Sleep Dependent Memory Consolidation in Children with Autism Spectrum Disorder

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Study Objectives: Examine the role of sleep in the consolidation of declarative memory in children with autism spectrum disorder (ASD).
Design: Case-control study.
Setting: Home-based study with sleep and wake conditions.
Participants: Twenty-two participants with ASD and 20 control participants between 9 and 16 y of age.
Measurements and Results: Participants were trained to criterion on a spatial declarative memory task and then given a cued recall test. Retest occurred after a period of daytime wake (Wake) or a night of sleep (Sleep) with home-based polysomnography; Wake and Sleep conditions were counterbalanced. Children with ASD had poorer sleep efficiency than controls, but other sleep macroarchitectural and microarchitectural measures were comparable after controlling for age and medication use. Both groups demonstrated better memory consolidation across Sleep than Wake, although participants with ASD had poorer overall memory consolidation than controls. There was no interaction between group and condition. The change in performance across sleep, independent of medication and age, showed no significant relationships with any specific sleep parameters other than total sleep time and showed a trend toward less forgetting in the control group.
Conclusion: This study shows that despite their more disturbed sleep quality, children with autism spectrum disorder (ASD) still demonstrate more stable memory consolidation across sleep than in wake conditions. The findings support the importance of sleep for stabilizing memory in children with and without neurodevelopmental disabilities. Our results suggest that improving sleep quality in children with ASD could have direct benefits to improving their overall cognitive functioning.
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INTRODUCTION

Autism spectrum disorder (ASD) is a heterogeneous group of neurodevelopmental disorders defined by core impairments in social interaction and communication, and restricted and repetitive behaviors.[1] Sleep problems are endemic in children with ASD, with a prevalence ranging from 40% to 86%, and persist through childhood and adolescence.[2] Based on actigraphy data and parental questionnaires, the sleep problems can be best characterized as sleep onset and maintenance insomnia.[3–7] Polysomnographic sleep studies have produced discrepant results for the differences between children with ASD and typically developing (TD) children on such variables as total sleep time, sleep efficiency, and sleep stage amounts.[4,8,9]

Poor sleep is associated with higher ratings of ASD severity, stereotypies, and repetitive behaviors,[6,10,11] as well as poorer social interaction skills.[4] Likewise, problematic daytime behaviors in realms such as attention and anxiety are associated with parental reports of sleep disturbances in children with ASD.[4,12,13] Although cognition and academic achievement are known to be affected by sleep deprivation and disruption in TD children,[14–17] similar relationships have been underexplored among children with ASD. In one study, IQ scores for children with ASD were correlated with subjective sleep quality and quantity, though causal relationships remain unclear.[13]

Memory consolidation refers to processes by which memory traces become more stable and resistant to interference over a period of time. Consolidation of declarative memory results from a dialogue between reactivated hippocampal memory traces and neocortical networks that retain long-term memory representations.[18] Over the past 20 y, an abundance of literature has shown that memory consolidation processes are often sleep dependent, whereby memory is both stabilized and enhanced by intervals of sleep compared to comparable wake intervals.[19–22] In adults, sleep dependent consolidation of declarative memory has been correlated with a range of neurophysiological measures, including the amount of electroencephalography (EEG) slow wave activity (1–4 Hz),[23,24] slow oscillations (0.5–1 Hz),[25,26] and sleep spindles [27–29] reflecting an active role of sleep in this hippocampal-neocortical dialogue. Recent data have shown similar relationships between sleep dependent memory consolidation, and sleep spindles[30] and slow oscillations,[31] in TD children. It is unknown whether a similar relationship exists in children with ASD. The current study characterizes declarative memory consolidation in children with ASD compared to controls, and demonstrates the effect of sleep and specific sleep architectural features on this consolidation process.

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Table 1—Participant demographic characteristics and cognitive and behavioral test scores.

	ASD (n = 22)	TD (n = 20)	P
Age (y)	11.3 (2.1)	12.3 (2.1)	0.15
Sex (%males)	86.0%	90.0%	0.66
Maternal education (≤ 12 y)	10.0%	11.0%	0.39
CBCL total problems score	63.4 (8.6)	43.2 (10.9)	**< 0.001**
SRS total score	83.0 (45, 90)	45.0 (35, 67)	**< 0.001**
NVIQ score	101.4 (12.7)	112.4 (18.3)	**0.03**
Towers test, TAS	6.9 (4.6)	11.7 (2.7)	**0.002**
Trails test composite score	7.8 (3.2)	12.4 (1.4)	**< 0.001**

Mean (standard deviation) is presented for normally distributed data and median (min, max) for non-normally distributed data. ASD, autism spectrum disorder; TD, typical developing controls, CBCL, child behavior checklist; NVIQ, nonverbal intelligence quotient; SRS, social responsiveness scale; TAS, total achievement scale. P values that met significance levels of < 0.05 are bolded.

METHODS

Participants

Study participants with ASD ages 9–16 y were recruited from a pool of subjects enrolled in a larger study conducted through the Simons Simplex Collection and The Autism Consortium at Boston Children's Hospital. Participants in the ASD group had a clinical diagnosis of ASD and additionally were required to meet cutoff scores for ASD on the Autism Diagnostic Observation Schedule[32] and the Autism Diagnostic Interview, Revised.[33] In addition, individuals with ASD were required to have a nonverbal intelligence quotient (NVIQ) of not more than 1.33 standard deviations below the mean (a standard score of 80 or higher) on the Differential Abilities Scales II.[34] Age-matched, TD control participants were recruited through announcements placed in community newspapers and a classified advertisement website (Craigslist) seeking healthy children with normal development who were interested in sleep research.

Exclusion criteria for all participants included (1) significant hearing or vision loss; (2) metabolic disease, neurogenetic disorders, or comorbid neurological disorders (e.g., cerebral palsy, history of seizures); (3) a previously diagnosed sleep disorder; and (4) an unstable chronic medical condition such as asthma, diabetes, cystic fibrosis, or cardiac disease. In addition, potential control participants were excluded if they had a sleep disorder, psychiatric disorder, or neurodevelopmental condition (including ASD and attention deficit hyperactivity disorder [ADHD]) diagnosed by a health care provider and/or used a medication known to affect sleep, memory, or daytime vigilance (e.g., psychotropic medications, sedatives, or hypnotics) at the time of the study. The study was approved by the Boston Children's Hospital Institutional Review Board. All participants provided assent and their parents gave written informed consent. Participants were reimbursed for their participation with gift cards provided at the completion of each phase: neuropsychological testing, Wake training and testing, and Sleep training and testing.

All 22 enrolled participants with ASD and 20 of the 23 enrolled TD participants completed both the sleep and wake memory conditions; two of the TD participants were lost to follow-up (participated in only one of the two wake or sleep sessions) and test data from one were lost, and thus their data were excluded from all analyses. Participants' demographic characteristics (age, maternal education level, and sex) are presented in Table 1. Among the 42 participants who completed both memory conditions, 19 ASD and 17 TD participants completed the overnight sleep study (data from 3 ASD and 3 TD participants were lost because of equipment failures and failures to reconnect the headbox during the night).

In total, 7 of the 22 participants with ASD who completed memory testing (31.8%) took medications for behavior and/or mood problems. Three took stimulants alone, two took an antidepressant alone, one took guanfacine (day use) and an antidepressant, and one took a mood stabilizer and stimulant. No participants with ASD reported taking anti-seizure medications or sleep aids. Control participants reported no medication use.

Procedures

Participants and parents/guardians came to the Clinical & Translational Study Unit (CTSU) at Boston Children's Hospital, met with study staff, signed informed consent/assent forms, completed cognitive and neuropsychological testing, and received both sleep logs and a wrist actigraph to use for 7 d prior to the first test session. Approximately 1 w later, the participants partook in either the sleep retention period (Sleep) or wake retention period (Wake), the order of which was counterbalanced within each group (Figure 1A), and, at least 1 w later, they partook in the other condition. Both Sleep and Wake conditions were carried out in the participants' homes.

In the Sleep condition, participants were trained and tested on a declarative spatial memory task 60 min before their habitual bedtime, and then wired for overnight PSG. The next morning, the researcher returned and waited for participants to awaken before ending the recording, removing PSG electrodes, and retesting the participants. In the Wake condition, participants were trained and tested 30 min after habitual wake time. The Sleep condition was longer (11.2 ± 0.04 h) than in the Wake condition (9.1 ± 0.2 h), which, everything else being equal, should lead to poorer retest performance in the Sleep condition. Between tests, participants in the Wake condition were asked to proceed with their normal daily activities and parents kept a log of any unusual stresses or changes in routine. Participants were also asked not to nap during the day.

Spatial Declarative Memory Task

Sleep dependent memory processing was measured with a nonverbal, two-dimensional visual spatial memory task that has previously shown sleep dependent consolidation in children[30,35] (Figure 1B), and that is suitable for children with and without autism. It is similar to the children's game variously known as "Memory" or "Concentration," and consists of 15 colored card pairs with images of animals and common objects

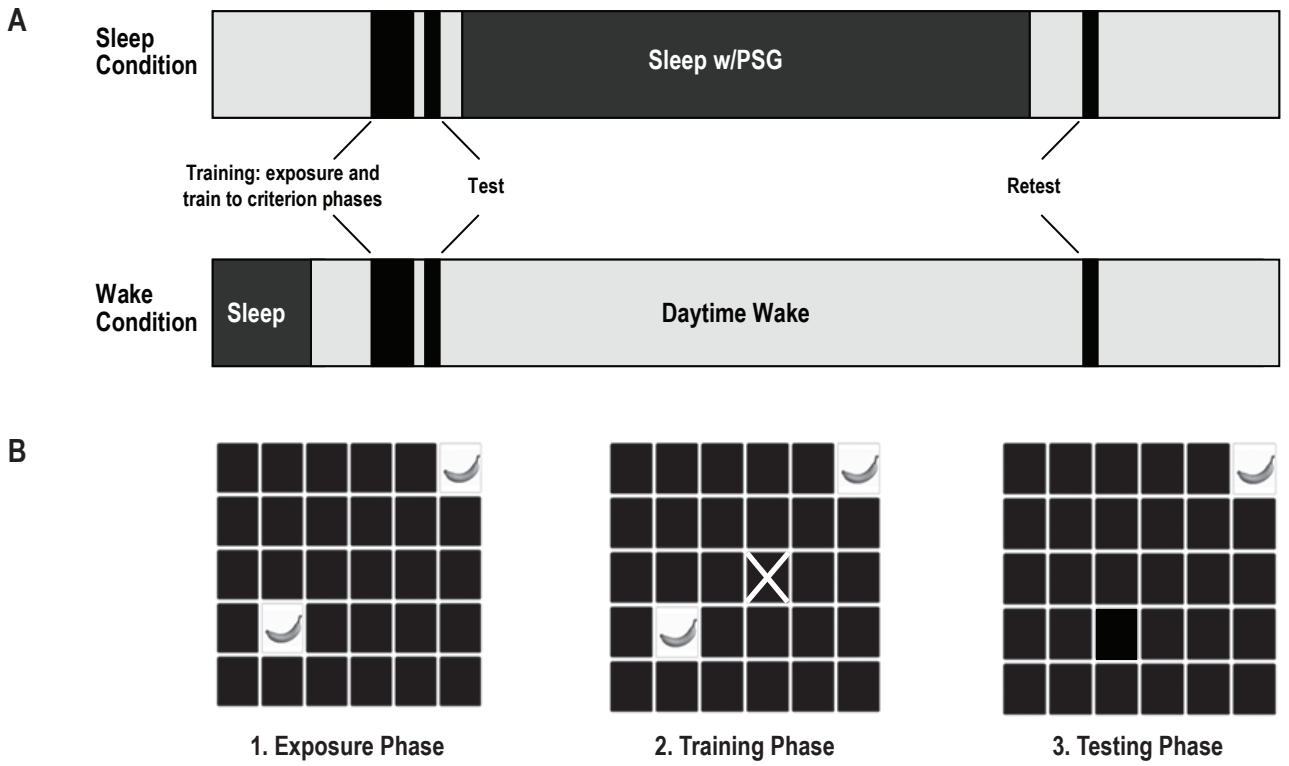

Figure 1—Study protocol. (A) Timeline. Comparison of Test to Retest reflects sleep dependent memory consolidation in the Sleep condition, and memory consolidation during an equivalent period of wakefulness in the Wake condition. (B) Screen displays. 1. During the exposure phase, the spatial locations of each card pair is displayed, one pair at a time. 2. During the training phase, one item is presented to participants and they are asked to click on to the matching card; here, the participant selects the wrong card (as indicated by an "X" over its back), and the correct location of the matching card is displayed (feedback). This phase continues until the participant reached 40% accuracy. 3. Immediately after the training phase, participants are tested. The participants are again shown an item and asked to select the correct location of the matching card. In this phase, feedback is not provided. Delayed recall was tested after a period of wake or sleep.

arranged in a 5 × 6 array on a laptop computer. A brief description of the task is described in the next section and a full description is included in the supplemental material.

Learning occurs in two steps, an exposure phase and a training phase. At the start of the exposure phase, the participants are told to pay attention, and that they will be tested shortly. The screen initially displays the backs of all the cards. Then one card is displayed followed by its matching pair. Both cards are then turned over. This process is repeated until all card pairs have been displayed, and then the entire procedure is repeated a second time. The order of presentation of card pairs is randomized each time the cards are displayed.

In the training phase, a block of feedback trials is conducted, testing the participants' knowledge of the location of all card pairs. One card of each pair is exposed in turn, and for each one, participants click on the back of the card they believe matches the exposed card. If they choose the correct card, it is turned over, displaying the matching picture. If they choose an incorrect card, the correct matching card is turned over, revealing its location After all card pairs have been tested, additional feedback blocks are conducted until participants reach a criterion score of at least 6 correct responses (40% of card pairs) in one block.

Immediately after the criterion feedback block, the testing phase, consisting of a single block of trials without feedback, is begun. Again, one card of each pair is exposed, and participants attempt to identify the matching card. In this case, the participant is not told if their selection is correct nor shown the correct card location. At the end of the test, the number of correct pairs is displayed. Immediate recall is calculated as the relative change in number of card pairs correctly recalled from the end of learning to the immediate test ([test-last training score]/last training score). Then, approximately 10 h later, participants are retested on the task. Memory consolidation is calculated as the relative change in the number of correct card pairs from retest to end of learning ([retest score-last training score]/last training score).[35]

At least 7 d later, participants are trained and tested in the opposite condition (Wake or Sleep) using the identical procedure as in the first session. The two versions of the memory task used in the Wake and Sleep conditions used different pictures on the cards. Task version was counterbalanced across Wake and Sleep conditions as well as across first and second sessions.

Cognitive and Behavioral Measures

Parents of enrolled participants completed the Child Behavior Checklist (CBCL)[36] and Social Responsiveness Scale (SRS)[37] Participants were administered the Differential Abilities Scale II (DAS-II)[34] to obtain nonverbal IQ scores (NVIQ

scores) and the Tower and Trail Making subtests of the Delis-Kaplan Executive Function System (D-KEFS).[38] Descriptions of these neurobehavioral tests are in the supplemental material and results presented in Table 1.

Sleep Measures

Children's Sleep Habits Questionnaire (CSHQ)

Parents of participants completed the CSHQ,[39] a 35-item questionnaire validated in children ages 4–10 y, to examine habitual behavioral sleep problems in domains including bedtime resistance, sleep anxiety, sleep onset delay, night awakenings, daytime sleepiness, and parasomnias. Scores greater than 40 reflect clinically significant sleep problems[39] and the survey has been used in a number of research studies of children with ASD.[3,4]

Actigraphy/Sleep Logs

Participants wore an Actiwatch-64 (Phillips Respironics-Minimitter, Inc., Bend, OR) for 7 nights prior to the polysomnography (PSG) night, as well as during the PSG night itself. Actigraphy data provide estimates of sleep timings. Data were recorded in 15-sec epochs, and long wake episodes were defined as ≥ 5 min, and analyzed using Actiware® software, version 5.0 (Phillips Respironics-Minimitter, Bend, OR). Analyses provided time in bed (TIB), total sleep time (TST), and sleep efficiency (SE = TST/TIB). During the same 7 d, parents completed a daily sleep report, providing the time participants went to bed, woke during the night, woke in the morning, and napped during the day. Families were called midweek to confirm use of the Actiwatch and sleep logs. Data were retrieved at the end of the week. Data from a given night were excluded from analysis if (1) discrepancies were found between sleep log and actigraphic recording that could not be clarified by parental interview, (2) if parents reported that the participant's schedule was atypical due to illness or other stresses, or (3) if the participant did not wear the Actiwatch reliably over a 24-h period. All told, 37 of the 42 participants who completed the memory testing protocol (18 ASD and 19 TD) provided useful actigraphy data. Participants in the two groups reliably wore the Actiwatch for a comparable number of sleep periods (ASD: 6.7 ± 1.0, TD: 5.8 ± 0.6, P = 0.5).

Home PSG

Home PSG recording was performed using an Embla A-10 ambulatory PSG system (Medcare Systems, Buffalo, NY, USA) with a standard montage including seven channels of EEG (F1, F2, C3, Cz, C4, O1, and O2), two of electro-oculography (EOG) and two of electromyography (EMG). All channels were digitally recorded at 200 Hz. Although a desensitization protocol was developed to help participants with ASD adapt to electrodes and offered to families, only one subject opted to use the desensitization protocol.

Interest/Fatigue/Mood Scales

Immediately prior to both training and retesting in Wake and Sleep conditions, participants rated their current interest in participating in the memory task, level of fatigue, and mood, on three separate three-item Likert scales, adapted from a questionnaire used in a prior study evaluating sleep dependent memory consolidation in children.[35] Higher Likert scores reflect more interest, less fatigue and better mood.

Data Analysis

Sleep Analyses

Sleep recordings were scored in 30-sec epochs using standard criteria[40] by a physician board certified in sleep medicine (KM), blinded to participants' group and test scores. Sleep onset latency (SOL, time to fall asleep), wake time after sleep onset (WASO), total sleep time (TST), sleep efficiency (SE, time asleep/time in bed), and time (in min and as a fraction of TST) spent in sleep stages nonrapid eye movement (NREM) stage 1 (N1), NREM stage 2 (N2), NREM stage 3 and 4 (slow wave sleep or SWS), and REM were calculated.

Sleep recordings were then preprocessed and further analyzed using BrainVision Analyzer 2.0 (Brain Products, Munich, Germany) and MatLab R2010a (The Math Works, Natick, MA, USA) software. Artifacts were manually rejected by visual inspection, and the EEG filtered at 0.3 to 35 Hz. Spectral power density was calculated by fast Fourier transform, applying a Hanning window to successive 3-sec epochs of NREM sleep with 50% overlap. Spectral power was calculated for slow wave oscillation (0.5–1 Hz), delta (1–4 Hz), theta (4–7 Hz), alpha (8–11 Hz), sigma (12–15 Hz), and beta (16–20 Hz) frequency ranges.

Sleep spindles in N2 were visually scored by KM at Cz (midline central electrode) as bursts of synchronous 12–15 Hz EEG activity, lasting 0.5–2.0 sec. No amplitude criterion was applied. Attempts to use an automated spindle detection algorithm, previously validated for healthy adults as well as adults with schizophrenia[41] failed to produce reliable estimates in participants with ASD (correlation with hand-counted spindles n = 19, r = 0.16, P = 0.53), although significant correlations were obtained for controls (n = 17, r = 0.65, P = 0.01). As a result, only hand-scored spindles at Cz were used in subsequent analyses.

Statistical Analyses

Data were maintained in a REDCap[42] database and analyses performed using SPSS for Windows (version 19; IBM Corp, Armonk, NY, USA). Data were inspected visually to check for normality and potential outliers (points that extend more than 1.5 box-lengths from edge of box plot). Memory task improvement was normally distributed in both Wake and Sleep conditions in both groups. The participants' demographic and cognitive and behavioral test results are reported as means and standard deviations, and unpaired two-tailed *t*-tests were applied for group comparisons. For non-normal data, medians with minimum and maximum values are reported, and the Wilcoxon rank sum test was used for group comparisons. For categorical and ordinal data such as sex and coded maternal education, we used Fisher exact test for comparisons. Sleep measures are reported as means and standard error of means; group comparisons were performed using unpaired two-tailed *t*-tests. Group differences in PSG measures were additionally adjusted for age and medication use (scored as yes/no). These were selected as *a priori* confounding terms, given their

known association with sleep architecture.

For analysis of the memory data, the dependent variable is memory consolidation, which is the relative change in card pairs remembered from last training trial to retest (mean, standard error margin). Statistical analysis of memory consolidation was performed using a mixed-effects regression model and unstructured covariance matrix, in order to take into account any within-subjects correlations between memory consolidation in Sleep and Wake conditions. The following confounding variables were assessed in our model building: age, sex, maternal education, NVIQ, total sleep time measured by actigraphy, medication use (yes/no), number of trials to criterion on the memory task, and scores on the SRS, CBCL, and CSHQ. Confounding variables for group and memory consolidation across Sleep and Wake conditions were assessed separately by looking at bivariate associations. Covariates with $P < 0.20$ on the group-adjusted tests were included in a candidate list to be included in the model. Using purposeful selection, each covariate on the candidate list was added to a multivariate regression model that included group and condition as fixed factors. Covariates were tested to see if there was at least a 20% increase in the β_{group} and no more than 10% change in its standard deviation to ensure appropriate confounders were entered in to the model and to avoid collinearity. Covariates associated with outcome ($P < 0.1$) in this multivariate model were also retained as possible alternant predictors. Only age, sex, and NVIQ were found to be appropriate confounders, and these are included in the adjusted mixed-effects regression model. Baseline learning capabilities on the task (number of trials to meet criterion, immediate recall) and fatigue/mood/interest self-evaluations prior to training and retesting were also assessed using mixed-model regression analyses.

Last, for the Sleep condition, Pearson correlation tests were used to explore relationships of memory consolidation with TST and SE as well as specific sleep parameters that have been shown to be related to sleep dependent memory consolidation, i.e., SWS percentage,[23,25,43] sleep spindle density,[29] and slow wave oscillation (0.5–1 Hz) power.[26] For correlations that met significance ($P < 0.05$), we performed additional analyses controlling for age and any medication use using linear regression.

Statistical significance was taken at $P = 0.05$ level for all regression output. Memory task version and order of condition did not significantly affect performance analyses, and hence all such analyses were collapsed across these parameters.

Table 2—Group subjective and objective sleep characteristics.

CSHQ Scores	**ASD (n = 22)**	**TD (n = 20)**	**P**
CSHQ total score	49.0 (36, 68)	40.0 (35, 46)	**< 0.001**
Subscales			
Bedtime resistance	7.8 (0.5)	6.6 (0.2)	**0.03**
Sleep onset delay	1.9 (0.2)	1.4 (0.1)	**0.02**
Sleep duration	4.9 (0.4)	3.8 (0.3)	**0.04**
Sleep anxiety	6.1 (0.5)	4.2 (0.1)	**0.001**
Nocturnal wakenings	3.6 (0.2)	3.2 (0.1)	0.09
Parasomnias	9 (0.4)	7.7 (0.2)	**0.02**
Disordered breathing	3.4 (0.2)	3.2 (0.1)	0.21
Daytime sleepiness	14 (0.8)	11.7 (0.4)	**0.02**
Prestudy Actigraphy	**ASD (n = 18)**	**TD (n = 19)**	**P**
TST (min)	504 (10)	497 (12)	0.62
SE (%)	82.8 (1.1)	82.5% (1.6)	0.88
Home PSG	**ASD (n = 19)**	**TD (n = 17)**	**P**
TIB (min)	583 (17)	506 (17)	**0.01**
SOL (min)	27.3 (5, 101)	11.0 (0, 39)	**0.01**
WASO (min)	45.9 (8.1, 172.1)	21.5 (8.8, 51.5)	**0.02**
Number of wakings	12.3 (2.5)	6.5 (1)	**0.04**
SE (%)	86.0 (2)	93.0 (1)	**< 0.001**
TST (min)	469 (14)	500 (16)	0.16
REM (%)	18.9 (1.6)	22.9 (1.1)	**0.049**
N1(%)	4.1 (0.6)	3.2 (0.4)	0.24
N2(%)	47.3 (2.5)	44.4 (2)	0.37
SWS (%)	29.7 (1.9)	29.5 (1.5)	0.92
Spindle density in N2(%)	1.1 (0.1)	1.3 (0.2)	0.24
Sigma power (12–15 Hz) in N2 (μV^2Hz^{-1})	2.07 (0.6)	1.5 (0.2)	0.39
Slow oscillation power (μV^2Hz^{-1})	226 (21)	164 (13)	0.09

ASD, autism spectrum disorder; TD, typical developing controls; CSHQ, children's sleep habits questionnaire; TST, total sleep time; SE, sleep efficiency; TIB, time in bed; SOL, sleep onset latency ; WASO, wake after sleep onset; REM, rapid eye movement sleep; N1, stage 1 nonrapid eye movement (NREM) sleep; N2, stage 2 NREM sleep; SWS, slow wave sleep (N3 + N4 NREM sleep); spindle density, #spindles / N2 minutes; slow oscillation power = 0.5–1 Hz over NREM sleep. P values that met significance levels of < 0.05 are bolded.

RESULTS

Sleep Questionnaire and Actigraphy Measures

A comparison of sleep measures is presented in Table 2. Parents of participants with ASD reported more total sleep problems on the CSHQ than did parents of TD participants ($P < 0.001$), as well as on all subscales except for sleep disordered breathing and number of nocturnal wakings. Participants with ASD and TD participants who completed actigraphy had comparable sleep in terms of TST and SE prior to the PSG study night. For the 16 TD and 16 ASD participants who completed both pre-study actigraphy and PSG testing, TD

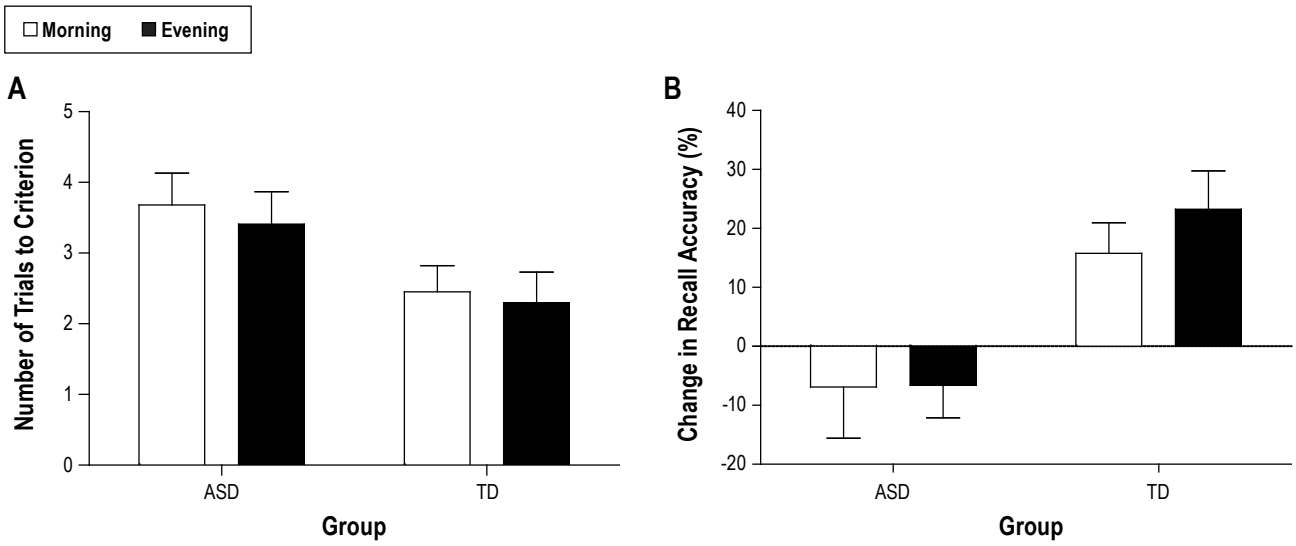

Figure 2—Raw data on number of trial trials to criterion and Immediate recall scores for the ASD and TD groups. **(A)** ASD participants required more trials to reach criterion compared to controls (P = 0.03) but there was no main effect of time of testing (morning versus evening), P = 0.47. **(B)** Likewise, participants in the ASD group demonstrated poorer immediate recall (testing immediately after training) in both the morning and evening conditions compared to controls (P < 0.001). No circadian effects of learning were detected (main effect of time of testing, P = 0.58). Error bars represent standard error of mean. ASD, autism spectrum disorder; TD, typically developing.

participants slept 22.5 ± 11.3 minutes less on the PSG night than on actigraphy nights (P = 0.06), whereas participants with ASD slept similar amounts (PSG – actigraphy = −2.5 ± 15.1 min; P = 0.87).

PSG Sleep Architecture Differences Between Groups

Overnight home PSG data are reported in Table 2. Participants with ASD had more than twice as long SOLs, nearly twice as much WASO, and, as a result, significantly reduced sleep efficiencies. However, they also spent more than 1 h longer in bed than TD participants (P = 0.01), and, in the end, had similar TSTs and percentages of TST spent in all NREM sleep stage (all Ps > 0.1). Participants with ASD spent significantly less of their sleep in rapid eye movement (REM) sleep compared to controls but no group differences in N2 spindle density nor N2 sigma frequency (12–15 Hz) were noted. Similarly, NREM power in the delta (1–4 Hz), theta (4–7 Hz), alpha (8–12 Hz), or beta (13–25 Hz) frequency bands were comparable across groups (all Ps > 0.2). Slow wave oscillation power (0.5–1 Hz) showed a trend toward being higher in participants with ASD (P = 0.09).

Controlling for age and the presence or absence of medication use, the only group differences that persisted were SOL (P = 0.02) and SE (P = 0.01), with WASO (P = 0.05), sleep maintenance (P = 0.05), and number of wakings (P = 0.07) trending toward significance (Table S1, supplemental material).

Sleep Dependent Memory Consolidation

Participants with ASD had more difficulty learning the spatial memory task than did TD children, based on the number of trials required to meet criterion [ASD: 3.5 ± 0.40 trials; TD: 2.4 ± 0.38 trials; F(1,40) = 5.17, P = 0.03; Figure 2A]; this was unaffected by the time of training [morning versus evening main effect, F(1,40) = 0.52, P = 0.47] and there was no interaction between group and time of training [F(1,40) = 0.04, P = 0.83].

Similarly, participants with ASD demonstrated poorer relative immediate recall than TD participants [ASD: −6.7 ± 4.8 , TD: 19.5 ± 5, F(1,40) = 16.50, P < 0.001]; Figure 2B], again with no time-of-training effect [morning: 4.4 ± 5.2, evening: 8.3 ± 4.2, F-test (1,40) = 0.35, P = 0.56] or interaction between group and training time [F(1,40) = 0.33, P = 0.57]. There were no differences in the significance of immediate recall main effects or interaction terms when adjusting for age, NVIQ, and sex [group: F(1,37) = 16.68, P < 0.001; time of testing: F(1,37) = 0.31, P = 0.58; group × time of testing: F(1,37) = 3.39, P = 0.56].

In an unadjusted model of memory consolidation, memory performance deteriorated significantly more across the Wake condition than in Sleep [Wake: −20.9 ± 4.9, Sleep: −4.0 ± 4.7, F (1,40) = 7.95, P = 0.01; Figure 3] and the ASD group demonstrated poorer overall memory recall than participants with TD [ASD: −21.8 ± 5.1, TD: −3.2 ± 5.4, F (1,40) = 6.2, P = 0.02]. However, there was no interaction between group and condition [F (1,40) = 0.02, P = 0.88]. Group differences in memory consolidation remained significant in an adjusted model controlling for age, sex, and NVIQ [ASD: −17.6 ± 4.5, TD: −4.2 ± 4.5, F (1,37) = 4.12, P = 0.049]. Importantly, Wake and Sleep condition differences also remained significant [Wake: −18.8 ± 4.3, Sleep: −2.9 ± 4.4, F (1,37) = 6.71, P = 0.01]. Again, no interaction between group and condition was noted (P = 0.97), indicating that the ASD group benefited from sleep as much as the control group.

Mixed-model regression analyses revealed no interaction between group and reported interest (P = 0.29) or mood (P = 0.09) based on the self-reported interest/fatigue/mood scales. However, there was a significant interaction between subjective fatigue scores and group [F(1,31) = 4.43, P = 0.01],

with participants with ASD reporting more fatigue in the morning, whether at training in the Wake condition [ASD: 1.6 ± 0.1, TD: 1.9 ± 0.2, P = 0.053] or at retest in the Sleep condition [ASD: 1.4 ± 0.1, TD: 1.8 ± 0.2, P = 0.04]. But importantly, subjective fatigue ratings did not correlate with either immediate or delayed recall improvement in the Wake or Sleep conditions in either group (P > 0.1).

Relationships between Sleep Measures and Cognition

Relationships between sleep dependent memory consolidation and specified sleep measures collected from the home PSG night were further explored using Pearson correlations and adjusting for age and medication use. On univariate testing, TST correlated with sleep dependent memory consolidation in the TD group only (ASD: r = −0.01, P = 0.98; TD: r = 0.58, P = 0.02, Figure 4). Conversely, slow oscillation power correlated with sleep dependent memory consolidation in the ASD group only (ASD: 0.52, P = 0.03; TD: r = 0.16, P = 0.55). No other significant correlations were noted for sleep efficiency, SWS percentage, and N2 spindle density with sleep dependent memory consolidation (all P > 0.1).

Controlling for age and any medication use (yes/no), we found a main effect for TST on sleep dependent memory performance [β = 0.29, 95% confidence interval: 0.03–0.55, F(1,30) = 5.03, P = 0.03, and a trend toward a significant interaction effect between TST and group [F(1,30) = 3.30, P = 0.08]. Similar regression analysis performed for a main effect of NREM slow oscillation (0.5–1Hz) power did not demonstrate a linear relationship with sleep dependent memory consolidation (F = 0.01, P = 0.91) nor did a significant interaction emerge between NREM slow oscillation and group.

DISCUSSION

This is the first study to investigate sleep dependent memory consolidation in children with ASD. Based on home PSG testing, children with ASD had poorer sleep quality than TD children, with longer SOLs and lower SEs. Unexpectedly, we found that this period of sleep, though disrupted, still effectively stabilized memory in children with ASD though to a lesser degree than for control participants. Controlling for potential confounders of age, NVIQ, and sex, we still found significant differences in memory consolidation between groups but did not detect an interaction between group and condition (Sleep/Wake). Consistent with other adult[20,44]and pediatric studies,[35,45] participants in this study demonstrated more stable memory functioning after sleep with less forgetting over a night of sleep (4.0%) than across a shorter period of time awake (20.9%).

This is also the first study to use home PSG to both characterize sleep and assess its micro-architectrual details in children with ASD. Despite parental reports consistently showing more disturbed sleep in the ASD population,[2,5,12] research with in-laboratory sleep studies[4,8,46] and actigraphy[3,7] have not

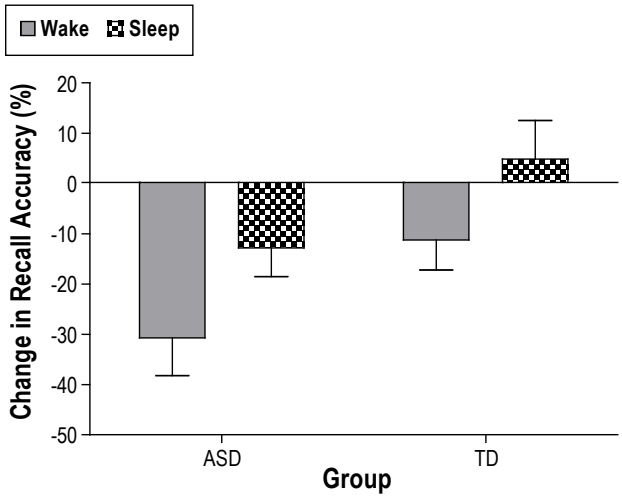

Figure 3—Memory consolidation across sleep and wake intervals for ASD and TD participants. Error bars represent standard error of means. A mixed effects model adjusting for age, nonverbal IQ, and sex revealed that participants' showed significantly less forgetting over periods of sleep than wake across groups (main effect for condition, P = 0.01). Participants with ASD demonstrated more forgetting across conditions than controls (main effect for group, P = 0.049). No group × condition interaction was detected. ASD, autism spectrum disorder; TD, typically developing.

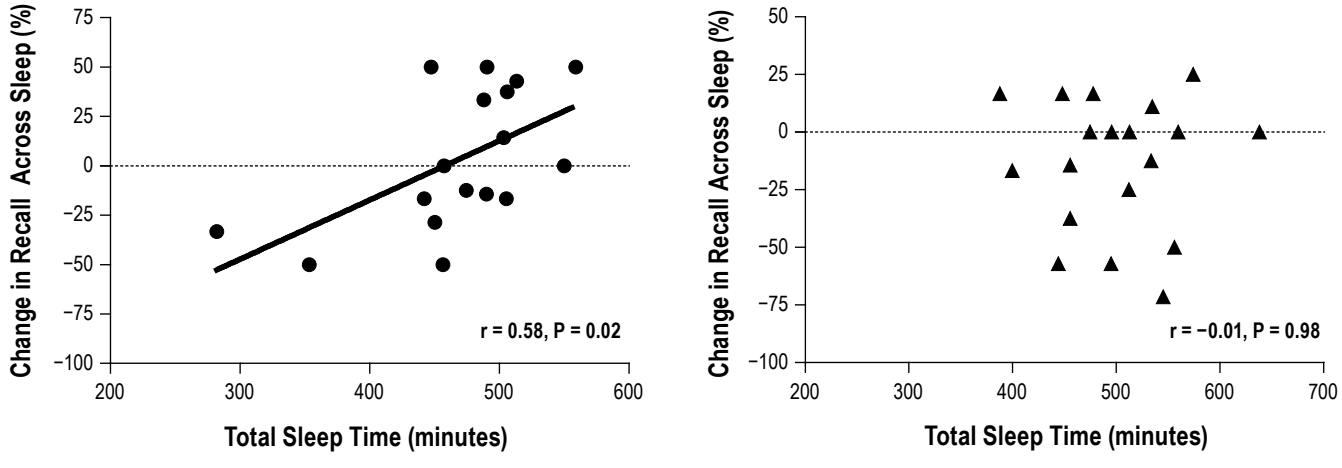

Figure 4—Group correlations between total sleep time and change in recall accuracy on task after sleep. There was a significant correlation between sleep duration and overnight task improvement in the control group (●) but not in the ASD group (▲).

consistently validated these reports of sleep disturbances. Our home PSG data did show more sleep disturbances in the ASD group with longer sleep onset times and lower SE compared to controls. Similar to Buckley et al.,[8] who collected laboratory PSGs of children with ASD, we found reductions in REM sleep in our ASD group, but this difference did not survive controlling for age and medication use. We were particularly interested in group differences in NREM sleep architecture such as SWS, sleep spindles, and slow oscillation power, as these factors have been shown to be associated with declarative memory consolidation in pediatric and adult studies.[23,26,30,31] To this end, we found no group differences in NREM sleep architecture, despite such differences being reported in patients with other neurological conditons such as ADHD[31] and schizophrenia.[41] In contrast to our findings, Limoges et al.[9] have reported significant reductions in sleep spindles among young adults with ASD using comparable spindle identification techniques. Overall, the heterogenity of sleep architecture findings reported in this and other studies may reflect the heterogenity of ASD itself and future meta-analysis accounting for age, ASD severity, medications, and associated comorbidities is needed to determine if there are specific sleep traits within this neurodevelopmental condition.

Despite objective sleep distrubances in the ASD group, both groups showed sleep dependent memory consolidation, with reduced memory loss across sleep compared to wake. The change in performance across sleep, independent of medication and age, showed no significant relationships with any specific sleep parameters other than TST and showed a trend toward less forgetting in the TD group. *Post hoc* tests showed the dependence on TST in the TD group, but not the ASD group. Given that TD participants (but not ASD participants) slept less on the PSG night compared to prestudy actigraphy nights, it is possible that an even greater benefit in memory performance across sleep could have been achieved if TD participants had slept normally on the test night. However, the finding that TST did not correlate with sleep dependent memory consolidation in the ASD group highlights the uncertainty of what the ideal amount of sleep for children with ASD should be. Furthermore, we did not detect an interaction between condition (Sleep/Wake) and group to suggest that sleep benefits one group over another. Although this may be due to lack of power to detect such an interaction, it also raises an interesting question of whether the lower sleep efficiency of children with ASD is still sufficient for their ability to achieve some sleep dependent memory consolidation. In this case, improving their sleep quality could yield even greater benefits to these memory processes.

Collapsing across the Wake and Sleep condition, TD children showed significantly better memory consolidation than the ASD group, even when controlling for confounding variables including age, sex, and NVIQ. We cannot determine if these group differences are due to ASD *per se*, the sleep disturbances found in the ASD group, or other factors, such as general fatigue. Future studies that include groups of children with ASD with and without chronic sleep disturbances are needed to confirm our findings as well as to help determine etiology. Certainly, impaired memory performance could be attributed to comordid conditions of children with ASD such as problems with attention, behavioral difficulties, and/or mood, but measures of these conditions as well as use of treating medications explained little of the variance in task improvement. Participants with ASD in our study took longer to learn the declarative learning task and tended to forget learned card pairs even at immediate testing. Such difficulties learning the task could account for the overall group differences in memory consolidation observed.

CONCLUSION

Our data show that while, in general, children with ASD had poorer memory consolidation than controls, both groups showed more consolidation after a period of sleep than after an equivalent period of daytime wake. Such findings suggest that sleep serves to enhance hippocampally mediated memory consolidation in children with and without neurodevelopmental disability. Improving sleep quality in children with ASD may offer a new approach to improving their cognitive functioning and memory retention.

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DISCLOSURE STATEMENT

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