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Atypical sleep architecture and the autism phenotype

Élyse Limoges,[1] Laurent Mottron,[1,2] Christianne Bolduc,[1] Claude Berthiaume[1] and Roger Godbout[1,2]

[1]*Centre de Recherche Fernand-Seguin, Neurodevelopmental Disorders Program, Hôpital Rivière-des-Prairies and* [2]*Department of Psychiatry, Université de Montréal, Québec, Canada*

Correspondence to: Roger Godbout PhD, Sleep Laboratory, Hôpital Rivière-des-Prairies, 7070 Perras Blvd., Montréal, Québec H1E 1A4, Canada
E-mail: roger.godbout@umontreal.ca

Summary

A growing body of evidence indicates that people with autism frequently experience sleep disorders and exhibit atypical sleep architecture. In order to establish whether sleep disorders truly belong to the autism spectrum disorder (ASD) phenotype, we conducted a subjective and objective study of sleep in a group of high-functioning adults with ASD but without sleep complaints, psychiatric disorders or neurological comorbidity. We compared the subjective data of 27 ASD participants with those of 78 healthy controls matched for chronological age and gender. Subjective measures of sleep in the clinical group were compatible with insomnia and/or a tolerable phase advance of the sleep–wake cycle. Subjective data were confirmed by objective laboratory sleep recordings in a subset of 16 patients and 16 controls. Persons with autism presented with a longer sleep latency ($P < 0.04$), more frequent nocturnal awakenings ($P < 0.03$), lower sleep efficiency ($P < 0.03$), increased duration of stage 1 sleep ($P < 0.02$), decreased non-REM sleep (stages 2 + 3 + 4, $P < 0.04$) and slow-wave sleep (stages 3 + 4, $P < 0.05$), fewer stage 2 EEG sleep spindles ($P < 0.004$), and a lower number of rapid eye movements during REM sleep ($P < 0.006$) than did control participants. On clinical scales, the scores of persons with ASD on the Beck Depression Inventory were similar to those of persons without, but their trait anxiety scores on the Spielberger Anxiety Scale were higher ($P < 0.02$). The state anxiety scores of the Spielberger scale and cortisol levels were the same in the two groups. Objective total sleep time correlated negatively with the Social (-0.52, $P < 0.05$) and Communication (-0.54, $P < 0.02$) scales of the Autism Diagnostic Interview—Revised. The sleep of clinical subgroups (10 with high-functioning autism, six with Asperger syndrome) did not differ, except for the presence of fewer EEG sleep spindles in the Asperger syndrome subgroup ($P < 0.05$). In conclusion, these findings indicate that atypicalities of sleep constitute a salient feature of the adult ASD phenotype and this should be further investigated in younger patients. Moreover, the results are consistent with an atypical organization of neural networks subserving the macro- and microstructure of sleep in ASD. We are furthering this research with quantified analysis of sleep EEG.

Keywords: autistic phenotype; EEG; sleep; anxiety; cortisol

Abbreviations: ADI-R = Autism Diagnostic Interview—Revised; ASD = autism spectrum disorder; HFA = high-functioning autism; IQ = intelligence quotient; PLMS = periodic limb movements during sleep; REM = rapid eye movement; SE = sleep efficiency; SWS = slow-wave sleep; TST = total sleep time.

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Introduction

Autism spectrum disorder (ASD) is a pervasive developmental disorder with neurological origins (Akshoomoff *et al*., 2002; Brambilla *et al*., 2003; Courchesne *et al*., 2004; Palmen and van Engeland, 2004). Persons with ASD are characterized by negative symptoms in the social, communication and imagination domains, and by positive symptoms in the domains of repetitive behaviours and restrictive interests (American Psychiatric Association, 1994). In addition to the behavioural phenotype, two related markers of abnormal neural functioning have been identified in a significant proportion: epilepsy and mental retardation. Still, approximately half of all individuals with ASD are of normal intelligence (Honda *et al*., 1996; Baird *et al*., 2000; Kielinen *et al*., 2000; Chakrabarti and Fombonne, 2001; Fombonne *et al*., 2004) and are referred to as 'high-functioning' individuals with autism. Although

high-functioning persons with autism are broadly divided into two subgroups based on the presence [high-functioning autism (HFA)] or absence (Asperger syndrome) of a delay in the development of language, there is not enough evidence at present to distinguish between these two subgroups (Macintosh and Dissanayake, 2004). A growing body of literature contains reports of sleep disorders as a third indicator of abnormal neural functioning in autism and, therefore, a characteristic of the ASD phenotype (Stores and Wiggs, 1998; Richdale, 1999; Richdale, 2001). Both subjective (self or parent reports) and objective (EEG or actigraphic recordings) measures have served as markers of sleep disorders in this recent literature.

Two papers published to date (Tani *et al*., 2003, 2004*a*) have analysed subjective sleep data from adults with autism, using responses from the same group of 20 persons with Asperger syndrome, 16 of which presented with psychiatric comorbidity (including one or more anxiety disorders, mild to moderate depression and obsessive–compulsive disorder). Results indicated a sleep latency twice as long in the clinical group compared with controls, as well as prolonged waking after sleep onset and a lower sleep efficiency index. However, the difference in total sleep time was unremarkable. The authors also noted a greater night-to-night variability of sleep parameters in the clinical group. Finally, it was observed that the clinical group reported a lower sleep quality and more daytime sleepiness than controls.

Parents' subjective reports of sleep parameters have revealed similar patterns of sleep latency in children and adolescents with ASD (Hoshino *et al*., 1984; Richdale and Prior, 1995; Taira *et al*., 1998; Patzold *et al*., 1998; Honomichl *et al*., 2002), along with more awakenings after sleep onset than in children and adolescent controls (Richdale and Prior, 1995; Patzold *et al*., 1998; Honomichl *et al*., 2002). Parents of children with ASD have also reported lower sleep quality in their children (Hoshino *et al*., 1984; Honomichl *et al*., 2002) than have parents of control children, along with greater variability in night-to-night sleep parameters among patients (Takase *et al*., 1998; Hoshino *et al*., 1984). In contrast to the majority of findings in studies of adults with ASD, these authors also observed lower total sleep time in children with ASD than in controls (Patzold *et al*., 1998; Honomichl *et al*., 2002).

There are only two studies of laboratory sleep recordings (polysomnography) taken from individuals with autism that did not include participants of different ages or levels of intellectual functioning (Godbout *et al*., 1998; Tani *et al*., 2004*b*). The first one (Godbout *et al*., 1998) is a single-case study of a person with Asperger syndrome and comorbid neurological illnesses (Fahr's disease and primary hypoparathyroidism). The participant exhibited lower levels of slow-wave sleep (SWS), higher levels of stage 1 sleep, and a larger number of awakenings than did people in a group of control participants. All other sleep variables were normal in this patient, including rapid eye movement (REM) sleep parameters, while the visual analysis of phasic EEG events revealed a very low number of sleep spindles. In the second study, Tani *et al*. (2004*b*) recorded polysomnographically the same group of persons with Asperger syndrome, frequent insomnia and psychiatric comorbidity that they described previously with subjective measures (Tani *et al*., 2003, 2004*a*). They found no differences with a group of 10 control participants, including an unremarkable density of sleep spindles, which were scored with automatic detection software. In the two other published polysomnographic studies of adults with autism, one included Asperger syndrome participants who ranged in age from 7 to 53 years (Godbout *et al*., 2000), and the other was an examination of the sleep of participants with low intelligence quotient (IQ < 30; Diomedi *et al*., 1999). Polysomnographic recordings of sleep in children with autism have revealed decreased time in bed, sleep period time, total sleep time, REM sleep latency, and proportion of stage 1 sleep as well as a greater number of muscle twitches compared with healthy controls (Elia *et al*., 2000). Thus, although subjective sleep parameters appear to be roughly similar in adults and children with ASD, there are inconsistencies in the objective sleep profiles obtained from actual sleep recordings.

Perhaps the confusion and inconsistencies in this nascent literature stem from the heterogeneity in age, IQ, and comorbidity with other physical or psychological disorders that characterizes the vast majority of the studies conducted thus far. This casts doubt on the reliability of published findings and, ultimately, on the conclusion that sleep disorders in individuals with autism are manifestations of the autism phenotype rather than transient disorders of development or comorbidity.

First, most studies rely on heterogeneous populations of participants, including the mentally retarded, the young, or both (Tanguay *et al*., 1976; Ornitz *et al*., 1965; Ogawa *et al*., 1982; Hoshino *et al*., 1984; Elia *et al*., 1991; Segawa *et al*., 1992; Richdale and Prior, 1995; Wiggs and Stores, 1996; Patzold *et al*., 1998; Taira *et al*., 1998; Takase *et al*., 1998; Diomedi *et al*., 1999; Hering *et al*., 1999, 2000; Richdale *et al*., 2000; Shreck and Mulick, 2000; Hayashi *et al*., 2001; Honomichl *et al*., 2002; Thirumalai *et al*., 2002). Yet intellectual functioning and age are two factors that are likely to confound both the subjective and objective measurement of sleep.

The mixed results in the literature on the sleep of participants with ASD might also be due to the inclusion of more than one pervasive developmental disorder subgroup in the same experimental cohort, which acts as an artefact. It is therefore important to compute sleep measures in participants with HFA and Asperger syndrome separately and compare them before tendering any general hypothesis about their sleep. No direct statistical comparison between adults with HFA and Asperger syndrome on objective and subjective measures of sleep is currently available in the literature.

A second problem with the existing literature on sleep disorders in ASD is the inclusion in most studies of participants with a neurological or psychiatric comorbidity, or an

absence in the majority of analyses of controls for these variables. A neurological or other medical comorbidity is present in approximately 10% of individuals with HFA; this is referred to as the 'aetiological fraction' of autism. Neurological or medical comorbidity occur more frequently in individuals with ASD and mental retardation (Volkmar *et al*., 2004). Psychiatric comorbidity is not part of the autism phenotype but it might contribute to the sleep disorders that have been reported. In the only study of subjective sleep data exclusively in adults with ASD (Asperger syndrome), Tani *et al*. (2003, 2004*a*) found that 75–90% of participants self-reported elements of insomnia [75% in sleep diaries, 85% using free, detailed description (short essays), 90% with sleep questionnaires], whereas 80% presented with a psychiatric comorbidity. Polysomnographic recordings in the same group of 20 patients revealed no differences compared with 10 control participants (Tani *et al*., 2004*b*). The authors concluded that subjective insomnia was either due to comorbid psychiatric disorders, to the Asperger syndrome itself, or to a combination of both factors. They discuss their lack of objective findings in terms of the masking effects that anxiety may have on polysomnographic measures. Unfortunately, no laboratory study of sleep in a homogeneous group of adults with ASD, with normal intellectual capacities and without comorbidity, is available at present and the relationship between sleep and clinical status has never been statistically tested. In a study of parents' subjective reports of sleep in their autistic children, Patzold *et al*. (1998) found an association between psychopathology and increased reports of sleep problems. No one has explored this association between sleep patterns and daytime functioning in adults with ASD only.

A third problem with establishing sleep disorders as part of the phenotype of ASD is that existing conclusions in the literature on sleep disorders in autism are based almost exclusively on subjective measures. Moreover, it has been suggested that caregivers are biased when reporting that the sleep of their children is problematic (Hering *et al*., 1999; but see Honomichl *et al*., 2002; Wiggs and Stores, 2004). In any case, sleep studies that feature both subjective and objective recordings have not yet confirmed results obtained by behavioural assessments of sleep.

Most studies in the neuroscience of autism are now performed with adult participants of normal intelligence and without neurological or psychiatric comorbidity (Mottron, 2004), in an effort to discard the confounding effects of development and mental retardation and to document 'genetic autism' rather than the heterogeneous aetiological fraction of autism. Moreover, autism with normal intelligence is bound to better represent 'pure' genetic autism, as shown by the fact that the incidence of the broader autistic phenotype is greater in the families of high-functioning probands than in the families of low-functioning probands (Szatmari *et al*., 2000; for a review see Nicolson and Szatmari, 2003). For this reason, new investigations with updated methods of evaluating the sleep of persons with ASD are needed. It is imperative to select patients on the basis of stringent diagnostic criteria [Autism Diagnostic Interview—Revised (ADI-R), Autism Diagnostic Observation Schedule, no comorbidity, no medication, normal IQ or better], separate analyses of HFA and Asperger syndrome data, and careful selection of comparison groups in order to eliminate the confounding effects of these parameters. Studying *adults* with ASD might also help to identify the autism phenotypic sleep profile independent of developmental effects, since sleep reaches stability during young adult age. Both self-reported (subjective) and objective measures of sleep recorded in the same individuals are also required to achieve consistency. These methodological refinements will allow the determination of the extent to which sleep disorders are actually a component of the autistic phenotype, of whether or not a proportion of these disorders is associated with psychiatric comorbidity, and of the respective contributions of HFA and Asperger syndrome to these sleep disorders. The aim of the present research was to study sleep in ASD using such standards.

Methods

Participants

Sleep habits questionnaire

Twenty-seven high-functioning adults (25 men, two women) with ASD (mean age = 21.1 years, SD = 3.6, range 16–27) entered the study. The diagnosis was based on the results of the ADI-R (Lord *et al*., 1994), which one of the authors (L.M., who had received training on this instrument and who achieved a reliability of 0.9 with its developers) conducted with participants. Diagnosis was confirmed through careful scrutiny of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV) (APA, 1994) criteria for ASD and differential axis-1 diagnoses combined with direct observation of the participant. Six of the participants received diagnoses of Asperger's syndrome; all participants were above the ADI-R cut-off for autism. Participants presented with no other current axis-I diagnoses besides ASD, except for one Asperger syndrome participant with attention deficit hyperactivity disorder and one HFA individual with expressive language disorder (not included in the sleep recording group and not included in the cortisol data). The statistical analyses we report below were also performed excluding these two participants, without affecting the results. All participants were unmedicated except two patients who were still treated with risperidone but not included in the sleep recording group (and not included in the cortisol data). Three patients were withdrawn from methylphenidate or antidepressants for at least 18 months. Most patients lived with their family (n = 19/27; 70%) or independently (n = 7/27; 26%) while one (4%) lived in a supervised apartment. All patients were screened for psychiatric disorders through an in-depth clinical investigation performed by one of us (L.M., a psychiatrist) at the time of passing a standardized diagnostic instrument for autism; neurological comorbidity was assessed through file and anamnesis information. The comparison group included 78 healthy controls (mean = 21.8 years old, SD = 2.8, range 16–30) recruited through advertisements in the community. They filled in a questionnaire asking for previous health disorders, diagnoses, treatments or hospitalization. Exclusion criteria were: a personal history of sleep disorders; a chronic or current illness; a recent history of night work; evidence of psychopathology or drug abuse; or current use of CNS-active drugs.

Only participants with a full-scale IQ of at least 80, as indicated by their results on the Wechsler Adult Intelligence Scale, 3rd Edition (Wechsler, 1997), were included. The full-scale IQ of both groups ranged from 82 to 136.

Laboratory sleep study

Laboratory sleep recordings for two consecutive nights were obtained for 16 of the participants with ASD and 16 of the control participants (Table 1). These persons also completed additional subjective sleep scales, including a chronotype questionnaire, psychiatric scales, and saliva cortisol measures (see below). Participants were asked to keep a regular sleep–wake schedule for 14 days before coming to the laboratory, to complete a sleep diary during this period, and to refrain from napping during the day prior to the recording. Beverages containing caffeine and alcohol were not permitted after 12:00 noon.

All participants received financial compensation for their involvement in this research. We followed the guidelines of the Declaration of Helsinki (BMJ 1991; 302: 1194) in obtaining their consent to participate, and the research project was approved by the Ethical Committee of the Institution where the study took place.

Sleep-related measures

Sleep habits questionnaire

Participants filled in a sleep questionnaire containing open questions about sleep habits for the past month: bedtimes and rise times on weekdays and weekends, sleep latency, and nocturnal awakenings (frequency and duration). Respondents indicated their perceptions of restfulness after sleep on a four-point scale (feeling very, moderately, little, or not at all restful); they gave 'yes' or 'no' responses to questions regarding their sleep satisfaction and daytime naps. Answers were used to determine the following variables: bedtime shift (difference between weekend and weekdays bedtimes), wake time shift (difference between weekend and weekdays rise times), time in bed (time elapsed from bedtime to rise time in the morning), total sleep time (TST) (time in bed – [time falling asleep + duration of nocturnal awakenings]), and sleep efficiency or SE ([TST/TST + duration of nocturnal awakenings] $\times$ 100).

Chronotype

We used a French translation of Horne and Östberg's (1976) questionnaire to determine morningness–eveningness typology. Established cut-off scores are: 16–30 for extreme eveningness preference, 31–41 for moderate eveningness, 42–58 for the intermediate group, 59–69 for moderate morningness and 70–86 for extreme morningness.

Laboratory sleep measures

Participants were recorded for two consecutive nights in individual bedrooms using a Grass Neurodata Model 15 Acquisition System assisted by Harmonie 5.0B software (Stellate System, Montréal, Canada). All participants had the opportunity to go to bed at their preferred time. Sleep was recorded and scored blind relative to group condition using 20-s epochs according to standard methods, including central and occipital EEG (C3, C4, O1, O2), submental EMG and periorbital electro-oculogram (Rechtschaffen and Kales, 1968). Oronasal airflow and thoracic and abdominal respiratory effort were monitored during the adaptation night. Sleep onset latency was defined as the first occurrence of either 10 consecutive minutes of stage 1 sleep or the first epoch of any other sleep stage. Sleep stage latencies were defined as the interval between sleep onset and the first epoch of that stage. Total sleep time equals the total number of minutes spent in any of the sleep stages during the sleep period (i.e. from sleep onset to final awakening). Total sleep time was broken down into thirds of the sleep period. Periodic leg movements in sleep (PLMS) were recorded and scored according to standard criteria (Coleman, 1982; Montplaisir *et al*., 2000), with a pathological index set at $\geqslant$10 movements/h of sleep. Periodic leg movements during wake time following sleep onset were also scored as an estimate of the restless legs syndrome (Montplaisir *et al*., 1985).

Three sleep phasic activities were scored (Godbout *et al*., 2000). Stage 2 sleep spindles were visually identified on the C3 (left central) and Fp1 (left frontal) leads (referred to linked earlobes) as bursts of EEG activity at 12–15 Hz, lasting 0.5–2.0 s. No amplitude criteria were applied. Stage 2 K-complexes were visually identified on the C3 lead according to the following criteria: a negative-going biphasic wave with sharp onset and smoother offset, lasting 0.5 to 1.5 s, and with an amplitude of at least 75 μV. REM density was defined as the number of two-second REM sleep epochs containing at least one rapid eye movement. We calculated the density of EEG sleep spindles and K-complexes by dividing the total number of events by the time (in h) spent in stage 2. We computed REM density by dividing the total number of events by the time (in h) spent in REM sleep. All polysomnographic data presented below are from the second night in laboratory.

Psychological functioning

Participants completed the following scales during the first and second evening of sleep recordings.

Table 1 *Characteristics of the participants recorded in the sleep laboratory*

	Controls (n = 16)	ASD (n = 16)	HFA (n = 10)	Asperger syndrome (n = 6)	Controls versus ASD P	HFA versus Asperger syndrome P
Male/female	15/1	15/1	9/1	6/0	–	–
Active[(1)]/inactive	16/0	13/3	8/2	5/1	–	–
Age (years): mean $\pm$ SD	20.6 $\pm$ 3.9	22.1 $\pm$ 3.6	20.9 $\pm$ 3.8	24.2 $\pm$ 2.1	0.22	0.08
Age range	16–26	16–27	16–26	22–27		
Full IQ: mean $\pm$ SD	114.4 $\pm$ 14.2	102.1 $\pm$ 10.3	100.3 $\pm$ 10.7	105.2 $\pm$ 9.8	0.01	0.38
Full IQ: range	91–136	83–120	83–115	94–120		

Statistical comparisons were made using Student's t-tests. IQ = intelligence quotient. [(1)]active = regular work, or attend school daily. – not calculated. P values between 0.06 and 0.09 are shown as an indicator of tendencies.

Achenbach Youth Self-Report scale (Achenbach, 1991)

This is a measure of adaptive behaviours. It generates a total score and two 'broadband' scales, i.e. Internalizing (withdrawn, somatic complaints, anxious-depressed, social problems, thought problems, attention problems) and Externalizing (delinquent behaviour, aggressive behaviour), as well as two competence scales (Activities and Social).

Anxiety scale

The State-Trait Anxiety Inventory (Spielberger *et al*., 1970) adapted in French by Bergeron *et al*. (1976) was used. The State-Anxiety subscale evaluates how respondents feel 'right now', as they fill in the questionnaire. The Trait-Anxiety subscale indicates how respondents generally feel in daily-life situations. There is no cut-off score for the State-Trait Anxiety Scale that clearly indicates pathology.

Depression scale

Participants filled in the 21-item Beck Depression Inventory, 2nd Edition (Beck *et al*., 1998). The Beck Depression Inventory is not a diagnostic instrument but grades the magnitude of cognitive consequences of depression.

Cortisol

The use of salivary cortisol as an index of hypothalamic–pituitary–adrenal axis activity and emotional distress is widespread (Biondi and Picardi, 1999). Cortisol levels in healthy and clinical populations tend to increase during states of anxiety, stress or depression (Goodyer *et al*., 2000; de Kloet 2003; Tse *et al*., 2004). Observed psychoendocrine response patterns seem to be related to individuals' subjective perception of a particular situation (Kirschbaum and Hellhammer, 1989; Biondi and Picardi, 1999).

Samples of saliva were collected in the evening (five samples) and in the morning (two samples) of nights 1 and 2, using neutral Salivettes (Sarstedt, Montréal, Canada) in 12 ASD participants and 12 controls. Experimenters took samples of participants' saliva upon their arrival at the laboratory, 20 min after arrival, 40 min before bedtime, 20 min before bedtime, at bedtime, at rise time, and 20 min after rise time. The soaked cotton swabs were immediately centrifuged; the saliva was transferred to aliquots and stored at $-20°C$ until analysis. Cortisol concentration was measured in duplicate using a commercially available direct 125I radioimmunoassay kit modified for saliva (Coat-a-Count®; Diagnostic Products Corporation, Los Angeles, CA, USA). Since some of the samples could not be used because of low saliva volume, results of the two nights were averaged into one data set.

Statistical analyses

Statistical comparisons were conducted first between groups (ASD versus their comparison group) then within groups (HFA versus Asperger syndrome) with a criteria for significance set at 0.05.

Sleep measures

We compared subjective and objective sleep parameters between groups using Student's *t*-test and non-parametric Mann–Whitney *U*-tests. When both statistical tests yielded similar results, only Student's *t*-tests are reported; whenever a discordance prevailed, only the more conservative Mann–Whitney *U*-test is reported. Categorical data were analysed using χ^2 tests. Analysis of variance (ANOVA) per thirds of night were also performed to evaluate the distribution of SWS and REM sleep throughout the night. Main effects were further analysed with Newman–Keuls tests for pairwise comparisons.

Psychological functioning

We compared the results on each scale between the two groups using Student's *t*-test and non-parametric Mann–Whitney *U*-tests. For the reasons stated above, we only report the results of the *t*-test.

Cortisol

Saliva cortisol levels were compared between the two groups using repeated- measures ANOVA, with diagnosis as the between-subject factor and time as the within-subject factor. Main effects were further analysed with Newman–Keuls tests for pairwise comparisons.

Correlation

We calculated correlation coefficients between comparable objective and subjective sleep parameters using Spearman's ρ. Correlation coefficients between objective sleep parameters and clinical measures were also calculated. The correlation of psychological functioning with certain laboratory sleep measures (sleep onset latency, REM sleep latency, percentage of REM sleep, TST, wake time after sleep onset and SE) was computed because these sleep parameters are affected in depression and anxiety (Benca *et al*., 1992). We also examined the correlation between autistic symptomatology (ADI-R) on the one hand and TST and REM density on the other, since an association between those variables has already been demonstrated in autistic children (Patzold *et al*., 1998; Elia *et al*., 2000; Shreck *et al*., 2004). Exact tables of percentiles were used for each correlation analysis, using critical values for the number of subjects involved.

Results

Sleep-related measures

Sleep habits

Table 2 contains the subjective sleep parameter descriptive statistics and the results of Student's *t*-test and χ^2 test comparisons.

Subjective sleep reports revealed several differences on sleep initiation and other sleep continuity measures (sleep latency, nocturnal awakenings, total sleep time, sleep efficiency). Participants with ASD demonstrated more prolonged sleep latency, more wakefulness after sleep onset, and decreased sleep efficiency than did control participants. More specifically, 13 out of 27 patients reported taking 30 min or more, three times or more per week to fall asleep. However, there was no significant difference in the total sleep time of the two groups, although there were differences in sleep–wake schedule between the two: adults with ASD reported earlier bedtime and rise time than did control participants. They also spent more time in bed on weekends. In contrast, there were no significant differences in napping habits and in the stability of sleep–wake schedules between individuals with and without ASD. Similarly, there was no significant difference in perception of sleep quality between the groups.

Table 2 *Sleep habits questionnaire measures in ASD participants versus comparison participants (mean ± SEM)*

Sleep parameters	Controls (n = 78)	ASD (n = 27)	HFA (n = 11)	Asperger syndrome (n = 16)	Controls versus ASD P	HFA versus Asperger syndrome P
Sleep initiation and continuity						
Sleep onset latency (SOL)[a] (min)	15.46 ± 1.01	31.79 ± 4.32	30.03 ± 5.43	33.00 ± 6.38	0.001	ns
SOL >30 min[b] (nights/week)	1.17 ± 0.15	2.81 ± 0.44	2.55 ± 0.64	3.00 ± 0.62	0.00005	ns
Nocturnal awakenings[b] (no.)	0.95 ± 0.11	1.46 ± 0.25	1.27 ± 0.30	1.62 ± 0.39	0.006	ns
Nocturnal awakenings[a] (min)	4.49 ± 1.11	12.83 ± 2.93	8.91 ± 2.72	16.15 ± 4.81	0.01	ns
Total sleep time[a] (h)	8.28 ± 0.11	8.55 ± 0.23	8.30 ± 0.26	8.75 ± 0.36	ns	ns
Sleep efficiency[a] (%)	99.08 ± 0.23	97.57 ± 0.57	98.30 ± 0.50	96.94 ± 0.95	0.02	ns
Sleep–wake schedule						
Bedtime (weekdays)[a] (clock hour)	11.32 ± 0.10	10.24 ± 0.27	10.16 ± 0.37	10.29 ± 0.38	0.001	ns
Rise time (weekdays)[a] (clock hour)	7.78 ± 0.14	7.12 ± 0.28	6.88 ± 0.30	7.29 ± 0.43	0.03	ns
Bedtime (weekend)[a] (clock hour)	12.84 ± 0.14	11.58 ± 0.32	11.33 ± 0.47	11.75 ± 0.45	0.001	ns
Rise time (weekend)[a] (clock hour)	9.74 ± 0.14	9.42 ± 0.27	8.87 ± 0.41	9.79 ± 0.33	ns	ns
Bedtime shift[a]	1.53 ± 0.14	1.34 ± 0.16	1.17 ± 0.24	1.46 ± 0.21	ns	ns
Rise time shift[a]	1.96 ± 0.16	2.29 ± 0.31	1.99 ± 0.49	2.49 ± 0.39	ns	ns
Time in bed[a] (weekdays) (hours)	8.47 ± 0.12	8.89 ± 0.28	8.72 ± 0.42	9.00 ± 0.38	ns	ns
Time in bed[a] (weekend) (hours)	8.89 ± 0.13	9.84 ± 0.24	9.55 ± 0.33	10.04 ± 0.33	0.001	ns
Naps (weekdays)[b] (no.)	0.17 ± 0.04	0.24 ± 0.09	0.27 ± 0.14	0.21 ± 0.11	ns	ns
Naps (weekend)[b] (no.)	0.19 ± 0.05	0.24 ± 0.09	0.27 ± 0.14	0.21 ± 0.11	ns	ns
Qualitative perception						
Feeling of restfulness[b] (1 = min.; 4 = max)	2.97 ± 0.07	3.19 ± 0.13	3.00 ± 0.19	3.31 ± 0.18	ns	ns
Sleep satisfaction[b] (yes = 1; no = 0)	0.84 ± 0.04	0.92 ± 0.05	1.00 ± 0.00	0.87 ± 0.09	ns	ns

[a]Student's t-test; [b]Pearson's χ^2-test. P values between 0.06 and 0.09 are shown as an indicator of tendencies. ns = not significant.

Table 3 *Chronotype scores in ASD participants versus comparison participants (mean ± SEM)*

	Controls (n = 16)	ASD (n = 16)	HFA (n = 10)	Asperger syndrome (n = 6)	Controls versus ASD P	HFA versus Asperger syndrome P
Chronotype	48.5 ± 2.5	48.2 ± 1.9	51.3 ± 1.8	43.0 ± 3.1	ns	0.03

Statistical comparisons were made using Student's t-test.

Chronotype

Student's t-test comparisons did not indicate any group differences in morningness–eveningness (Table 3). None of the participants reported an extreme chronotype. Four patients and five controls reported an evening or morning moderate type.

Laboratory sleep measures

Table 4 summarizes sleep macrostructure.

Participants with ASD exhibited more prolonged sleep latencies and less sleep efficiency than did controls. We found no significant differences in total sleep time between the two groups, but participants with ASD showed more wakefulness after sleep onset, together with a tendency to wake up more often and to shift between wakefulness and stage 1 sleep more often than did control participants. Analyses of sleep stages showed that the ASD group spent significantly more time in stage 1 sleep during the last two-thirds of the night, more time in stage 2 sleep in the first third of the night, and less SWS (stages 3 + 4) than did the control group. Analysis of REM sleep macrostructure did not yield any differences between participants with ASD and the controls.

Figure 1 shows the distribution of SWS and REM sleep across the night. ANOVA for repeated measures on SWS proportion revealed a significant main effect of thirds of the night ($P < 0.0001$) and groups ($P < 0.05$), but no interaction ($P = 0.13$). The main effect of SWS thirds of night was analysed using Newman–Keuls tests, which revealed a significant difference between first and second thirds ($P < 0.05$) but not between second and third thirds ($P > 0.05$). ANOVA for repeated measures on REM sleep proportion revealed a significant main effect of thirds of night ($P < 0.001$), but no main effect of groups ($P = 0.34$) and no interaction ($P = 0.61$). Main effect of REM sleep thirds of night was analysed using Newman–Keuls tests, which revealed a significant difference between first and second thirds of night ($P < 0.05$) and between second and third thirds ($P < 0.05$). Both groups presented typical decreases in SWS and increases in REM sleep through the night.

Analysis of EEG phasic activity during stage 2 showed that participants with ASD generated significantly fewer sleep spindles over the central electrode than did control participants. The difference in K-complex density did not reach statistical significance. Analysis of electro-oculogram

Table 4 *Laboratory sleep measures in ASD participants versus comparison participants (mean ± SEM)*

Sleep parameters	Controls (n = 16)	ASD (n = 16)	HFA (n = 10)	Asperger syndrome (n = 6)	Controls versus ASD P	HFA versus Asperger syndrome P
Sleep initiation and continuity						
Sleep latency[b] (min)	10.0 ± 1.7	17.7 ± 3.7	13.6 ± 2.6	24.4 ± 8.5	0.04	ns
Total sleep time[a] (min)	463.7 ± 11.5	448.8 ± 14.3	464.5 ± 17.7	422.5 ± 21.7	ns	ns
Sleep efficiency[b] (%)	96.4 ± 0.9	94.6 ± 1.0	94.8 ± 1.1	94.2 ± 2.2	0.03	ns
Wake after sleep onset[b] (no)	18.4 ± 2.4	26.2 ± 3.9	26.8 ± 4.5	25.2 ± 7.8	0.07	ns
Wake after sleep onset[b] (%)	3.6 ± 0.9	5.4 ± 1.0	5.2 ± 1.1	5.8 ± 2.2	0.03	ns
Duration of wake after sleep onset[b] (min)	16.9 ± 4.2	25.3 ± 4.6	25.3 ± 5.4	25.2 ± 9.3	0.03	ns
Stage shifts: wake–stage 1[b] (no.)	25.2 ± 3.5	37.2 ± 5.7	37.3 ± 5.8	37.0 ± 12.7	0.08	ns
Non-REM sleep parameters						
Non-REM sleep (stage 2 + 3 + 4) (%)	73.2 ± 1.0	69.2 ± 1.6	70.5 ± 1.8	67.1 ± 2.9	0.04	ns
1[a] (%)	4.3 ± 0.5	6.5 ± 0.9	6.1 ± 0.7	7.1 ± 2.0	0.02	ns
1/3	0.8 ± 0.3	1.3 ± 0.3	1.1 ± 0.3	1.7 ± 0.6	ns	ns
2/3	1.2 ± 0.1	1.8 ± 0.3	1.8 ± 0.3	1.8 ± 0.5	0.05	ns
3/3	2.2 ± 0.2	3.4 ± 0.5	3.2 ± 0.4	3.6 ± 1.0	0.03	ns
2[a] (%)	60.1 ± 2.1	61.2 ± 2.1	60.9 ± 3.2	61.8 ± 2.1	ns	ns
1/3	18.6 ± 1.3	22.1 ± 1.1	21.7 ± 1.7	22.8 ± 0.9	0.05	ns
2/3	22.7 ± 0.8	21.2 ± 0.9	20.7 ± 1.2	22.1 ± 1.7	ns	ns
3/3	18.8 ± 0.5	17.9 ± 0.9	18.4 ± 1.1	16.9 ± 1.6	ns	ns
Stage 3 + 4[a] (%)	13.0 ± 1.9	7.9 ± 1.7	9.6 ± 2.4	5.2 ± 1.6	0.05	ns
SWS latency[a] (min)	15.8 ± 2.3	20.9 ± 2.7	21.5 ± 3.4	20.1 ± 4.8	ns	ns
EEG phasic events						
C3 spindle density[a] (no./h S2)	215.4 ± 16.6	146.2 ± 15.3	168.8 ± 16.7	108.5 ± 24.0	0.004	.05
Fp1 spindle density[a] (no./h S2)	62.1 ± 9.9	46.9 ± 11.9	64.8 ± 17.0	20.0 ± 8.3	ns	ns
K-complex density[a] (no./h S2)	93.1 ± 14.4	69.5 ± 8.4	72.9 ± 13.5	64.4 ± 6.9	ns	ns
REM sleep parameters						
REM sleep latency[a] (min)	71.6 ± 4.2	71.1 ± 3.8	72.5 ± 5.1	68.7 ± 5.9	ns	ns
REM sleep[a] (%)	22.6 ± 0.7	24.3 ± 1.6	23.4 ± 1.9	25.8 ± 3.1	ns	ns
REM periods (no.)[a]	4.9 ± 0.2	4.6 ± 0.2	4.6 ± 0.3	4.5 ± 0.2	ns	ns
REM sleep efficiency[a] (%)	89.7 ± 1.3	89.9 ± 1.7	91.6 ± 2.1	87.2 ± 2.9	ns	ns
EOG phasic events						
Density during REM sleep[a]	549.9 ± 28.5	382.1 ± 33.3	352.7 ± 41.8	426.2 ± 54.0	0.0006	ns
Density during non-REM sleep[a]	17.4 ± 7.8	30.9 ± 14.6	15.9 ± 9.4	53.6 ± 33.2	ns	ns
PLMS						
PLMS index[a] (stage 1 + 2)	5.9 ± 2.8	5.5 ± 1.6	4.7 ± 2.2	6.7 ± 2.6	ns	ns
PLMs index[a] (REM sleep)	7.8 ± 2.5	12.2 ± 3.2	8.8 ± 3.8	17.9 ± 5.4	ns	ns
PLMs index[a] (total sleep time)	5.9 ± 3.2	7.4 ± 2.3	4.9 ± 1.4	11.4 ± 5.4	ns	ns

[a]Student's t-test; [b]Mann–Whitney U-test. P values between 0.06 and 0.09 are shown as an indicator of tendencies. SWS = slow-wave sleep; C3 = left central electrode; FP1 = left frontal electrode; REM = rapid eye movement; EOG = electro-oculogram; PLMS = periodic limb movement during sleep; ns = not significant.

phasic activity during REM sleep showed that ASD participants generated significantly fewer rapid eye movements in REM sleep than did control participants.

We found no group differences for sleep apnoea index or PLMS index. Analysis of individual records, however, uncovered a pathological PLMs index in five ASD participants (three with HFA, two with Asperger syndrome, with the following PLMS indexes: 10.0, 10.4, 11.6, 15.3 and 36.7) and in one control (index = 39.4). Frequency analysis using a χ^2 test revealed a greater proportion of participants with pathological PLMS in the ASD group than in the comparison group ($P = 0.07$). Removing the participants with pathological PLMS did not affect the significant differences described in Table 4 (data not shown). There was no indication of restless legs syndrome based on the number of periodic movements during nocturnal awakenings in any participant.

Correlation between objective and subjective sleep measures in ASD participants was significant for wake time after sleep onset ($\rho = 0.58$, $P < 0.05$) and for SE ($\rho = 0.58$, $P < 0.05$). We also found a significant correlation between subjective sleep latency and objectively measured TST ($\rho = 0.63$, $P < 0.01$), subjectively measured wake time after sleep onset and objective SE ($\rho = 0.59$, $P < 0.05$), subjectively measured SE and objectively measured wake time after sleep onset ($\rho = 0.56$, $P < 0.05$). There were no significant correlations between subjectively measured total sleep time and other sleep parameters.

Psychological functioning

Compared with controls, participants with ASD exhibited higher Trait-Anxiety (39.4 ± 2.9 versus 30.6 ± 2.1; $P < 0.02$),

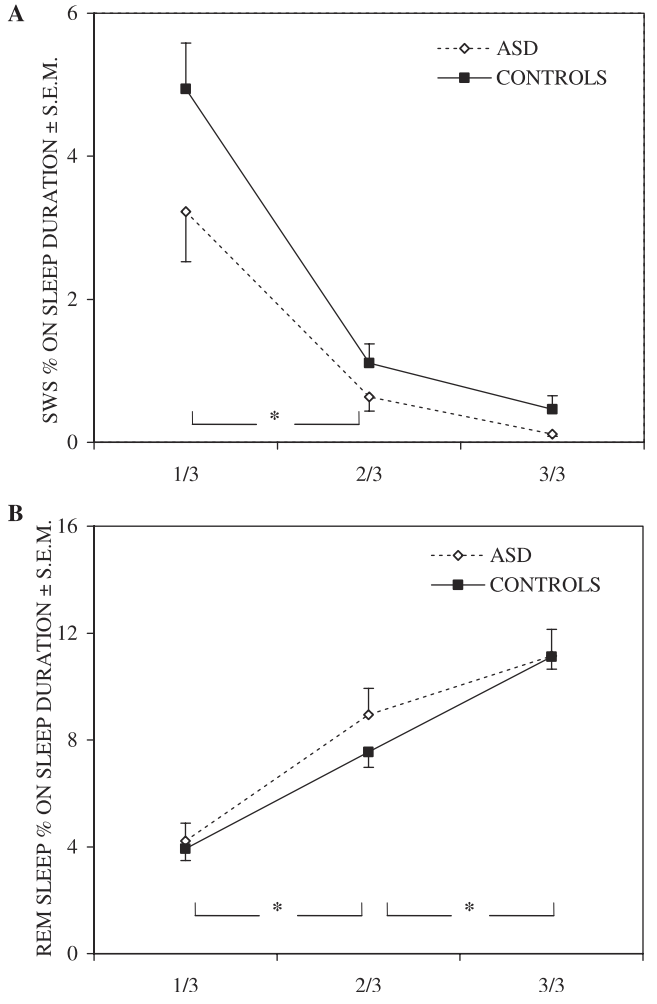

Fig. 1 (**A**) SWS proportion by thirds of night in participants with ASD versus comparison group. (**B**) REM sleep proportion by thirds of night in ASD versus comparison group. Both groups present the typical decrease in SWS and increase in REM sleep throughout the night.

more Achenbach total symptoms (44.3 ± 6.3 versus 27.5 ± 2.8, $P < 0.02$) and more Achenbach internalizing symptoms (16.5 ± 2.6 versus 9.1 ± 1.8, $P < 0.02$). There were no significant differences between groups on indices of State Anxiety, depression as measured by the Beck Depression Inventory, and externalizing problems as assessed by the Achenbach scales.

ANOVA for repeated measures revealed significant main effects of time for saliva cortisol levels ($P < 0.0001$), but no significant main effect of group ($P = 0.16$). There was also no group × time interaction ($P = 0.13$). *A posteriori* contrasts using Newman–Keuls' method revealed a significant difference between rise time on the one hand and the two other moments' cortisol levels (arrival and bedtime; $P < 0.05$ for both variables) on the other. Cortisol level difference between arrival and bedtime was not significant ($P > 0.05$) (Fig. 2).

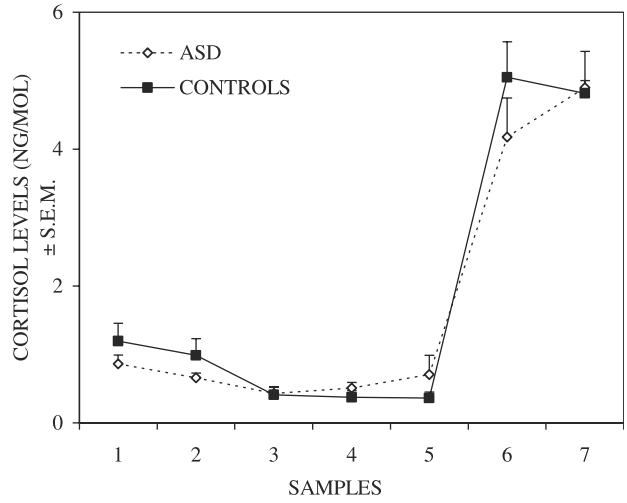

Fig. 2 Mean saliva cortisol levels in participants with ASD versus comparison group ($n = 12$ each). Samples: 1 = arrival at the laboratory; 2 = 20 min after arrival; 3 = 40 min before bedtime; 4 = 20 min before bedtime; 5 = bedtime; 6 = rise time; 7 = 20 min after rise time. Mean saliva cortisol levels are not significantly different between the two groups.

Correlations between sleep and clinical measures

Percentage of REM sleep was positively correlated with total internalizing symptoms in participants with ASD ($\rho = 0.54$, $P < 0.05$). TST correlated negatively with two of the three scales of the ADI-R, i.e. with the Social ($\rho = -0.52$, $P < 0.05$) and Communication ($\rho = -0.54$, $P < 0.05$) dimensions. There was no correlation between REM density and ADI-R scores.

Comparisons between participants with HFA and Asperger syndrome on sleep-related measures

Sleep habits

We observed no significant differences in the sleep habits of participants with HFA and participants with Asperger syndrome (Table 2).

Chronotype

Student's *t*-test comparisons showed a significant difference between morningness—eveningness preference in the two subgroups (Table 3). Persons with HFA were found to lie on the 'morning side' of the intermediate zone and persons with Asperger syndrome were found to lie on the 'evening side' of the intermediate zone.

Laboratory sleep measures

Table 4 also shows the results of exploratory statistical analyses performed to compare the results of laboratory sleep recordings taken from individuals with HFA and with Asperger syndrome. Sleep spindle density at the C3 electrode was significantly lower in participants with Asperger syndrome than it was in participants with HFA. Other parameters did

not differ significantly between the two subgroups. Figure 3 shows the distribution of SWS and REM sleep across the night. ANOVA for repeated measures (with Greenhouse–Geiser adjustment for departure from sphericity) on SWS distribution revealed a trend for a groups × third of night interaction ($P < 0.08$), and a significant main effect of third of night ($P < 0.001$), but no significant main effect of group ($P = 0.21$). The main effect of SWS thirds of night was analysed using Newman–Keuls tests, which revealed a significant difference between the first and second thirds of night ($P < 0.05$) but not between second and third thirds of night ($P > 0.05$). ANOVA for repeated measures on REM sleep distribution exposed a main effect of third of night ($P < 0.0004$), but no significant group effect ($P = 0.50$) and no group × third of night interaction ($P = 0.37$). Analysis of the main effect of REM sleep thirds of night using Newman–Keuls tests indicated a significant difference between the first and second thirds of night ($P < 0.05$) but not between second and third thirds of night ($P > 0.05$). Both subgroups presented typical decreases in SWS and increases in REM sleep during the night.

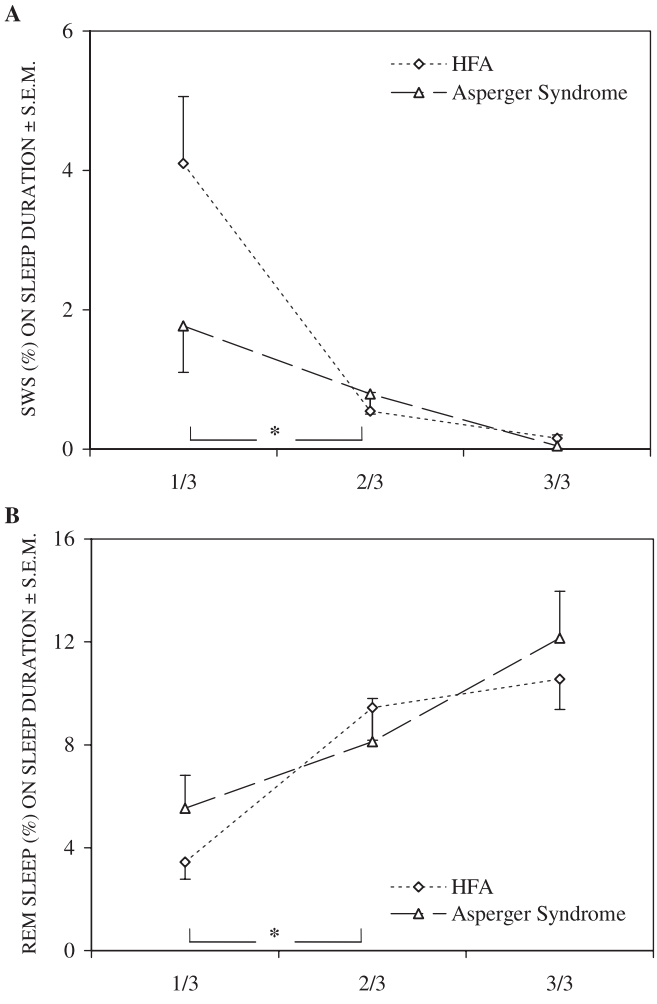

Fig. 3 (**A**) SWS proportion by thirds of night in participants with HFA versus participants with Asperger syndrome. (**B**) REM sleep proportion by thirds of night in participants with HFA versus participants with Asperger syndrome. Both subgroups present typical decreases in SWS and increases in REM sleep throughout the night.

Psychological functioning

Statistical comparisons of the HFA and the Asperger syndrome subgroups showed no significant differences.

Correlations

We found no significant correlations between sleep parameters and psychological functioning in participants with HFA. However, in participants with Asperger syndrome there were significant negative correlations between REM sleep latency and symptoms of depression on the one hand and between REM sleep latency and total internalizing symptoms on the other hand. Higher scores for depression and internalizing symptoms were associated with lower REM sleep latency. Positive correlations were also obtained between the percentage of REM sleep and symptoms of depression, total symptoms, internalizing symptoms, and externalizing symptoms.

Discussion

This research represents the first evaluation of sleep patterns in a group comprising solely adults with ASD but without any psychiatric or neurological comorbidity. It is also the first study to feature a combination of both subjective self-reports and objective laboratory polysomnography measures.

Sleep disturbances

The main finding of the present study is that adults with ASD who do not have spontaneous sleep complaints nevertheless show subjectively and objectively measured sleep disturbances. However, subjective satisfaction with sleep quality and morning restfulness in the clinical group was equivalent to that of the comparison group.

On subjective measures of sleep, participants with ASD reported significantly more difficulties initiating and maintaining sleep than did controls. Individuals with ASD also reported more symptoms related to the sleep–wake schedule than did controls. Our findings on the subjective evaluation of sleep initiation and maintenance in adults with Asperger syndrome are for the most part in accordance with the results of Tani *et al.*'s (2003) investigation of adults with Asperger syndrome and sleep complaints. An exception to this is that the participants in Tani *et al.*'s (2003) study reported less satisfaction with their sleep and less restfulness than the comparison group. This suggests that symptoms related to the sleep–wake schedule and to the perception of the qualitative dimension of sleep are susceptible to the influence of comorbid psychiatric disorders, since almost all of the participants in the previous study (Tani *et al.*, 2003, 2004*a*) (i.e. 16 participants out of 20) had both a psychiatric disorder and Asperger syndrome.

The information garnered from most of the subjective measures of sleep coincides with that generated in the laboratory using objective measures, including difficulties initiating and maintaining sleep, more light sleep (stages 1 and 2) and less SWS (stages 3 + 4). Analysis of phasic activity showed less EEG spindle activity during stage 2 and electro-oculogram activity during REM sleep in participants with ASD than in controls. These results are very similar to those obtained in a previous case study of an adult with Asperger syndrome and Fahr's syndrome (Godbout *et al*., 1998) while the study of Tani *et al*. (2004*b*) did not find any differences in their sample of Asperger syndrome patients with psychiatric comorbidity. The fact that Tani *et al*. (2004*b*) did not find differences in EEG sleep spindle density may be attributed to the use of a different method, namely their use automatic detection software instead of actual visual identification of waveforms. On the other hand, our results do not confirm those of Diomedi *et al*. (1999) and Godbout *et al*. (2000) regarding REM sleep macrostructure and maintenance (shorter duration, stage shifts in and out of REM sleep, REM sleep efficiency, dissociated REM sleep). This is probably due to the fact that the criteria employed in the present study were more stringent in terms of homogeneity of participants' age and IQ. The present results therefore suggest that objective sleep difficulties documented in persons with ASD may not be solely attributed to neurological/psychiatric comorbidity.

Contrary to some of our previous findings, (Godbout *et al*., 2000), the ASD group in this study did not show a pathological mean PLMS index, and the PLMS index of the ASD group did not differ from that of the comparison group. There was, however, a greater proportion of individuals with ASD with a pathological PLMS index ($P < 0.07$). This was also noted in our previous paper describing a different group of participants with Asperger syndrome (Godbout *et al*., 2000). PLMS is found in approximately 10% of adults without complaints (Bixler *et al*., 1982). Although it is known that moderate levels of PLMS do not readily interfere with sleep organization (Coleman *et al*., 1980; Mendelson, 1996), the increased incidence we found here calls for closer analysis since it may point towards a physiopathological substrate common to ASD and PLMS (Montplaisir *et al*., 2000).

Relation between clinical measures and sleep measures

The current findings indicate that TST correlates with variables that belong to the core definition of autism, namely social and communication autistic symptoms scores. This appears to be a robust finding, as an association between sleep profile and autistic symptomatology has also been documented in children with ASD (Patzold *et al*., 1998; Segawa *et al*., 1992; Elia *et al*., 2000; Richdale *et al*., 2000; Shreck *et al*., 2004). The correlation between social and communication deficits and rapid eye movements during sleep reported by Elia *et al*. (2000) has not been replicated here, but their group of participants was composed of younger children and adolescents. In sum, these findings form an additional and independent argument in favour of an intrinsic relation between atypical sleep architecture and the phenotype of autism, at least at an adult age.

Differential sleep patterns among persons with HFA and with Asperger syndrome

A secondary goal of this series of studies was to determine the relative contributions of the diagnostic subgroups HFA and Asperger syndrome to sleep findings documented in the ASD group. We did not detect subgroup differences in subjective or objective measures of sleep macrostructure. Chronotype did not differ either, although the information in Table 3 shows that HFA participants were pooled at the 'morning-type' end of the intermediate zone whereas participants with Asperger syndrome were pooled at the 'evening-type' end of the intermediate zone. The only sleep variable that was significantly different between the two subgroups was the density of EEG sleep spindles, which was significantly more reduced in individuals with Asperger syndrome than in individuals with HFA (see below).

Sleep atypicalities and the neurobiology of autism

It is possible to subdivide the group differences observed in the present study between controls and persons with ASD into three main categories: (i) disorders of initiating and maintaining sleep; (ii) disorders of EEG synchronization; and (iii) hypoactivation of rapid eye movements during REM sleep.

Disorders of initiating and maintaining sleep

Both subjective and objective measures of sleep in the ASD group indicated increased sleep latencies and increased nocturnal awakenings (number and/or duration), as well as soft signs of a phase advance of the sleep–wake schedule (earlier bedtime and rise time compared with control participants). This may appear to be compatible with the higher trait anxiety exhibited by the ASD group. However, persons with chronic insomnia or chronic anxiety generally experience subjective and objective states of hyperarousal (Pavlova *et al*., 2001; Richardson and Roth, 2001). Yet we found that individuals in the ASD group did not have high cortisol levels or actual subjective sleep complaints, which prevents further association between ASD and clinically significant insomnia. This unusual, dissociated sleep phenotype points towards a specific arrangement of neurobiological markers of unstable sleep not accompanied by daytime symptoms.

Disorders of EEG synchronization

EEG sleep spindles and slow waves are generated by a thalamocortical reverberating loop that aims to synchronize cortical postsynaptic potentials through hyperpolarization

and consequently to decrease the influence of peripheral sensorial input to the brain (Steriade *et al*., 1993; Steriade, 2000). A recent series of post-mortem studies on cortical organization of minicolumns in young patients with autism or Asperger syndrome and normal IQ (for a review see Buxhoeveden and Casanova, 2002) showed that single cortical radial minicolumns are narrower and more numerous, with more dispersed cells and reduced neuropil in individuals with ASD (Casanova *et al*., 2002*a*, *b*). This abnormal column morphology and cell distribution might possibly lead to a different pattern of connections, such as a pattern of GABAergic interneurons delimiting the territory of each column by lateral inhibition. Casanova *et al*. (2002*a*) further hypothesized that if thalamic terminals are unaffected, this may result in greater innervation of minicolumns by thalamic output. The supernumerary cortical columns and anomalies in lateral inhibition may thus lead to integration deficits of each processing unit, as well as to the thalamocortical dysregulation reflected in EEG atypicalities. We have recently reported EEG atypicalities in persons with ASD during waking and REM sleep (Daoust *et al*., 2004). The present results on SWS and stage 2 sleep spindles (see also Godbout *et al*., 1998, 2000) further extend these observations to non-REM sleep.

Beyond local cortical neurophysiology, these results may also be implicated in atypical daytime functioning in persons with ASD. Stage 2 EEG sleep spindles have indeed been associated with procedural memory using sensorimotor integration tasks (Smith and MacNeill, 1994; Nader and Smith, 2003). There is evidence for differences in procedural learning between individuals with and without ASD (Mostofsky *et al*., 2000), and we are presently investigating whether procedural sensorimotor performance correlates with non-REM sleep EEG in persons with ASD (Limoges *et al*., 2003). If this proves to be the case, it would definitively link the sleep phenotype of persons with ASD with daytime functioning atypicalities.

Hypoactivation of rapid eye movements during REM sleep

The lower number of rapid eye movements per hour of REM sleep we found in the clinical group points toward abnormalities of the cortical and subcortical substrates associated with this measure. Using magnetoencephalography, Ioannides *et al*. (2004) have recently described a REM sleep-selective bottom-up flow of information processing: rapid eye movements during human REM sleep are generated by the activation of a right hemisphere-dominant loop comprising the midpontine region, the frontal eye field and limbic structures (orbitofrontal cortex, amygdala, and parahippocampal gyrus) until an excitatory threshold is reached and eye movements are actually recorded. According to these authors, the preferential involvement of the right hemisphere is shown by the prevalence of leftward eye movements in REM sleep (see also Hong *et al*., 1995). The low incidence of rapid eye movements in the ASD group in the present study might thus support the 'right-hemisphere' theory of autism (Klin *et al*., 1995; Sabbagh, 1999; Gunter *et al*., 2002) and suggests that oculomotor activity during REM sleep may serve as a probe to investigate this issue further.

In conclusion, the present findings indicate that abnormalities in the typical macro- and microstructures of sleep are salient features of the adult ASD phenotype. This might be associated with the atypical cortical organization that was recently demonstrated in persons with ASD.

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