ARTICLE

Rapid Eye Movement Sleep Percentage in Children With Autism Compared With Children With Developmental Delay and Typical Development

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Objective: To compare objective polysomnographic parameters between 3 cohorts: children with autism, typical development, and developmental delay without autism.

Design: Overnight polysomnographic recordings were scored for sleep architecture according to American Academy of Sleep Medicine criteria by a board-certified sleep medicine specialist blind to diagnosis for studies collected between July 2006 and September 2009.

Setting: Subjects were evaluated in the pediatric ward in the Clinical Research Center of the National Institutes of Health.

Participants: First 60 consecutive children with autism, 15 with typical development, and 13 with developmental delay matched for nonverbal IQ to the autism group, ranging in age from 2 to 13 years, selected without regard to the presence or absence of sleep problem behavior.

Main Outcome Measures: Total sleep time, latencies to non–rapid eye movement (REM) and REM sleep, and percentages of total sleep time for stages 1 and 2 sleep, slow-wave sleep, and REM sleep.

Results: There were no differences between the typical vs developmental delay groups. Comparison of children with autism vs typical children revealed shorter total sleep time ($P=.004$), greater slow-wave sleep percentage ($P=.001$), and much smaller REM sleep percentage (14.5% vs 22.6%; $P<.001$). Comparison of children with autism vs children with developmental delay revealed shorter total sleep time ($P=.001$), greater stage 1 sleep percentage ($P<.001$), greater slow-wave sleep percentage ($P<.001$), and much less REM sleep percentage (14.5% v 25%; $P<.001$).

Conclusion: A relative deficiency of REM sleep may indicate an abnormality in neural organization in young children with autism that is not directly associated with or related to inherent intellectual disability but may serve as a window into understanding core neurotransmitter abnormalities unique to this disorder.

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AUTISM IS A NEURODEVELOPMENTAL disorder characterized by abnormalities in social interaction and communication and by the presence of repetitive behaviors.[1] Abnormalities in gross brain structure, neuronal growth patterns, and neurotransmitter profiles have all been preliminarily explored with little consensus on findings as they relate to pathophysiology.[2] Consistent behavioral disturbances may offer insights into core physiologic or anatomic abnormalities and may help to elucidate biological signatures or endophenotypes. Disturbances in sleep are well-known correlates of autism[3] and sleep disturbances in children with autism are a major clinical concern for caretakers and clinicians. The prevalence has been estimated to be between 44% and 83% for this population.[4] Irregular sleep, frequent night awakenings, prolonged awakenings, and hypersomnia alternating with severely reduced sleep times are the most often reported abnormalities.[5] Most of the previous studies addressing sleep in autism have relied on parent-report measures alone[6-9] or in conjunction with actigraphic recordings,[8,10] which may allow for the tracking of overall sleep-wake cycles more objectively but does not inform on specific sleep architecture, such as relative ratios of rapid eye movement (REM) and non-REM sleep. Although there is clearly a great need for therapeutic interventions that will alleviate these sleep disturbances, progress toward developing such therapies has been stymied by a lack of useful information regarding the underlying neurobiological abnormality.[11]

Markers of sleep architecture and sleep state can be objectively and noninvasively measured and referenced to developmental norms. Polysomnography is a reliable, noninvasive tool used to study the basic mechanisms of sleep and has proven

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useful to neuropsychiatric medicine by serving to identify trait markers for diseases such as narcolepsy and depression.[12] Previous studies in people with autism have identified various abnormalities in REM sleep, including immature organization, decreased quantity, abnormal twitches, undifferentiated sleep, and REM sleep behavior disorder, which is characterized by the absence of the muscle atonia that is normal during REM sleep.[13-16] There have been relatively few exclusively pediatric polysomnographic studies of autism to date. Existing studies have consistently confirmed various abnormalities of sleep but are often difficult to compare because of dissimilar exclusion and inclusion criteria, different age groups, and small number of patients.[17,18]

Given the recent progress in delineating the neurobiology of sleep, investigating putatively abnormal sleep architecture (as it may reflect abnormal neurotransmission) in a large, well-defined, young cohort of children with autism offers the opportunity of identifying trait markers in autism that may be rapidly linkable to emerging genetic findings. Even if such an ambitious goal is not realized, the information gained could have immediate benefits in terms of developing more targeted therapies for the sleep disturbances of autism.

METHODS

SUBJECTS

Our institutional review board approved this study and the cohort presented is a subset from 2 ongoing National Institute of Mental Health investigations, a small clinical trial of minocycline and a larger phenomenologic investigation of the medical and clinical subtypes of autism. Children were recruited to participate in the studies without regard to the presence or absence of sleep problem behavior. This report includes the first 60 children between the ages of 2 and 13 years to be given a research diagnosis of autism (see later), complete an overnight polysomnogram at the National Institute of Health Clinical Research Center, and have a technically complete study (studies where eye leads were lost were not included). Autism symptoms were assessed using the Autism Diagnostic Observation Schedule,[19] a clinician-administered structured play interview designed to elicit behaviors relevant to a diagnosis of autism, and the Autism Diagnostic Interview–Revised,[20] a semistructured parent interview concerning all domains of impairment in autism spectrum disorders. The developmentally delayed group was ascertained for matching on developmental and adaptive capacity to the autism group. Criteria for this group included a non–autism spectrum disorder clinical judgment based on administration of the Autism Diagnostic Interview–Revised and Autism Diagnostic Observation Schedule. Of the first 15 children with developmental delay to complete an overnight polysomnogram, 13 (aged 2-7 years) had technically complete studies and are included in this data set. The typical control group was recruited at a younger age to better match maturational and neurodevelopment levels with the delays seen in the autism group and consists of the first 15 children (aged 1-5 years) to complete an overnight study. Each parent or guardian also completed the Children's Sleep Habits Questionnaire.[21] Medication histories were obtained from all participants to evaluate potential effects of medication on sleep architecture.

POLYSOMNOGRAM

Children were admitted for a continuous overnight recording that included a referential, 21-lead electroencephalogram montage, electro-oculogram, electrocardiogram, and surface electromyogram (chin, anterior tibialis). Respiratory parameters were not measured. Lights out approximated child's actual bedtime. All recordings were videotaped and ended at a median wake up time of 7 AM for all groups. The clinical readings were provided by the same neurophysiologist (S.S.) using National Institute of Neurological Disorders and Stroke electroencephalogram laboratory standards for sleep architecture; these early reports of decreased REM sleep percentage among the children with autism were the impetus for this systemic investigation. A second, blinded reading for sleep architecture and leg movements was done using Grass telefactor software (Grass Technologies, West Warwick, Rhode Island) by a different neurologist, board certified in neurology, neurophysiology, and sleep medicine (A.J.R.). Wake/sleep was subdivided into 30-second epochs and scored according to the guidelines contained in *The AASM* [American Academy of Sleep Medicine] *Manual for the Scoring of Sleep and Associated Events*.[22] The following sleep variables were calculated: total sleep time (the entire sleep period minus the time spent in wakefulness after sleep onset), sleep efficiency index (total sleep time divided by time in bed $\times$ 100), the minutes spent in each sleep stage (stage 1, stage 2, stage 3 or slow-wave sleep, and REM sleep), the percentage of each stage relative to total sleep time, the latency to sleep onset (measured from lights out to the first epoch of stage 1), and the latency to REM sleep (measured from the first epoch of stage 1 to the first epoch of REM sleep).

All participants were allowed to continue taking any prescribed medications during the hospitalization. One child in the typical group was taking diphenhydramine and cetirizine on the night of the study. Four children in the development delay group reported taking a medication on the night of the study that could potentially affect sleep architecture: clobazam (1), somatostatin (1), cetirizine (1), and montelukast (1). In the autism group, 11 children took the following medications on the night of the study: clonidine alone (2); risperidone alone (2); melatonin alone (1); carbamazepine and fluoxetine (1); melatonin and quetiapine (1); melatonin, fluvoxamine, oxcarbazepine, and trazodone (1); topiramate and clonazepam (1); cetirizine (1); and valproate (1).

STATISTICAL ANALYSIS

Descriptive statistics, including medians and interquartile ranges, were computed for all sleep parameters and additional measures (age, nonverbal ratio IQ). The normality of distributions of the sleep parameters was assessed using the Shapiro-Francia W′ test, revealing significant nonnormality in 4 of the 8 measures (wakefulness after sleep onset, sleep efficiency, stage 1 sleep percentage, and latency to REM sleep; $P < .001$). Sample variances for all parameters were compared between groups using the Brown and Forsythe robust test using the sample median as the measure of location; no variances were found to be statistically significantly different at the $P = .01$ level. Pairwise differences between groups (autism, typical, and developmentally delayed) on all measures were thus evaluated by comparing medians to account for nonnormality, and statistical significance was assessed via the Mann-Whitney U test. Tests were 2-sided, and a P value of .01 was considered to indicate statistical significance. In addition, 99% confidence intervals for median differences were computed based on the Hodges-Lehmann statistic.[23] All calculations were generated using Stata statistical analysis software, version 10.1 (StataCorp, College Station, Texas).

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Table 1. Descriptive Statistics

	Mean (SD) [Range]		
	Autism	Typical	DD
No. of observations	60	15	13
Proportion male	0.82	0.73	0.54
Age, y	4.81 (1.88) [2.24-13.11]	3.69 (1.33) [1.35-5.84]	4.29 (1.19) [2.69-7.11]
Nonverbal ratio IQ	56.92 (17.96) [25.07-114.20]	107.97 (15.86) [80.57-142.81]	58.06 (18.84) [9.61-76.63]
Total sleep time, h	7.59 (1.66) [3.23-11.59]	8.81 (0.93) [7.61-10.85]	9.01 (0.88) [6.91-10.13]
Latency to sleep, min	39.4 (41.2) [0.0-144.0]	44.8 (32.8) [6.5-114.0]	33.2 (22.7) [0.0-93.5]
Sleep efficiency, %	80.2 (12.7) [43.5-97.3]	84.7 (7.7) [69.3-95.0]	84.6 (8.1) [63.2-92.5]
Wake after sleep onset, min	73.5 (72.2) [0.5-358.9]	51.7 (52.1) [10.0-178.7]	66.2 (59.5) [14.0-203.9]
Stage 1 sleep, %	5.4 (3.4) [0.4-16.6]	4.0 (1.6) [2.0-7.9]	2.3 (1.5) [0.6-4.8]
Stage 2 sleep, %	56.9 (7.7) [37.8-75.3]	55.9 (5.7) [47.6-69.5]	60.9 (8.2) [50.6-74.4]
Stage 3 or SWS sleep, %	22.6 (6.6) [6.3-39.6]	16.3 (5.4) [4.4-23.5]	13.1 (6.8) [0.0-22.6]
REM sleep, %	15.1 (5.6) [1.4-28.8]	23.0 (4.9) [12.9-30.6]	23.7 (6.2) [9.6-31.8]
REM sleep latency, min	126.3 (86.8) [36.5-556.0]	79.8 (34.2) [36.0-144.5]	76.0 (28.6) [32.5-149.0]

Abbreviations: DD, developmental delay; REM, rapid eye movement; SWS, short-wave sleep.

RESULTS

Means, standard deviations, and ranges of the observed data are presented in **Table 1**. **Table 2** presents medians, interquartile ranges, and the results of Mann-Whitney tests and Hodges-Lehmann confidence intervals. As Table 2 shows, compared with the typically developing group, the subjects with autism showed a significantly shorter total sleep time ($P=.004$), a significantly higher percentage of stage 3 sleep ($P=.001$), and a significantly lower percentage of REM sleep ($P<.001$).

Compared with the developmental delay group, the subjects with autism showed a significantly shorter total sleep time ($P=.001$), a significantly longer stage 1 sleep ($P<.001$), a significantly higher percentage of stage 3 sleep ($P<.001$), and a significantly lower percentage of REM sleep ($P<.001$).

There were no statistically significant differences between the typical group and the developmental delay group on any sleep measurements. Notably, sleep efficiencies and minutes awake after sleep onset did not differ between groups.

The median wake time in the clinical setting was 6:17 AM for the autism group (range, 3:10 AM to 8:34 AM), 6:45 AM for the developmental delay group (range, 5:46 AM to 7:51 AM), and 6:46 AM for the typical group (range, 6:03 AM to 8:36 AM). The median habitual wake time as reported on the Children's Sleep Habits Questionnaire was 7 AM for the autism group, 6:30 AM for the group with developmental delay, and 7 AM for the typical group (n=80 after listwise deletion of Children's Sleep Habits Questionnaire nonrespondents).

Figure 1 presents differences among the 3 cohorts in age, total sleep time, stage 1 sleep percentage, and stage 3 sleep percentage graphically. **Figure 2** shows the group differences in REM sleep percentage.

COMMENT

Our data reveal autism-specific differences in sleep architecture, with the largest median differences occurring in the percentage of REM sleep attained in the autism group in comparison with both a typically developing cohort and a cohort of children with nonspecific developmental delay. This relative deficiency of REM sleep warrants further investigation. The function of REM sleep and its relationship to cognition and overall neurological health is unknown and a subject of ongoing research. We know from animal studies that REM sleep increases after intensive learning sessions,[24,25] which may imply that this stage is important for particular cognitive processes and that REM sleep may be useful as an indicator of brain plasticity. Current studies continue to add support for this postulate.[26-29] Rapid eye movement sleep has most recently been implicated in the process of human memory consolidation and several studies suggest that it is crucial to normal cognitive function and in the processing of emotion in memory systems.[30,31]

Additionally, there is converging evidence that REM sleep serves a specific developmental role. The amount of time spent in REM sleep decreases over the life span. About 50% of a neonate's sleep is devoted to REM vs about 20% to 25% of adult sleep.[32] The decline is the most rapid over the first few years of life and adult values are achieved before puberty.[33] One hypothesis, first proposed in 1966 by Roffwarg and associates[34] and continuing to be explored today, is that the increased ponto-thalamo-cortical activity evident during REM sleep provides the endogenous stimulation needed to form and stabilize durable synaptic connections in the developing brain.[35,36] In support of the theory that REM sleep abnormalities early in life may have long-term consequences, Vogel et al[37,38] have shown that REM sleep deprivation in the neonatal rat induces social deficiencies in the adult animal. Furthermore, in recent animal models of learning and memory exploring this question, REM sleep deficiency has been found to have differential effects on markers of neuronal plasticity (as measured by changes in molecular components of glutamatergic synapses) that are age dependent.[39] For example, in work published by Lopez and colleagues in 2008, they suggest that REM sleep deprivation early in life may interfere with the correct for-

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Table 2. Children With Autism Have Shorter Total Sleep Time, Increased SWS, and Relative REM Sleep Deficiency

	Median (IQR)			*P* Value (99% CI)[a]		
	Autism	Typical	DD	Autism vs Typical	Autism vs DD	Typical vs DD
Age, y	4.49 (1.95)	3.60 (2.42)	3.91 (1.44)	.04 (–0.22 to 2.07)	.37 (–0.75 to 1.54)	.26 (–1.95 to 0.86)
Nonverbal ratio IQ	56.06 (24.11)	105.90 (26.96)	67.25 (22.55)	<.001 (–64.71 to –38.54)	.41 (–17.97 to 12.50)	<.001 (29.80 to 66.34)
Total sleep time, h	7.70 (2.04)	8.83 (1.66)	9.15 (1.14)	.004 (–2.13 to –0.15)	.001 (–2.39 to –0.33)	.34 (–1.23 to 0.72)
Latency to sleep, min	28.5 (65.5)	37.5 (34.5)	33.0 (11.5)	.29 (–34.0 to 20.0)	.84 (–27.0 to 31.0)	.38 (–16.5 to 37.5)
Sleep efficiency, %	83.7 (16.5)	86.2 (11.8)	87.8 (8.9)	.29 (–11.3 to 4.4)	.36 (–12.0 to 4.2)	.89 (–8.7 to 7.4)
Wake after sleep onset, min	50.1 (82.7)	37.0 (40.0)	45.1 (43.8)	.31 (–16.3 to 52.0)	.97 (–34.1 to 46.5)	.42 (–54.5 to 23.0)
Stage 1 sleep, %	4.7 (4.9)	3.7 (1.2)	2.1 (2.3)	.14 (–0.8 to 2.8)	<.001 (0.6 to 4.7)	.02 (–0.1 to 3.1)
Stage 2 sleep, %	56.4 (12.3)	55.8 (8.5)	57.3 (10.7)	.62 (–4.4 to 7.0)	.18 (–10.9 to 3.1)	.10 (–13.8 to 2.7)
Stage 3 or SWS sleep, %	21.5 (9.0)	18.6 (5.4)	13.7 (7.1)	.001 (1.1 to 10.4)	<.001 (3.1 to 15.1])	.08 (–3.3 to 9.7)
REM sleep, %	14.5 (8.4)	22.6 (6.5)	25.0 (6.8)	<.001 (–12.1 to –3.7)	<.001 (–13.9 to –4.1)	.61 (6.7 to 4.8)
REM sleep latency, min	108.5 (80.3)	64.0 (59.0)	69.0 (27.5)	.02 (–2.5 to 71.0)	.012 (–0.5 to 74.0)	.89 (–28.0 to 42.0)

Abbreviations: CI, confidence interval; DD, developmental delay; IQR, interquartile range; REM, rapid eye movement; SWS, short-wave sleep.
[a] *P* values are from pairwise, 2-tailed Mann-Whitney *U* tests and 99% CIs are for the Hodges-Lehmann median differences. Number of observations=60, autism; 15, typical; and 13, DD.

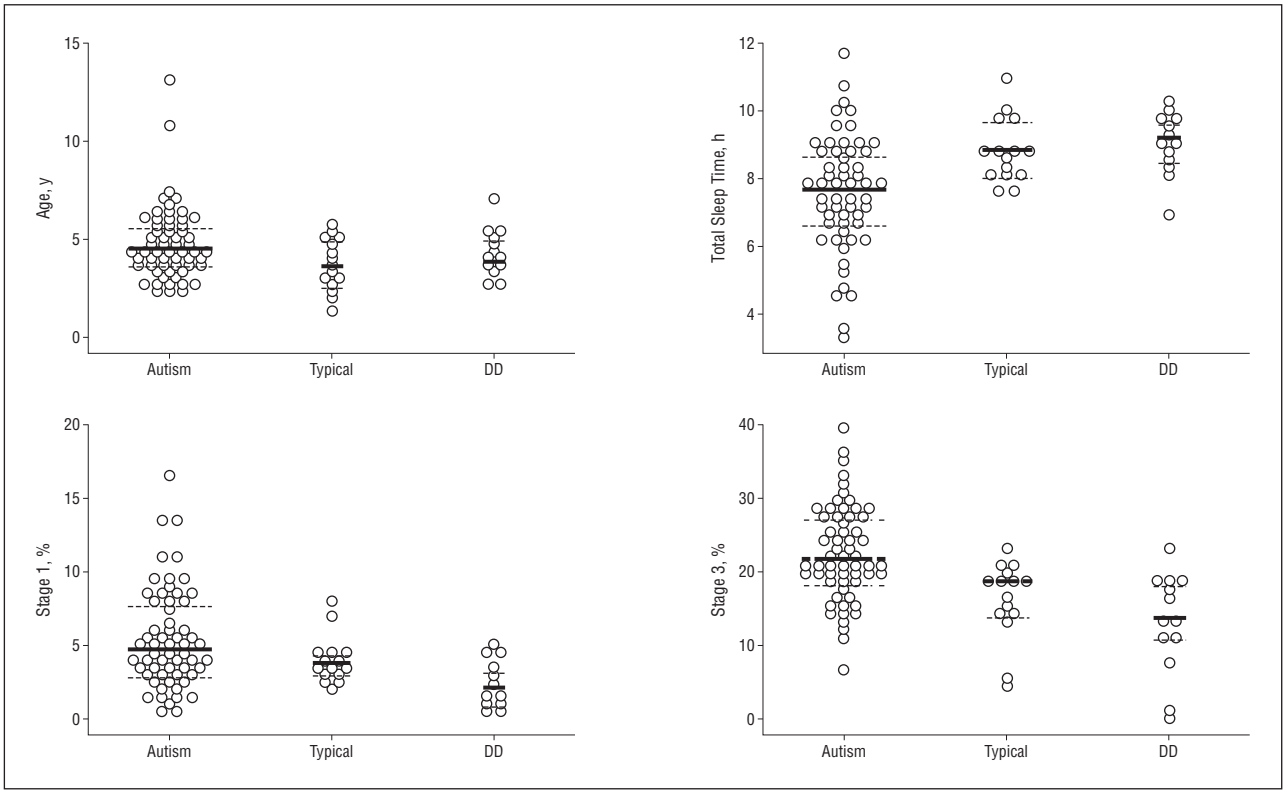

Figure 1. Age, total sleep time, stage 1 sleep percentage, and stage 3 sleep (slow-wave sleep) percentage by group. Dark lines denote group medians; dashed lines, interquartile range. DD indicates developmental delay.

mation of neural circuits in the hippocampus "possibly by hindering expression of mature glutamatergic synaptic components."[39(p44)]

Our study has several limitations. The recordings were conducted on a regular pediatric ward and not in a specialized sleep laboratory. While the total sleep times for the typical controls are comparable with other pediatric laboratory-based studies,[40] the sleep efficiency is not as great for any of the 3 groups as might have been obtained in a more controlled environment. Another limitation is that respiratory parameters were not measured, rendering it impossible to know the potential contribution of obstructive sleep apnea to sleep architecture in any of the cohorts. The prevalence of obstructive sleep apnea in the general pediatric population is estimated at 2%. This is an important consideration, but it may not have a direct impact on the interpretation of these results. While it is true that obstructive sleep apnea is more likely to occur in REM than non-REM sleep in children, sleep architecture appears to be preserved in children with obstructive sleep apnea without the associated electroencephalogram arousal and measurable sleep fragmentation that often follows obstructive events in adults.[41] A third limitation is the potential effects of various medications on sleep stages. Being medication

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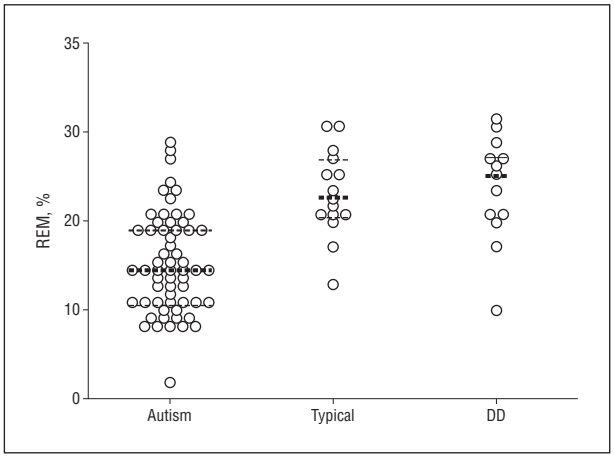

Figure 2. Rapid eye movement (REM) sleep percentage by group. Dark lines denote group medians; dashed lines, interquartile range. DD indicates developmental delay.

free was not an inclusion criterion for either of the parent studies. In the autism group, there was no statistically significant difference in the median REM sleep percentage among those taking any medication (11.1%) and those not (14.7%; $P = .17$).

Investigation of sleep-state transitions in autism offers an opportunity to speculate on the underlying neurotransmission. The control of wake/non-REM/REM rhythms is complex, involving γ-aminobutyric acid, glutamate, and 3 major neurotransmitter systems: serotonin, produced by cells in the dorsal raphe nucleus; norepinephrine, from the locus coeruleus; and acetylcholine, with neurons in the basal forebrain and the brainstem and interneurons in the striatum. Acetylcholine is the main driver of REM sleep and in concert with serotonin and norepinephrine, it acts on brainstem structures in the pons and adjacent areas of the midbrain via "REM/on" and "REM/off" cells to coordinate REM and non-REM sleep.[42] It is this reciprocal model of inhibitory aminergic neurons and excitatory cholinergic neurons that modulates brain activity between the non-REM and REM states. An imbalance in either arm may result in state instability. It is our conjecture that in the developing brain the proper stabilization of synaptic pathways is at least partly dependent on the rich periods of disinhibition that occur during the REM state. Neuropathologic investigations by Bauman and Kemper[43] in 1994, Perry et al[44] in 2001, Lee et al[45] in 2002, and Martin-Ruiz et al[46] in 2004 implicate the cholinergic system in the abnormal development of the autistic brain. When considered in conjunction with the knowledge that cholinergic afferents innervate the cerebral cortex during a period of intense neuronal differentiation and synapse formation,[47] the findings highlight the relevance of further investigation of the cholinergic system in autism, particularly early in development.

The differences in slow-wave sleep percentage between the autism group and both the typically developing cohort and the developmental delay group without autism may offer further clues as to whether the underlying differences in sleep architecture between cohorts are mediated by cholinergic abnormalities. During slow-wave sleep, a different neurotransmission milieu is evident than is present during REM sleep. Slow-wave appearance is greatly influenced by the presence of acetylcholine. Unlike in REM sleep where cholinergic input is high, slow-wave sleep is characterized by a relative diminution of this neurotransmitter.[48,49] A more global (not just in the pontine brainstem where REM is orchestrated) cholinergic deficiency would predict a more permissive environment for slow-wave generation and could conceivably be represented by a higher percentage of this state, which was, in fact, what we found in the autism group.

In summary, the extant literature supports a far-reaching hypothesis that a primary cholinergic deficiency may simultaneously produce deficits in REM sleep in autism and contribute to the social-emotional deficits that are at the core of the autism phenotype both directly and indirectly (through the lack of appropriate developmental support provided by REM sleep early in development). Future studies should attempt to disentangle these possibilities as a means of linking the profound social and emotional processing deficits that characterize autism to a fundamental deficit in physiological regulation. Should such a link be discovered, it would provide an immediate target for pharmacologic therapies and could also lead to the development of an objective biomarker for identification of infants at risk for autism.

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While we may not be able to control all that happens to us, we can control what happens inside us.
—Ben Franklin

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