23 typically developing controls. We quantified SWA power, SWA slope, and "traditional" sleep architecture in 1-hour segments from sleep onset, and assessed whether significant differences were apparent across groups during specific segments of sleep. In addition, we examined whether individual differences in SWA could explain differences in the severity of sleep disturbances as observed in the sleep laboratory and as reported by the parents at home.

Methods

Subjects

We recruited 34 children with ASD (9 females), mean age 4.6 years old (range 1.9-7.8), from the National Autism Research Center of Israel [42], which is part of Ben Gurion University of the Negev and located inside Soroka University Medical Center (SUMC). Approximately 70% of ASD cases in the south of Israel are diagnosed at the autism center and participating children with ASD were randomly recruited from this clinical population.

All children completed a PSG evaluation at the Sleep-Wake Disorder Unit of SUMC. We excluded five children with ASD from the final analysis due to poor PSG quality (n=4) or evidence of obstructive sleep apnea (OSA, n=1). All children with ASD were diagnosed by a physician according to DSM-5 [1] criteria, and in 25 of the 29 analyzed cases, the diagnosis was confirmed using the autism diagnostic observation schedule (ADOS) [43]. Mean ADOS scores were: Social Affect 14.9±5, Restricted and Repetitive Behaviors 4.3±1.7 and total score 19.2±6. Parents of all children with ASD signed an informed consent form and were reimbursed for their participation. Parents of 26 children with ASD scored their child's sleep behavior at home using the Hebrew version of the child sleep habit questionnaire (CSHQ) [44,45].

The control group included 23 children who were identified retrospectively from children who were referred to the same sleep lab for a PSG evaluation, but did not exhibit symptoms of any sleep disorder. All of the control children were screened negative for neurological, psychiatric, or developmental disorders, using a detailed clinical history questionnaire that was completed by the parents. The Helsinki committee at SUMC approved this study, which was carried out under the guidelines of the Helsinki declaration.

Polysomnography

All parents were instructed to keep a regular sleep-wake schedule on the day of the PSG evaluation. The PSG study started at 8:30PM and ended at 6:00AM on the following morning. Children were connected to a clinical PSG system (SomniPro 19 PSG, Deymed Diagnostic, Hronov, Czech Republic) by a technician with over 5 years of experience. The sleep technician connected six EEG electrodes, (C3, C4, O1, O2, A1, and A2 according to the international 10-20 system; sampling frequency: 128Hz; resolution: 16 bit), EOG, EMG and ECG electrodes, abdomen and chest effort belts to measure respiratory activity, and an oxygen saturation sensor. In some cases, where the child did not cooperate, this procedure was completed after the child fell asleep. Four children with ASD were being treated with Melatonin, but did not take Melatonin on the day of the exam. Derivations C3/A2 and C4/A1 were used for sleep-stage scoring, which was determined blindly by one of the investigators (AT) according to the American Academy of Sleep Medicine criteria [46]. An Apnea Hypopnea Index (AHI) was calculated as the number of respiratory events resulting in either arousal or oxygen desaturation of >4%, per hour of sleep[47].

EEG analysis

Preprocessing

Data were analyzed offline using MATLAB (*Mathworks Inc. USA*) and the EEGLAB toolbox [48]. EEG data was re-referenced to the bilateral mastoids, filtered using a 0.75Hz FIR high-pass filter (cutoff frequency at -6db: 0.37Hz, transition band width: 0.75Hz) and 20Hz FIR low-pass filter (cutoff frequency at-6db: 22.5, transition band width: 5Hz), and then divided into 30-sec epochs. Epochs with manually identified artifacts such as movement or muscles contractions were removed (mean percentage in ASD group: 18.9%, and in controls: 16.5%).

EEG data analysis

The power spectrum was computed for each 30 sec epoch using the fast Fourier transform algorithm as implemented in MATLAB. Absolute spectral power was computed in a sliding window of 4 sec with an overlap of 2 sec using a hamming window and a frequency resolution of 0.25Hz. Absolute power was then calculated for the Delta (1-4Hz), Theta (4-8Hz), Alpha (8-13Hz) and Beta (13-20Hz) frequency bands.

To compute the slope of SWA we re-filtered the EEG data using a 0.75-4Hz band-pass filter. Slow waves were identified in each epoch as negative peaks, with subsequent zero-crossing, that were separated by 0.25-1 sec. We calculated the slope of each wave as the amplitude of the negative peak divided by time to the closest zero crossing and computed the mean slope in each epoch.

Statistical analysis

Statistical analysis was performed using MATLAB (*Mathworks Inc. USA*). We compared SWA power\slope and sleep architecture using 2-way ANOVA analyses with group as one factor and time (i.e. hour since sleep onset) as a second factor. Additional comparisons across ASD and control groups were performed using two-tailed t-tests with unequal variance. We also computed the effect size for each comparison using Cohen's d. When performing comparisons across groups for each frequency or each 1-hour segment of the night (from sleep onset), we used the false discovery rate (FDR) correction[49] to control for the multiple comparisons problem. The relationship between CSHQ scores and EEG power was assessed using Pearson's correlations. The statistical significance of the correlation coefficients was tested with a randomization test where we shuffled the labels of the subjects before computing the correlation. We performed this procedure 10,000 times to generate a null distribution for each relationship and assessed whether the true correlation coefficient was higher than the 97.5th percentile or lower than the 2.5th percentile of this null distribution (equivalent to p=0.05 in a two-tailed t-test).

Results

Children with ASD spent significantly less time in bed, and their total sleep time was shorter than that of controls (Table 1). Sleep efficiency, percentage of wake after sleep onset (WASO), sleep latency, and arousal index did not differ across groups. The mean apnea-hypopnea index (AHI) was <1 in both groups, demonstrating that none of the participating children had OSA. Note that in ~50% of the ASD cases, children were connected to the PSG apparatus only after sleep onset. As a result, the PSG recordings in these cases began slightly after the children fell asleep. This is a common issue in PSG studies with ASD children, where measures of time in bed, sleep latency, and sleep efficiency are often distorted due to poor cooperation at the initiation of the exam.

Small differences in sleep architecture across groups were found when examining the proportion of sleep stages throughout the entire night. Children with ASD exhibited a significantly higher percentage of N2 sleep ($p=0.03$, Cohen's $d=0.61$; Table 1), and a marginally significant reduction in the percentage of REM sleep ($p=0.06$, Cohen's $d=0.54$). Larger differences across groups were revealed when dividing the sleep period of each child into two equal halves. Children with ASD had a significantly larger percentage of N2 sleep ($p=0.003$, Cohen's $d=0.87$) and lower percentage of N3 sleep ($p=0.001$, Cohen's $d=0.96$) during the first half of the sleep period as well as a lower percentage of REM sleep ($p=0.007$, Cohen's $d=0.79$) during the second half of the sleep period.

	Control (mean ± SD)	ASD (mean ± SD)	P-value
N	23 (8 females)	29 (8 females)	
Age (years)	5.3 ± 1.5	4.6 ± 1.7	0.16
Time in bed (min)	427 ± 40	391 ± 70	**0.02***
Total sleep time (min)	403 ± 38	362 ± 72	**0.03***
Sleep efficiency (%)	94.3 ± 3	92.5 ± 7	0.24
Sleep latency (min)	9.8 ± 8.5	7.5 ± 8.4	0.33
WASO (%)	3.7 ± 2.6	6.9 ± 10.1	0.16
Arousal index (events\h)	10.7 ± 4.4	11.5 ± 3.6	0.44
AHI (events\h)	0.43 ± 0.39	0.39 ± 0.35	0.69
Sleep stage N2 (%) – whole night	52.8 ± 7.3	57.8 ± 8.7	**0.03***
Sleep stage N3 (%) – whole night	29.2 ± 5.2	27.1 ± 9.1	0.33
Sleep stage REM (%) – whole night	17.5 ± 3.9	14.9 ± 5.4	0.06
Sleep stage N2 (%) – first half	40.1 ± 8.8	49.8 ± 12.5	**0.003***
Sleep stage N2 (%) – second half	64.2 ± 10.5	65.8 ± 9.6	0.66
Sleep stage N3 (%) – first half	50.5 ± 10.1	39.4 ± 12.4	**0.001***
Sleep stage N3 (%) – second half	10.1 ± 7.9	15.2 ± 10.6	0.06
Sleep stage REM (%) – first half	8.5 ± 5.6	10.6 ± 5.5	0.18
Sleep stage REM (%) – second half	25.6 ± 8	19.1 ± 8.5	**0.007***

Table 1: Sleep characteristics in children with ASD and controls. WASO: wake after sleep onset, AHI: apnea-hypopnea index. REM: repaid eye-movement. Asterisks: significant difference as assessed by a two-tailed t-test ($p<0.05$).

Differences in Delta power across groups

We focused our analyses of EEG power on occipital electrodes given that SWA at the examined ages is maximal in occipital cortex [50]. Children with ASD exhibited significantly weaker power in the Delta (i.e., SWA) and Beta bands during epochs of N3 sleep (Figure 1D). Spectral power in N2 and REM epochs did not differ significantly across groups (Figure 1B&F). Performing the same analyses with the central electrodes did not reveal any significant differences across groups in any of the sleep stages.

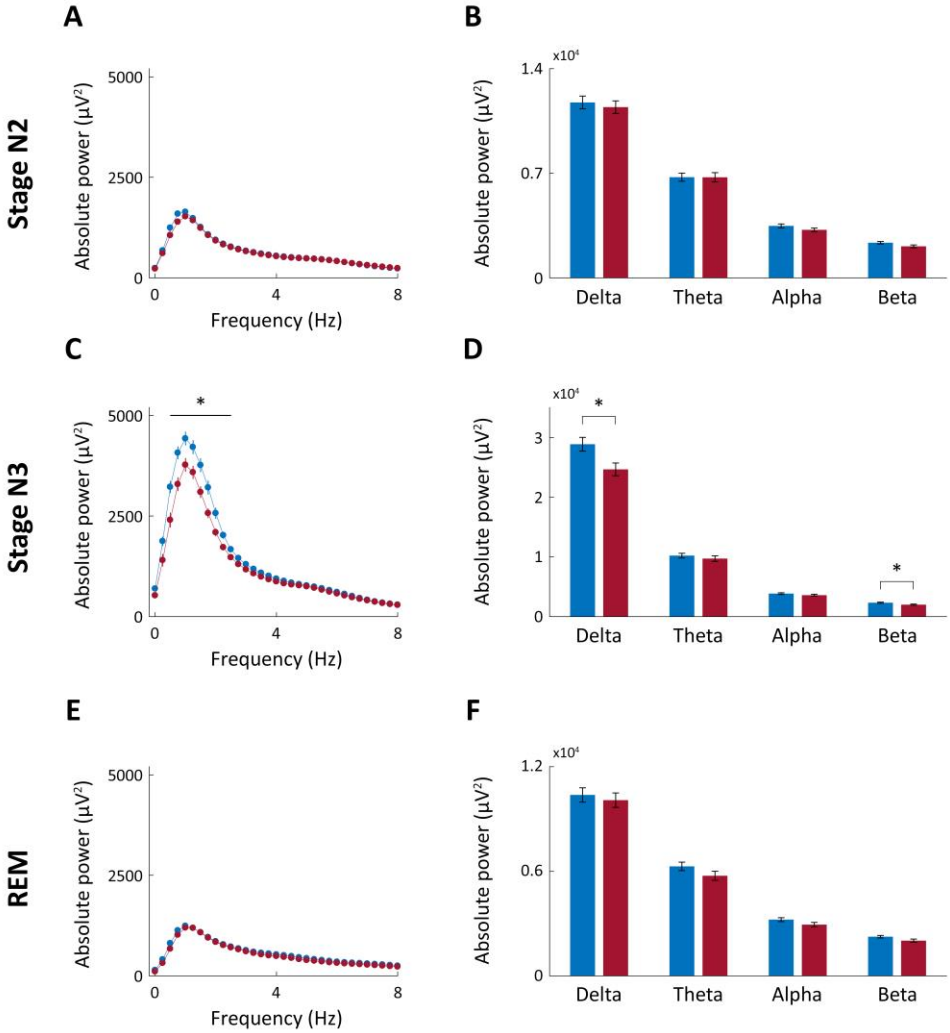

Figure 1: Absolute EEG power for ASD and control groups. Each panel represents the mean power across subjects for the control (blue) and ASD (red) groups during sleep stage N2 (A&B) sleep stage N3 (C&D) and REM sleep (E&F).

Power was computed as the mean across all artefact-free epochs from each sleep stage and plotted in 0.25Hz bins (A, C and E) or averaged within the Delta, Theta, Alpha, and Beta frequency bands (B, D and F). Error bar: standard error of the mean across subjects. Asterisks: significant difference across groups (two-tailed t-test, $p<0.05$, FDR correction).

SWA dynamics across the night

The power and slope of SWA (i.e., activity in the Delta band, 1-4 Hz) decreased gradually during the night in a manner that corresponded to changes in the proportion of the different sleep stages (Figure 2). These dynamics were similarly apparent in individuals of both groups, yet children with ASD exhibited weaker SWA power particularly in the first two hours of sleep.

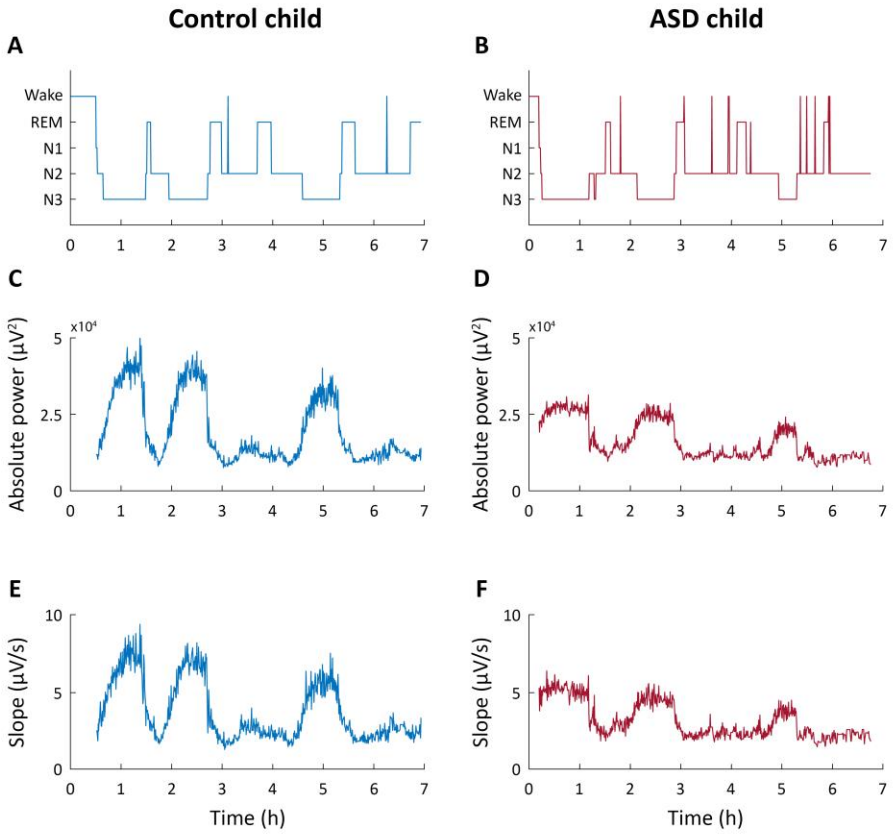

Figure 2: Examples of slow-wave-activity dynamics across the night from one child with ASD (red, right column) and one child from the control group (blue, left column). (A&B) Hypnogram with manual scoring of the different sleep stages in 30-second epochs. (C&D) Time courses of SWA power throughout the night. (E&F) SWA slopes throughout the night. Traces in C-F represent the mean across the two occipital electrodes (O1&O2).

To quantify differences in SWA across groups during specific sleep segments, we divided the night into 1-hour segments, from sleep onset to the end of the PSG evaluation/recording (Figure 3 A&B). A two-way ANOVA analysis revealed that SWA power differed significantly across groups ($p<0.001$) and over time ($p<0.001$), with a significant interaction across the two ($p=0.02$). SWA slope also differed significantly across groups ($p=0.001$) and over time ($p<0.001$), with a significant interaction across the two ($p=0.02$). Follow up comparisons within specific sleep segments using two-tailed t-tests (FDR corrected for multiple comparisons) revealed that children with ASD exhibited significantly weaker SWA power ($p<0.02$, Cohen's $d>0.82$) and shallower SWA slopes ($p<0.03$, Cohen's $d>0.8$) during the first two hours of sleep. No significant differences were found during the rest of the sleep period. We found similar trends when analyzing data from the central electrodes, but the differences across groups were not statistically significant.

In a complementary analysis we compared sleep architecture in the same 1-hour sleep segments (Figure 3C) using two-tailed t-tests (FDR corrected). Children with ASD exhibited significantly less N3 sleep during the first hour of sleep ($p=0.05$, Cohen's $d=0.78$), and marginally significant differences during the second hour ($p=0.12$, Cohen's $d=0.54$) as well as a corresponding increase in stage N2 sleep which was marginally significant during the first two hours of sleep ($p<0.11$, Cohen's $d>0.63$). Interestingly, ASD children exhibited significantly more REM sleep during the first hour of sleep and a reversed marginally significant trend during the end of the sleep period where they exhibited relatively less REM sleep than controls.

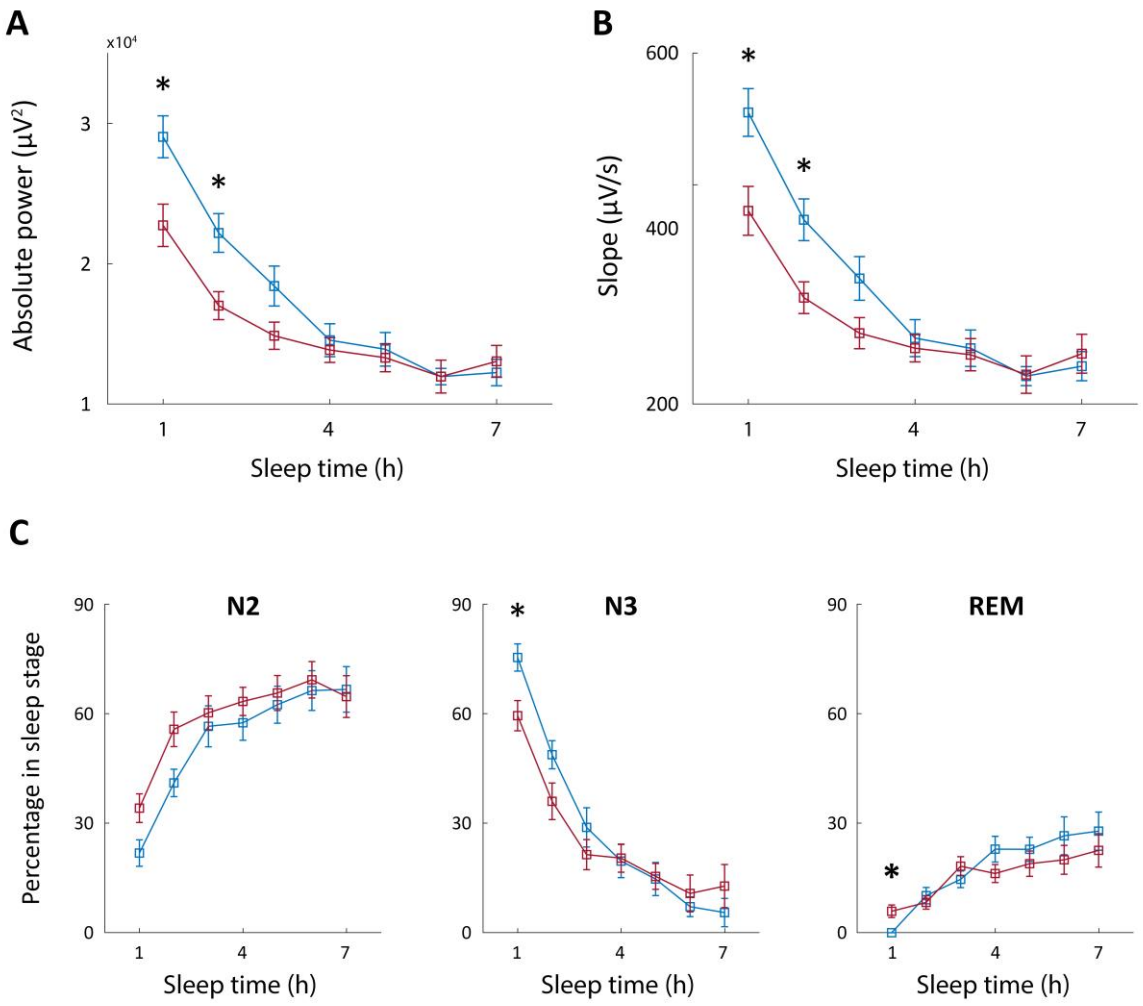

Figure 3: Differences in SWA and sleep architecture across ASD and control groups in 1-hour segments from sleep onset. Power (A) and Slope (B) of SWA were computed for each hour of the sleep period, starting at sleep onset, for children with ASD (red) and controls (blue). Percentage of each sleep stage were also computed for each hour (C). Error bars: standard error of the mean across subjects. Asterisks: significant differences across groups (two-tailed t-test; $p<0.05$, FDR correction).

Relationship between SWA and sleep disturbances in children with ASD

We computed the correlation between SWA power in the first hour of sleep and the behavioral sleep scores that parents reported using the CSHQ. Note that this analysis examines the relationship between

a single night of sleep in the lab and the parent reports of sleep problems at home. A significant negative correlation was found between bedtime resistance and SWA power (r(26)=-0.45, p=0.02; Figure 4B) as well as a negative marginally significant correlation between total sleep disturbances and SWA power (r(26)=-0.38, p=0.06; Figure 4A). Furthermore, there was a significant negative correlation between the absolute time that children fell asleep in the lab and SWA power (r(29)=-0.42, p=0.02, Figure 4D) as well as a negative non-significant trend between the child's sleep onset time at home (according to parent report) and SWA power (r(26)=-0.29, p=0.14, Figure 4C). These results suggest that weaker SWA power in children with ASD at the beginning of the night can partially explain individual problems of initiating sleep, resulting in late sleep onset.

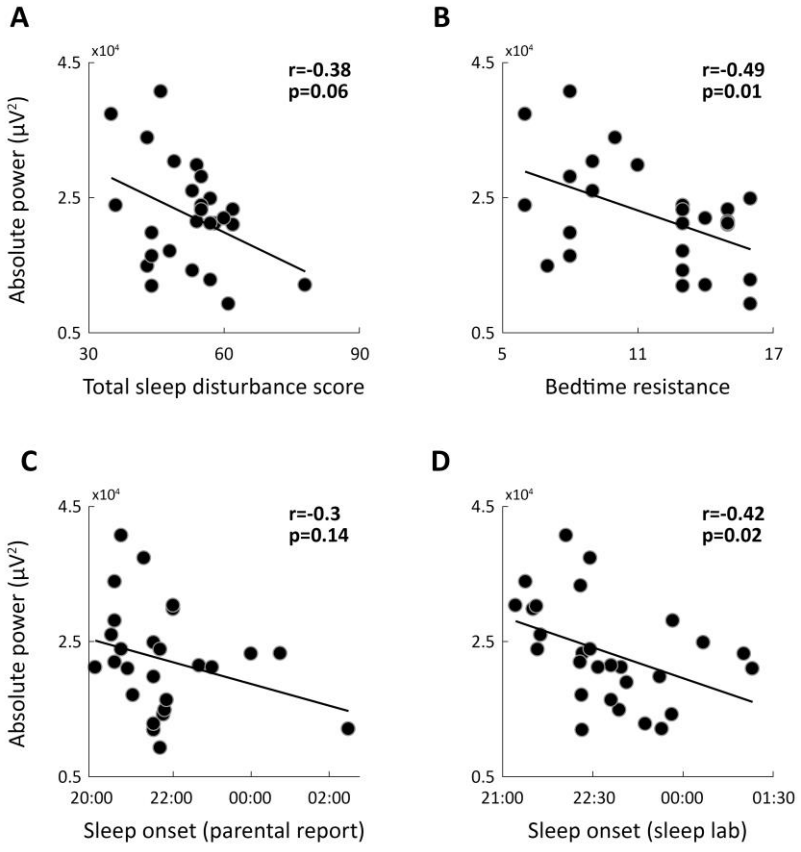

Figure 4: Relationship between SWA power during the first hour of sleep and (A) total sleep disturbance score (B) bedtime resistance score (C) parental report of sleep onset time at home and (D) sleep onset time in the sleep lab. Each point represents a single subject. Pearson's correlation coefficients and p-values are noted in each panel.

Discussion

Our study reveals that a considerable number of young children with ASD exhibit reduced pressure to sleep as manifested by weaker SWA power, shallower SWA slopes, and less N3 sleep during the first two hours of sleep (Figure 3). Moreover, SWA power during the first hour of sleep was significantly correlated with the severity of individual sleep disturbances and especially with sleep-onset difficulties (Figure 4). These results suggest that a disruption in sleep homeostasis reduces sleep pressure in children with ASD and exacerbates difficulties with sleep initiation and sleep maintenance.

Sleep disturbances in children with ASD

Clinical sleep disturbances are apparent in the majority of ASD cases [2,3,5]. While some have reported that sleep problems are more common in children with lower IQ [51] or higher autism severity [21,51], others have not [16,20]. More consistent reports have shown that sleep problems are associated with increased self-injury, anxiety, and aggression [18–21] as well as with sensory sensitivities [15–18], thereby generating considerable challenges and difficulties for ASD children and their families[52].

Previous studies have proposed that these sleep disturbances are caused by heightened levels of anxiety[21], poor sleep hygiene [29], abnormalities with the melatonin system (i.e., circadian rhythm) [30], and obstructive sleep apnea (OSA) [31]. Our results reveal that disrupted sleep homeostasis further contributes to sleep disturbances in children with ASD who do not have OSA. Note that similar disruptions of sleep homeostasis have also been reported in other populations with insomnia, such as aging adults [53].

In particular, our results reveal that quantifying SWA power during the first hour of sleep is informative for identifying children with reduced sleep pressure. Like children with OSA, are commonly identified with overnight PSG evaluations, and can benefit from effective targeted treatments [54], weak SWA during the first hour of sleep may act as a potent indicator of children with ASD who may benefit from specific

interventions with behavioral and pharmacological treatments that can increase the pressure to sleep[53,55].

Quantifying sleep pressure and architecture in children with ASD

We believe that previous PSG studies in children with ASD have not reported the reduced sleep pressure described in the current study for several reasons. First, previous studies did not quantify the amplitude of SWA, but rather relied on manual sleep staging, which is a categorical measure of sleep depth with a very limited range. Our results showed that differences across groups were larger and clearer when quantifying SWA (Figure 3). Nevertheless, one may expect that reduced sleep pressure would be apparent in smaller proportions of SWS (stage N3). This was indeed reported by some PSG studies [22–25], but not others [26–28]. Note that in our results, the proportion of SWS was not significant different across groups when examining the entire sleep period (Table 1). It was only after we split the night into 1-hour segments following sleep onset, that considerable differences in the proportion of SWS emerged in the first two hours after sleep onset (Figure 3).

This emphasizes a second key point: the importance of quantifying sleep pressure and sleep architecture in separate segments relative to sleep onset rather than averaging the measures across the entire sleep period. Sleep pressure (i.e., SWA power) and sleep architecture change dramatically throughout the night [32] (Figure 2). Meaningful abnormalities in sleep regulation may, therefore, appear in specific sleep segments and be obscured by averaging measures throughout the entire sleep period. Moreover, since children with ASD often sleep less during PSG evaluations [28], the relative proportion of sleep stages across the entire night will be biased by their shorter sleep durations, which vary across studies.

Taken together, these findings motivate using quantification of SWA power, rather than traditional measures of sleep architecture, and focusing on the first hour following sleep onset. This measure is not

biased by potential differences in overall sleep duration during the PSG and represents an objective and quantitative marker of initial sleep pressure in individual children.

The importance of deep slow wave sleep (SWS)

Contemporary sleep research highlights the importance of SWS for regulating the strength (i.e., the number and efficacy) of cortical synapses [36,38,56,57], which is critical for proper cognitive function including learning and memory consolidation[34,38,58–60]. In typically developing individuals, the amplitude of SWS (i.e. SWA power) increases as a function of time spent awake as demonstrated by studies with sleep deprivation [32]. A remarkable finding in our study is that children with ASD did not exhibit this canonical relationship. Indeed, children with ASD who fell asleep later in the night exhibited weaker SWA (Figure 4). This suggests that the ASD children with the larger sleep onset disturbances had greater sleep homeostasis impairments, and these particular children are likely to benefit most from targeted therapy.

Conclusions

Our study reveals that a considerable proportion of children with ASD exhibit weak sleep pressure, which contributes to their sleep disturbances and particularly to their sleep-onset difficulties. A variety of existing behavioral and pharmacological interventions are available for enhancing sleep pressure [53] including mild interventions such as increased exercise [61]. Since improving sleep quality is likely to reduce aberrant behaviors [18–21] in children with ASD and reduce parental stress [52], the initiation of clinical trials with these interventions is highly warranted.

Acknowledgments:

This work was supported by a SFARI explorer grant 439370, Israel Science Foundation grant 961/14, and an Israel Academy of Sciences Adams Fellowship to A.A.

References:

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (5th Ed.)*. Washington, DC: American Psychiatric Publishing.; 2013.

2. Souders MC, Mandell DS, Weaver TE, et al. Sleep Behaviors and Sleep Quality in Children with Autism Spectrum Disorders. *Sleep*. 2009;32(12):1566-1578.

3. Krakowiak P, Goodlin-Jones B, Hertz-Picciotto I, Croen LA, Hansen RL. Sleep problems in children with autism spectrum disorders, developmental delays, and typical development: A population-based study. *J Sleep Res*. 2008;17(2):197-206.

4. Cohen S, Conduit R, Lockley SW, Rajaratnam SMW, Cornish KM. The relationship between sleep and behavior in autism spectrum disorder (ASD): a review. *J Neurodev Disord*. 2014;6(44):1-10.

5. Moore M, Evans V, Hanvey G, et al. Assessment of Sleep in Children with Autism Spectrum Disorder. *Children*. 2017;4(8):72.

6. Calhoun SL, Fernandez-mendoza J, Vgontzas AN, Liao D, Bixler EO. Prevalence of insomnia symptoms in a general population sample of young children and preadolescents : gender effects. *Sleep Med*. 2014;15(1):91-95.

7. Fricke-oerkermann L, Plück J, Schredl M, et al. Prevalence and Course of Sleep Problems in Childhood. *Sleep*. 2007;30(10):1371-1377.

8. Goldman SE, Richdale AL, Clemons T, Malow BA. Parental sleep concerns in autism spectrum disorders: Variations from childhood to adolescence. *J Autism Dev Disord*. 2012;42(4):531-538.

9. Johnson CR, Turner KS, Foldes EL, Malow BA, Wiggs L. Comparison of sleep questionnaires in the assessment of sleep disturbances in children with autism spectrum disorders. *Sleep Med*. 2012;13(7):795-801.

10. Humphreys JS, Gringras P, Blair PS, et al. Sleep patterns in children with autistic spectrum disorders: A prospective cohort study. *Arch Dis Child*. 2014;99(2):114-118.

11. Malow BA, Marzec ML, Mcgrew SG, Wang L, Henderson LM, Stone WL. Characterizing Sleep in Children with Autism Spectrum Disorders : A Multidimensional Approach. *Sleep*. 2006;29(12):1563-1571.

12. Souders MC, Zavodny S, Eriksen W, et al. Sleep in Children with Autism Spectrum Disorder. *Curr Psychiatry Rep*. 2017;19(6):34.

13. Fletcher FE, Foster-Owens MD, Conduit R, Rinehart NJ, Riby DM, Cornish KM. The developmental trajectory of parent-report and objective sleep profiles in autism spectrum disorder: Associations with anxiety and bedtime routines. *Autism*. 2017;21(4):493-503.

14. Gail Williams P, Sears LL, Allard A. Sleep problems in children with autism. *J Sleep Res*. 2004;13(3):265-268.

15. Tzischinsky O, Meiri G, Manelis L, et al. Sleep disturbances are associated with specific sensory sensitivities in children with autism. *Mol Autism*. 2018;9(1):22.

16. Mazurek MO, Dovgan K, Neumeyer AM, Malow BA. Course and Predictors of Sleep and Co-occurring Problems in Children with Autism Spectrum Disorder. *J Autism Dev Disord*. 2019;49:2101-2115.

17. Mazurek MO, Petroski GF. Sleep problems in children with autism spectrum disorder: examining the contributions of sensory over-responsivity and anxiety. *Sleep Med*. 2015;16(2):270-279.

18. Mayes SD, Calhoun SL. Variables related to sleep problems in children with autism. *Res Autism Spectr Disord*. 2009;3(4):931-941.

19. Goldman SE, Mcgrew S, Johnson KP, Richdale AL, Clemons T, Malow BA. Sleep is associated with

problem behaviors in children and adolescents with Autism Spectrum Disorders. *Res Autism Spectr Disord*. 2011;5(3):1223-1229.

20. Shui AM, Katz T, Malow BA, Mazurek MO. Predicting sleep problems in children with autism spectrum disorders. *Res Dev Disabil*. 2018;83:270-279.

21. Hollway JA, Aman MG, Butter E. Correlates and Risk Markers for Sleep Disturbance in Participants of the Autism Treatment Network. *J Autism Dev Disord*. 2013;43(12):2830-2843.

22. Giannotti F, Cortesi F, Cerquiglini A, Vagnoni C, Valente D. Sleep in children with autism with and without autistic regression. *J Sleep Res*. 2011;20(2):338-347.

23. Lehoux T, Carrier J, Godbout R. NREM sleep EEG slow waves in autistic and typically developing children: Morphological characteristics and scalp distribution. *J Sleep Res*. 2018;28:1-6.

24. Lambert A, Tessier S, Rochette A-C, Scherzer P, Mottron L, Godbout R. Poor sleep affects daytime functioning in typically developing and autistic children not complaining of sleep problems: A questionnaire-based and polysomnographic study. *Res Autism Spectr Disord*. 2016;23:94-106.

25. Limoges É, Mottron L, Bolduc C, Berthiaume C, Godbout R. Atypical sleep architecture and the autism phenotype. *Brain*. 2005;128(5):1049-1061.

26. Elia M, Ferri R, Musumeci SA, et al. Sleep in subjects with autistic disorder: a neurophysiological and psychological study. *Brain Dev*. 2000;22(2):88-92.

27. Miano S, Bruni O, Elia M, et al. Sleep in children with autistic spectrum disorder: A questionnaire and polysomnographic study. *Sleep Med*. 2007;9(1):64-70.

28. Buckley AW, Rodriguez A, Jennison K, et al. REM sleep percentage in children in autism compared with developmental delay and typical develoment. *Arch Pediatr*. 2010;164(11):1032-1037.

29. Jan JE, Owens JA, Weiss MD, et al. Sleep Hygiene for Children With Neurodevelopmental

Disabilities. *Pediatrics*. 2008;122(6):1343-1350.

30. Rossignol DA, Frye RE. Melatonin in autism spectrum disorders: a systematic review and meta-analysis. *Dev Med Child Neurol*. 2011;53(9):783-792.

31. Harris J, Malow B, Werkhaven J. Descriptive Epidemiology of Obstructive Sleep Apnea in Children with Autism Spectrum Disorder. *Sleep*. 2018;41:A292-A293.

32. Borbély AA, Daan S, Wirz-Justice A, Deboer T. The two-process model of sleep regulation : a reappraisal. *J Sleep Res*. 2016;25:131-143.

33. Borbely AA. A Two-Process Model of Sleep Regulation. *Hum Neuuobiology*. 1982;1:195-204.

34. Derk-Jan D. Regulation and Functional Correlates of Slow Wave Sleep. *J Clin Sleep Med*. 2009;5(2):S6-S15.

35. Léger D, Debellemaniere E, Rabat A, Bayon V, Benchenane K, Chennaoui M. Slow-wave sleep: From the cell to the clinic. *Sleep Med Rev*. 2018;41:113-132.

36. Esser SK, Hill SL, Tononi G. Sleep Homeostasis and Cortical Synchronization : I . Modeling the Effects of Synaptic Strength on Sleep Slow Waves. *Sleep*. 2007;30(12):1617-1630.

37. Riedner BA, Vyazovskiy V V, Huber R, Massimini M, Esser S, Murphy M. Sleep Homeostasis and Cortical Synchronization : III . A High-Density EEG Study of Sleep Slow Waves in Humans. *Sleep*. 2007;30(12):1643-1657.

38. Tononi G, Cirelli C. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. *Neuron*. 2014;81(1):12-34.

39. Rochette A, Soulie I, Berthiaume C, Godbout R. NREM Sleep EEG Activity and Procedural Memory: A Comparison between Young Neurotypical and Autistic Adults without Sleep Complaints. *Autism Res*. 2018:1-11.

40. Tani P, Wendt N. Sleep in Young Adults with Asperger Syndrome. *Neuropsychobiology*. 2004;50:147-152.

41. Lázár ZI, Lázár AS, Bíró A, et al. Clinical Neurophysiology Reduced fronto-cortical brain connectivity during NREM sleep in Asperger syndrome : An EEG spectral and phase coherence study. *Clin Neurophysiol J*. 2010;121:1844-1854.

42. Meiri G, Dinstein I, Michaelowski A, et al. Brief Report: The Negev Hospital-University-Based (HUB) Autism Database. *J Autism Dev Disord*. 2017;47(9):2918-2926.

43. Lord C, Risi S, Lambrecht L, et al. The Autism Diagnostic Observation Schedule–Generic: A Standard Measure of Social and Communication Deficits Associated with the Spectrum of Autism. *J Autism Dev Disord*. 2000;30(3):205-223.

44. Owens JA, Spirito A, Melissa M. The Children ' s Sleep Habits Questionnaire (CSHQ): Psychometric properties of a survey instrument for school-aged children. *Sleep*. 2000;23(8):1-9.

45. Tzchishinsky O, Lufi D, Shochat T. Reliability of the Children's Sleep Habits Questionnaire Hebrew Translation and Cross Cultural Comparison of the Psychometric Properties. *Sleep Diagnosis Ther*. 2008;3(3):30-34.

46. Iber C, Ancoli-Israel S, Chesson A, Quan S. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications*. The American Academy of Sleep Medicine; 2007.

47. Standards and indications for cardiopulmonary sleep studies in children. American Thoracic Society. *Am J Respir Crit Care Med*. 1996;153(2):866-878.

48. Delorme A, Makeig S. EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods*. 2004;134(1):9-21.

49. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc B*. 1995;57(1):289-300.

50. Kurth S, Ringli M, Geiger A, LeBourgeois M, Jenni OG, Huber R. Mapping of Cortical Activity in the First Two Decades of Life: A High-Density Sleep Electroencephalogram Study. *J Neurosci*. 2010;30(40):13211-13219.

51. Veatch OJ, Sutcliffe JS, Warren ZE, Keenan BT, Potter MH, Malow BA. Shorter Sleep Duration is Associated with Social Impairment and Comorbidities in ASD. *Autism Res*. 2017;10:1221-1238.

52. Giallo R, Wood CE, Jellett R, Porter R. Fatigue, wellbeing and parental self-efficacy in mothers of children with an Autism Spectrum Disorder. *Autism*. 2013;17(4):465-480.

53. Dijk DJ. Slow-wave sleep deficiency and enhancement: Implications for insomnia and its management. *World J Biol Psychiatry*. 2010;11(S1):22-28.

54. Ben-Israel N, Zigel Y, Tal A, Segev Y, Tarasiuk A. Adenotonsillectomy improves slow-wave activity in children with obstructive sleep apnoea. *Eur Respir J*. 2011;37(5):1144-1150.

55. Wilckens KA, Ferrarelli F, Walker MP, Buysse DJ. Slow-Wave Activity Enhancement to Improve Cognition. *Trends Neurosci*. 2018;41(7):470-482.

56. Tononi G, Cirelli C. Sleep and synaptic down-selection. *Eur J Neurosci*. 2019;0:1-9. doi:10.1007/978-3-319-28802-4_8.

57. Cirelli C. Sleep, synaptic homeostasis and neuronal firing rates. *Curr Opin Neurobiol*. 2017;44:72-79.

58. Wilckens KA, Ferrarelli F, Walker MP, Buysse DJ. Slow-Wave Activity Enhancement to Improve Cognition. *Trends Neurosci*. 2018;41(7):470-482.

59. Walker MP. Slow Wave Sleep in Memory Processing. *J Clin Sleep Med*. 2009;5(2):S20-S26.

60. Helfrich RF, Mander BA, Jagust WJ, Knight RT, Walker MP. Old Brains Come Uncoupled in Sleep: Slow Wave-Spindle Synchrony, Brain Atrophy, and Forgetting. *Neuron*. 2018;97(1):221-230.

61. Wilckens KA, Ferrarelli F, Walker MP, Buysse DJ. Slow-Wave Activity Enhancement to Improve Cognition. *Trends Neurosci*. 2018;41(7):470-482.