Heart rate variability of typically developing and autistic children and adults before, during and after sleep.

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Running title: Sleep and heart rate variability

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This is the accepted manuscript of Tessier, M. P., Pennestri, M. H., & Godbout, R. (2018). Heart rate variability of typically developing and autistic children and adults before, during and after sleep. International Journal of Psychophysiology, 134, 15-21: https://doi.org/10.1016/j.ijpsycho.2018.10.004.

Abstract

Introduction. Studies suggest a sympathetic-parasympathetic disequilibrium in children with autism spectrum disorder (ASD), compared to typically developing (TD) children. The autonomic nervous system (ANS) shows profound modification with age but studies in ASD adults are lacking. The ANS is also influenced by vigilance states such as wakefulness and sleep. The aim of this study is to explore differences in ANS activity in typically developing (TD) and ASD individuals during sleep and wakefulness, as a function of age.

Methods. Four groups of participants (17 adults with ASD, 16 TD adults, 13 children with ASD and 13 TD children) were recorded for two consecutive nights in a sleep laboratory. Electrocardiogram (ECG) was sampled during wakefulness (before and after sleep) and during stage N2 and REM sleep. Groups were compared on their heart rate variability parameters (LFnu, HFnu, LF/HF ratio) in each vigilance state.

Results. Results show that ASD adults had lower HFnu in the morning than TD adults ($p<0.05$). During REM sleep, adults had higher LF/HF ratio than children, regardless of their clinical status ($p<0.05$).

Conclusions. Results of this study show autonomic distinctiveness during wakefulness specifically in ASD adults, suggesting a lower parasympathetic activity in the morning. Whether this characteristic represents a developmental feature or is related to lower sleep quality remains to be clarified.

Key words: Autism, typical development, children, adults, sleep, heart rate variability.

Acronyms:

ANS = Autonomic nervous system

ASD = Autism spectrum disorder

DSM = Diagnostic statistical manual

ECG = Electrocardiography

EEG = Electroencephalography

GIQ = General IQ

HF = High frequency

HFnu = Normalized values of High frequency

HR = Heart rate

HRV = Heart rate variability

Hz = Hertz

IQ = Intellectual quotient

LF = Low frequency

LFnu = Normalized values of Low frequency

PIQ = Performance IQ

PSG = Polysomnography

REM = Rapid eye movement

TD = Typically developing

VIQ = Verbal IQ

VLF = Very low frequency

1. Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder that is characterized by deficits in social interactions and social communication, as well as restrictive and stereotyped patterns of behaviours (American Psychiatric Association, 2013). A recent body of literature shows that autonomic nervous system (ANS) modulation could be dysregulated in ASD. Studies conducted in ASD children, using either respiratory sinus arrhythmia, pupil size or cardiac baroreflex sensitivity, have reported an atypical sympathetic/parasympathetic balance during the day, with an increase in sympathetic activity and a decrease in parasympathetic activity compared to typically developing (TD) children (Anderson et al., 2009; Billman, 2009; Ming et al., 2005; Vaughanet al., 2009; Zahn1987). There are fewer studies documenting diurnal ANS activity in ASD adults and results are less consistent. Zahn et al. (1987) reported faster respiratory rhythms and a lower skin temperature in male adult ASD participants in the sitting position compared to schizophrenia and TD participants, indicating a sympathetic hyperactivation. More recently, Mathersul et al. (2013) could not show any differences between ASD and TD adults electrodermal activity levels, while Eilam-Stock et al. (2014) documented a decrease of electrodermal activity in ASD adults, suggesting a decrease in the sympathovagal tone during the day.

Modulation of the ANS is greatly influenced by vigilance and sleep stages. In TD individuals, the transition from wake to sleep is characterized by an increase of parasympathetic activity (Baharav et al., 2015; Bonnet et al. 1997; Cabiddu et al., 2012) and a decrease of sympathetic activity (Busek et al., 2005; Cortelli et al., 2012). Parasympathetic activity further increases with depth of sleep, from stages N1 to N2 to

N3 sleep (Bonnet et al., 1998; Zemaityte et al. 1984). Rapid eye movement (REM) sleep is a state of autonomic instability, with substantial fluctuations and predominance of sympathetic activity (Baharav et al., 1995; Cabiddu et al., 2012; Stein et al., 2012). In the morning upon waking up, there is an increase of sympathetic activity compared to the evening (Boudreau et al., 2012; Furlan et al., 1990; Muller et al., 1995).

In accordance with the close association between sleep and ANS activity, the latter is known to be influenced by sleep disturbances (Bonnet et al., 1998). Now sleep disorders are one of the most common comorbidity in individuals with an ASD, ranging between 44 and 83% (Richdale et al., 2009). ASD individuals show both subjectively and objectively measured evidence of difficulties initiating and maintaining sleep: compared to TD individuals, they display longer and more frequent awakenings during the night, lower sleep efficiency and more tiredness during the day (Lambert et al., 2016; Limoges et al., 2005; Tani et al., 2003). Therefore, sleep disturbances have the potential to influence autonomic nervous system activity in ASD individuals.

Among the different ways of assessing autonomic modulation, heart rate variability (HRV) is a well-established and non-invasive tool to characterize autonomic sympathetic and parasympathetic modulation during sleep and wakefulness. This technique uses electrocardiography (ECG) to generate tachograms from which heart beats are computed and decomposed using a Fast Fourier transformation into frequency bands: high frequencies (HF), low frequencies (LF) and very low frequencies (VLF) (Task Force, 1996). To facilitate the interpretation of HRV data when comparing subjects with significantly different total frequency power and to evaluate changes over time within the same subject, LF and HF can be normalized (Burr, 2007; Task Force, 1996). This can be achieved with the following formula: [spectral power of each of the

components / (total spectral power - VLF)] * 100. Normalized values have been shown to correlate well with sleep measures (Task Force, 1996; Sato et al., 2014).

HF is a marker of parasympathetic activity and it predominates when the individual is at rest (Shaffer et al., 2014). Interpretation of LF is more controversial. It has long been considered as a marker of sympathetic activity since normalized LF (LFnu) was shown to increase during physical activity (Furlan et al., 1990; Malliani et al., 1991; Montano et al., 1994). However, a growing body of literature suggests that measures of LF could reflect both sympathetic and parasympathetic activity (Goldstein et al., 2011; Harder et al., 2016; Moak et al., 2007) or that they rather provide an index of baroreflex function (Goldstein et al., 2011). Although also controversial, the LF/HF ratio is often considered as a measure of the sympathetic/parasympathetic balance (Malliani et al., 1991; Task Force, 1996). Finally, VLF is also mentioned in the scientific literature, but its significance remains uncertain and it can only be quantified from sufficiently long segments (Task Force, 1996).

Only a few studies have characterized nocturnal HRV in children with ASD. Recently, Pace et al. (2016) studied the ANS activity of 19 ASD children and 19 TD children using a thoracic belt to record the R-R intervals, paired with actigraphy to monitor the rest-activity cycle during 1 to 3 nights at home. HRV analysis was conducted on a 30-minute continuous nocturnal period, using absolute values of LF, HF, total spectral power and LF/HF ratio. Results showed significantly higher absolute HF during the night in the ASD children, suggesting higher parasympathetic activity. In another study, both absolute and normalized values of LF (LFnu), HF (HFnu) and LF/HF ratios were compared between 21 ASD and 23 NT children based on ECG recordings obtained from a single night of in-lab polysomnography (PSG) (Harder et al., 2016).

ASD children displayed lower absolute and normalized LF and HF values during stages N3 and REM sleep while LF/HF ratio was higher. Authors concluded that ASD children may have higher sympathetic dominance during sleep associated with decreased vagal influence.

Discrepancies between these 2 studies are possibly related to methodological issues, each having its own shortcomings. In the Pace et al. (2016) study, R-R intervals were automatically detected and while the technology used might have been sufficient for heart rate (HR) determination, it did not permit the review of waveforms to remove ECG segments with artifacts, a prerequisite for the spectral analysis of HRV (Task Force, 1996). Moreover, sleep was monitored with an armband known to display questionable reliability and validity regarding sleep, with significant between-subject variability compared to PSG, together with large proportions of missing data due to technical issues (Roane et al., 2016), notwithstanding the inability to identify sleep stages. In the Harder et al. (2016) study, only one night of recording was performed, giving way to poor sleep due to the so-called first-night effect in neurotypical children (Coble et al., 1984). Moreover, ASD children were selected from a pool of participants that included poor sleepers (Goldman et al., 2009; Malow et al., 2005).

In TD individuals, ANS modulation also shows changes throughout the life span, with a decreased in both parasympathetic and sympathetic activity with aging (Finley et al., 1995; Jensen-Urstad et al., 1997). However, studies evaluating ANS activity in ASD as a function of age are lacking, as well as studies comparing nocturnal ANS activity in adults with or without ASD.

The general aim of the present study was to explore ANS activity during wakefulness and sleep across ages (children vs adults) and diagnostic groups (TD vs

ASD), using PSG and HRV. Because of the circadian rhythmicity of ANS activity, HRV during the wake state was measured both during the evening and the morning to as a control for the time-of-day effect. Moreover, since sleep parameters and autonomic function are closely related, sleep parameters were also compared between groups, to test whether HRV differences could be related to sleep disturbances.

Our main hypothesis was that ASD groups would show higher LF/HF ratio and lower HFnu than TD groups, both during wake (evening and morning) and sleep (stage N2 sleep and REM sleep). Since studies comparing ASD adults and children are lacking, the comparison between age groups was exploratory.

2. Methods.

2.1 Participants

A total of 59 participants (four groups) were recruited: 16 adults with ASD, 17 TD adults, 13 children with ASD and 13 TD children. Groups of adults and children were matched for age, gender and body mass index. ASD groups were recruited at the Autism Clinic at Rivière-des-Prairies Mental Health Hospital, Montréal, Canada. They were all diagnosed by an experienced clinician using Autism Diagnosis Interview-Revised (Lord et al., 1994) and the Autism Diagnostic Observation-Schedule (Lord et al., 2000), with confirmation by Diagnostic and statistical Manual of Mental disorders (DSM-IV-TR) criteria (American Psychiatric Association, 2013). The children and adult TD groups were recruited through advertisement in the community. Participants with an intellectual quotient (IQ) <80 based on the WAIS-III (Wechsler et al., 1997), diagnosed with a psychiatric of medical comorbid condition, or taking any medication were excluded. Anxiety symptoms, that are often present in ASD, did not constitute an exclusion criterion, unless there was a formal

diagnosis of anxiety disorder. Participants with a subjective complaint of poor sleep or presenting a primary sleep disorder (sleep apnea, restless leg syndrome) were excluded based on clinical interviews with one of the authors (RG) and PSG. All subjects signed a consent form approved by the Research Ethics Board of the Rivière-des-Prairies Mental Health Hospital.

2.2 Sleep laboratory measures

Participants spent two consecutive nights at the sleep laboratory of Rivière-des-Prairies Mental Health Hospital. The first night served to get used to testing conditions and to screen for sleep disorders. Only data from the second night was analyzed. 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 recording (none were regular nappers). Food and beverages containing stimulants (e.g. coffee, sodas, chocolate) were not permitted after noon. Participants had the opportunity to go to bed at their preferred time. PSG recordings included bilateral central, frontal and occipital electroencephalography (EEG) leads, submental electromyography, periorbital electrooculography and ECG. A Grass Neurodata Model 15 Acquisition System assisted by the Harmonie 6.2B software (Stellate System, Montréal, Québec, Canada) was used for recordings. Sleep was scored blind relative to group condition by 2 qualified PSG technologists according to standard methods (Iber et al., 2007), using 20-second epochs; discrepancies were resolved by mutual agreement. Total sleep time was defined as the total number of minutes spent in any of the sleep stages during the sleep period (i.e., from sleep onset

to final awakening). Sleep efficiency was calculated as follows: (Total sleep time / Recording period - Sleep latency) X 100.

2.3 ECG recordings

ECG was recorded continuously at a sample rate of 256 Hz before, during and after the night spent at the sleep laboratory. While the first electrode was placed under right clavicle as recommended by the American Electroencephalographic Society (1994), the second electrode was positioned under the left clavicle because of its easy access and the sensory oversensitivity to touch in some of the participants with ASD. ECG signals high-pass filter was set at 1 Hz and the low-pass filter was set at 100 Hz while sensitivity was set at 75 μv/mm.

The wake samples were recorded for five minutes, 15 minutes before lights-out and 15 minutes after awakening in the morning, in a semi-recumbent position. A technologist monitored the participants and their EEG to make sure none were sleeping during the wake recordings. Mean value of three samples of 5 minutes of uninterrupted stage N2 sleep and REM sleep distributed throughout the night was used for sleep ECG analyses. Recordings did not have long enough segments of stages N1 and N3 sleep without artifacts to be considered for analyses. A visual inspection of each 5-minute segment was performed to remove physiological or technical artifacts. Segments with more than three artifacts were excluded from the analyses.

2.4 Analyses

2.4.1 ECG

HRV analyses were performed with the Kubios commercial software (Tarvainen et al., 2009). Using a fast Fourier transform algorithm, the following parameters were extracted: LF (0.04–0.15 Hz), HF (0.15 to 0.4 Hz) and LF/HF ratio. Table 1 shows the absolute values of LF and HF power. The normalized LFnu and HFnu values were calculated using the following formula: [spectral power of each components / (Total spectral power – VLF)] *100 [52].

Table 1. Mean absolute values and standard deviations of low frequency and high frequency power across groups of participants and vigilance states.

	TD adults	ASD adults	TD children	ASD children
LF				
Evening	996.14 ± 179.74	1096.46 ± 390.45	2045.69 ± 747.75	2131.87 ± 606.69
Stage N2 Sleep	1505.62 ± 283.28	1200.34 ± 289.11	2070.63 ± 690,60	1990.17 ± 461.50
REM Sleep	2495.88 ± 533.82	2169.66 ± 490.06	2501.55 ± 608.61	2623.77 ± 734.40
Morning	3223.24 ± 1059,94	3114,93 ± 680,34	2893.24 ± 399.05	3098.60 ± 1256.56
HF				
Evening	1981.43 ± 538.39	1729,15 ± 769,26	2260.01 ± 731.48	2997.33 ± 640.45
Stage N2 Sleep	3308.22 ± 866.78	1917.81 ± 629.68	3094.68 ± 843.70	5210.59 ± 1579.69
REM Sleep	3416,45 ± 925,20	1933.64 ± 848.96	3461.16 ± 1233.11	5361.79 ± 1855.89
Morning	4664,60 ± 1819,52	2375,20 ± 1016,36	4028.32 ± 934.67	4525.88 ± 1914.31

TD: typically developing; ASD: autism spectrum disorder; REM: rapid-eye movement.

2.4.2 Statistical analyses

Data was analyzed using a commercial package (SPSS v 24.0, IBM Corp., Armonk, NY, USA). Logarithmic transformations of data were performed when not distributed normally. Independent t-tests were used to compare demographic variables and HR values between ASD and TD participants. For HRV measures, three-way ANOVAs with 2 independent factors (Group: ASD vs TD) X (Age: Children vs Adults) and one repeated measures (Time: Evening, Stage N2 sleep, REM sleep, Morning) were performed followed by planned comparisons according to Field (2009) when interactions were significant, otherwise main effects were reported with post-hoc multiple mean comparisons when necessary. Huynh-Feldt correction for sphericity was applied to repeated measures. Sleep parameters (total sleep time, sleep efficiency) were compared using two-way ANOVAs (Group: ASD vs TD) X (Age: Children vs Adults). P values of less than 0.05 were considered statistically significant.

3. Results

3.1 Descriptive data

Table 2 describes age and IQ values in the four groups of participants. Age was similar among children and adult subgroups. ASD adults showed lower verbal IQ, performance IQ and full-scale IQ compared to TD adults. There were no significant IQ differences between the two children subgroups.

Table 2. Summary of participant characteristics

(mean ± SD)	**TD adults (n=17)**	**ASD adults (n=16)**	**P**	**TD children (n=13)**	**ASD children (n=13)**	**p**
Age range (years)	16-27	16-27		6-13	7-12	

Age (years)	21.1 ± 4.0	22.0 ± 3.8	0.8	10.5 ± 1.8	10.2 ± 2.1	>0.9
VIQ	114.7 ± 12.1	101.4 ± 14.9	0.01	115.8 ± 13.1	103.8 ± 23.2	0.09
PIQ	113.1 ± 13.6	102.1 ± 14.2	0.04	114.9 ± 12.6	106.4 ± 13.8	0.13
FSIQ	114.2 ± 14.0	102.0 ± 10.5	0.01	116.5 ± 10.3	105.2 ± 19.8	0.13

TD: typically developing, ASD: autism spectrum disorder, SD: standard deviation, VIQ: Verbal intelligence quotient, PIQ: Performance intelligence quotient, FSIQ: Full scale intelligence quotient.

No significant differences were found between mean HR values of ASD and TD participants in the evening, stage N2 sleep, REM sleep and morning, both in children and adults groups (Table 3).

Table 3. Mean values and standard deviation of heart rate (beats per minute) for each vigilance state

	TD adults	**ASD adults**	***P***	**TD children**	**ASD children**	***P***
Evening	62.4 ± 7.6	61.2 ± 6.5	0.9	72.6 ± 8.8	75.4 ± 5.7	0.2
Stage N2 Sleep	55.4 ± 7.7	55.7 ± 6.9	0.6	66.0 ± 5.6	66.5 ± 4.8	0.7
REM Sleep	60.6 ± 8.4	58.5 ± 7.0	0.6	68.4 ± 4.2	70.3 ± 5.9	0.8
Morning	60.6 ± 10.0	63.1 ± 9.5	0.5	72.0 ± 6.6	75.1 ± 9.3	0.5

TD: typically developing; ASD: autism spectrum disorder; P: independent t-tests between groups; REM: rapid-eye movement.

3.2 Main comparative analyses

3.2.1 HRV

Absolute values. No significant Time X Group X Age interaction was observed for the LF absolute values ($F(3,38) = 1.41$; $p=0.25$). No significant simple interactions effects were found for Time X Age ($F(3,38) = 1.87$; $p=0.15$), and Time X Group ($F(3,38) = 0.13$; $p=0.92$). A main effect of Time was observed, with LF absolute values in the morning

being significantly higher than Stage N2, REM sleep and evening LF values. Evening LF values were significantly lower than LF values during stage N2 and REM sleep.

No significant Time X Group X Age interaction was observed for the HF absolute values ($F(3,38) = 1.75$; $p=0.18$). No significant simple interactions effects were found for Time X Age ($F(3,38) = 1.38$; $p=0.26$), and Time X Group ($F(3,38) = 1.36$; $p=0.26$). A main effect of Time was observed ($F(3,38) = 7.53$; $p<0.001$), with HF absolute values in the morning being significantly higher than Stage N2, REM sleep and evening HF values. HF values during REM sleep were significantly higher than HF values during stage N2.

Normalized values. No significant Time X Group X Age interaction was observed for the LFnu values ($F(3,38) = 1.80$; $p=0.17$). No significant simple interactions effects were found for Time X Age ($F(3,38) = 2.15$; $p=0.11$), Time X Group ($F(3,38) = 0.08$; $p=0.95$) and Age X Group ($F(3,38) = 0.87$; $p=0.35$). A main effect of Time was observed ($F(3,38) = 965.50$; $p<0.001$), with LFnu values in the morning (2.74 ± 0.02) being significantly higher than evening LFnu values (1.97 ± 0.07; $p<0.001$). Evening LFnu values were significantly higher than during REM sleep (1.67 ± 0.19; $p<0.001$) and stage N2 sleep (1.52 ± 0.20; $p<0.001$). No main effect of Group ($F(1) = 0.11$; $p=0.74$) or Age ($F(1) = 1.12$; $p=0.29$) were observed for LFnu.

A significant Time X Group X Age interaction was observed for the HFnu values ($F(3,38) = 2,89$; $p=0.05$). Analyses of simple interaction effects showed a Time X Group interaction only in adults. Figure 1a shows that lower HFnu values were found in the morning in the adult ASD group compared to the adult TD group ($p=0.03$) while no

differences were present during stage N2 sleep, REM sleep and during the evening ($p>0.05$). In children, no Time X Group differences were observed (Figure 1b) ($p>0.05$).

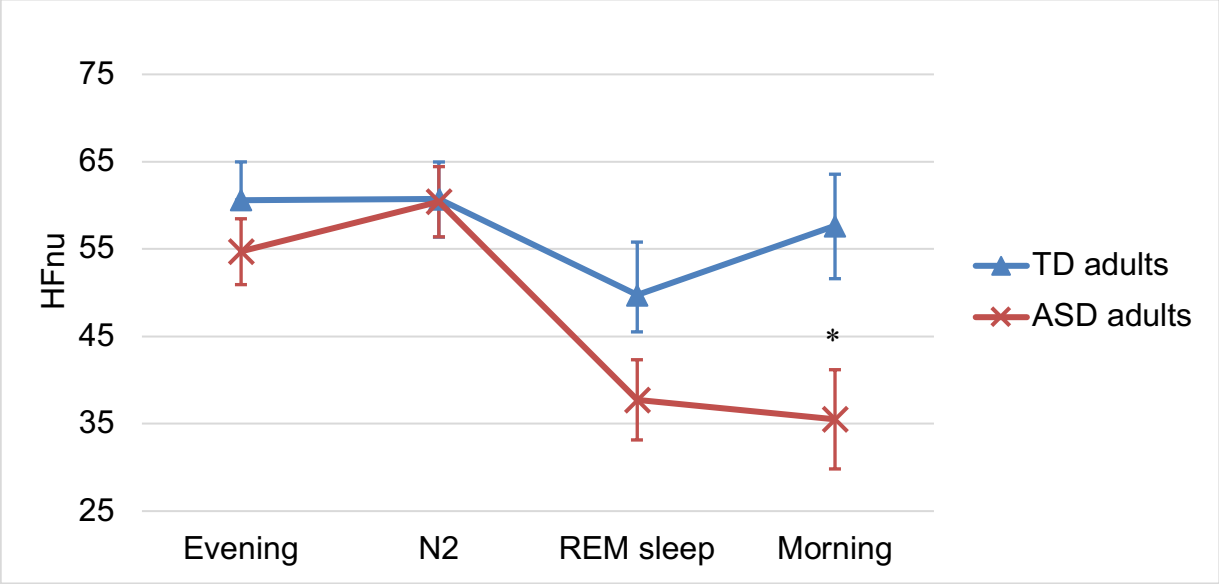

Figure 1a. Normalized values (± standard error of the means) of high frequency (HFnu) during the evening wake, stage N2 sleep, REM sleep and morning wake recordings in typically developing (TD) adults and autism spectrum disorder (ASD) adults (*$p<0.05$).

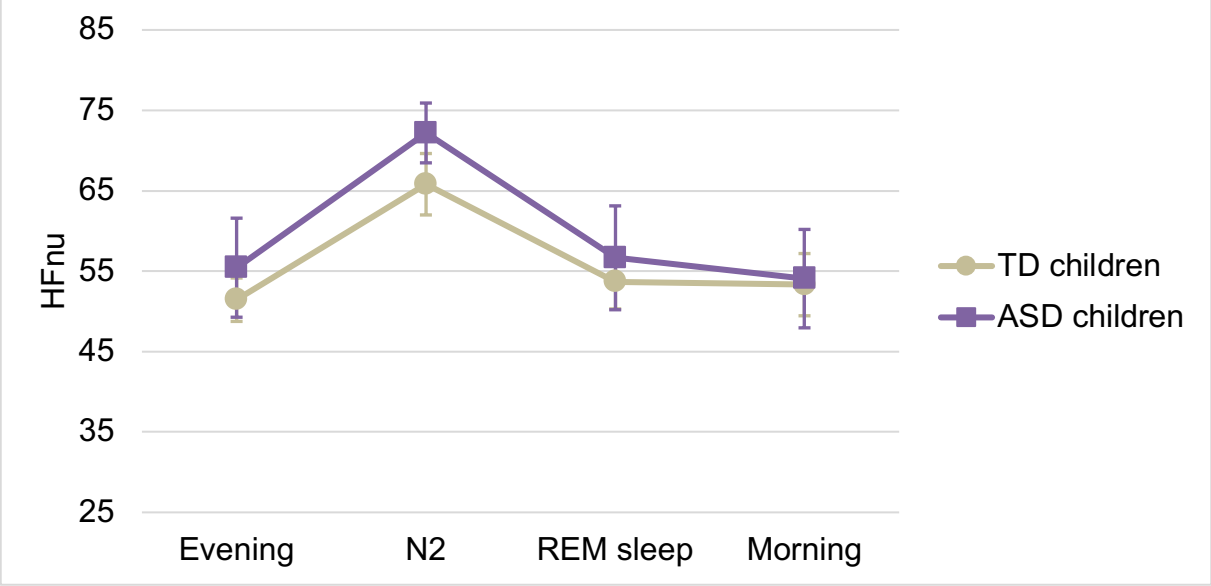

Figure 1b. Normalized values (± standard error of the means) of high frequency (HFnu) during the evening wake, stage N2 sleep, REM sleep and morning wake recordings in typically developing (TD) children and autism spectrum disorder (ASD) children.

No significant Time X Group X Age interaction was found for the LF/HF ratio ($F(3,38) = 0.87$; $p=0.46$). Figure 3 illustrates a significant interaction between Time and Age for LF/HF values ($F(3,38) = 3.41$; $p=0.02$). Simple effects showed lower LF/HF ratio in children compared to adults, only during REM sleep ($p=0.046$), regardless the Group status. The difference between morning values did not reach statistical significance possibly because of the larger dispersion of values. No Time X Group interaction ($F(3,38) = 1.82$; $p=0.15$) or Age X Group ($F(3,38) = 0.44$; $p=0.40$) was found.

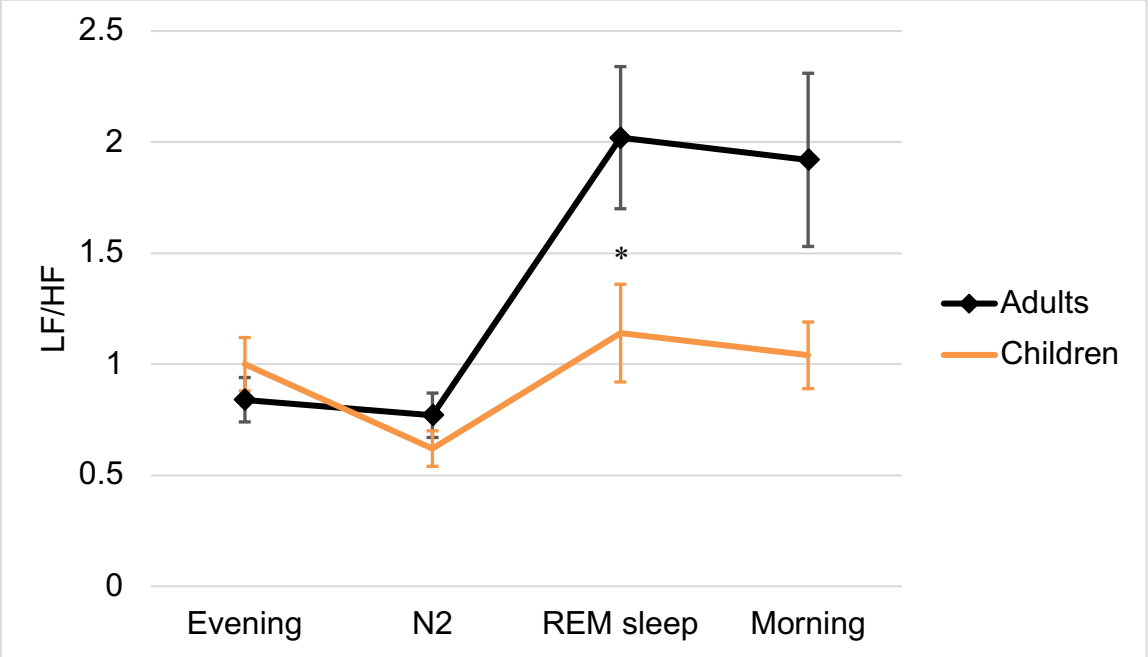

Figure 3. Mean values (± standard error of the means) of low frequency / high frequency ratio (LF/HF) during the evening wake, stage N2 sleep, REM sleep and morning wake recordings in adults and children, regardless the clinical status (*$p<0.05$).

3.2.2 PSG

No significant Group X Age interaction was found for total sleep time ($F(1,58) = 1.09$; $p=0.30$). As expected, a main effect of Age ($F(1,58) = 49.01$; $p<0.001$) is illustrated in figure 3, showing that children had a longer total sleep time than adults, regardless of the clinical status. No significant main Group effect was observed.

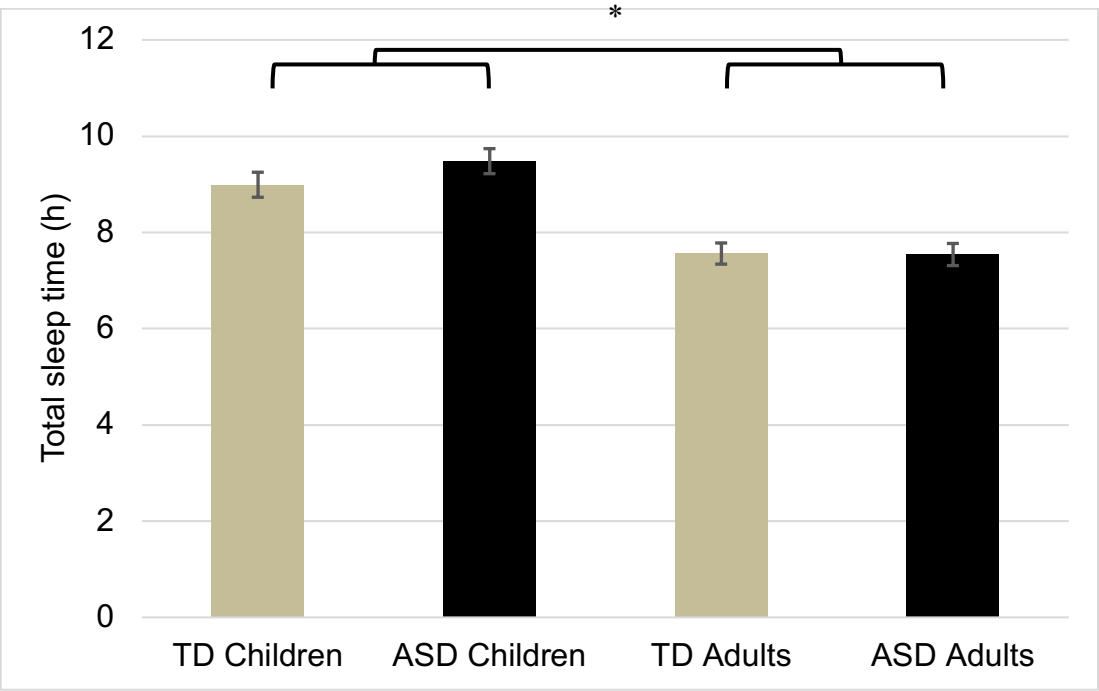

Figure 3. Mean values (± standard error of the means) of total sleep time in typically developing (TD) adults, autism spectrum disorder (ASD) adults, TD children and ASD children (*$p<0.05$).

Results showed no significant Group X Age interaction for sleep efficiency ($F(1,58) = 0.16$; $p=0.69$). Again as expected, figure 4 shows a significant main effect of Age ($F(1,58) = 5.35$; $p=0.02$), with a higher sleep efficiency for children compared to adults, regardless of clinical status. No significant main Group effect was observed.

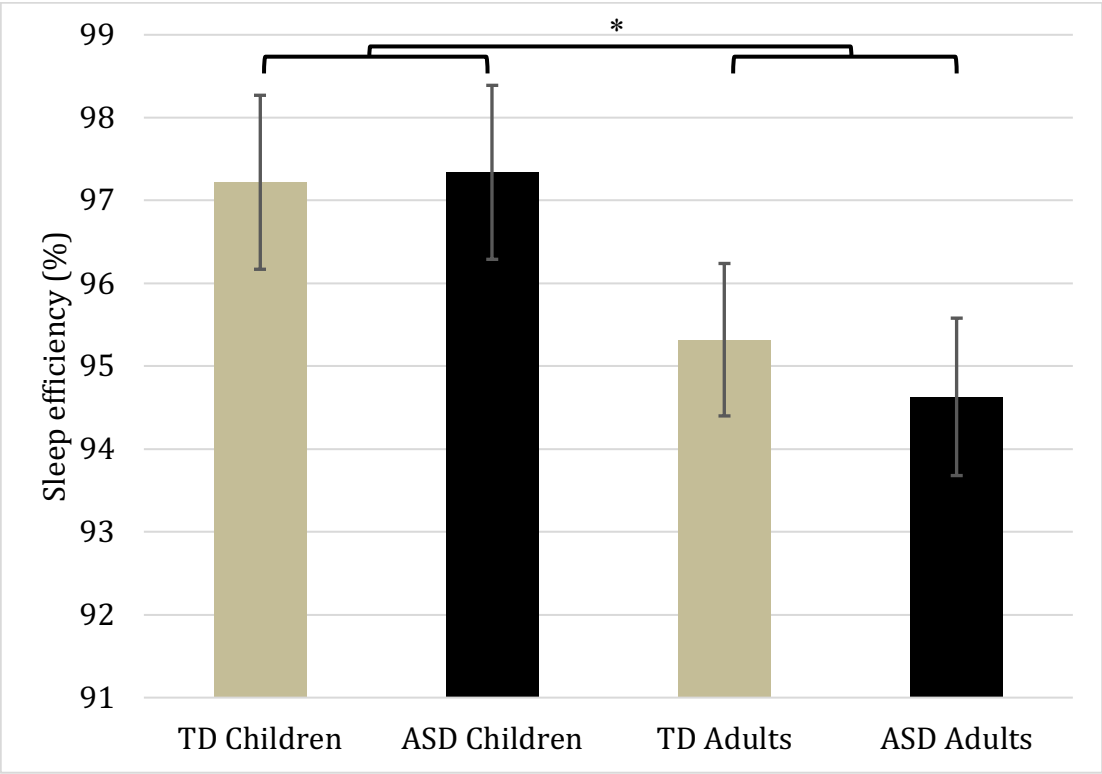

Figure 4. Mean values (± standard error of the means) of sleep efficiency in typically developing (TD) adults, autism spectrum disorder (ASD) adults, TD children and ASD children (*p<0.05).

4. Discussion

The objective of this study was to explore the differences in ANS activity during sleep and wakefulness between groups of TD and ASD adults and children using HRV. Our main hypothesis was partially confirmed: we found that ASD adults had a lower HFnu than TD adults during wake in the morning, reflecting a lower parasympathetic activity. However, no differences were observed between ASD and TD adults during wake in the evening or during sleep and no differences were observed between ASD and TD children whatsoever. In terms of age-specific differences, a higher LF/HF ratio (suggesting higher sympathetic/parasympathetic balance) was observed during REM sleep in adults compared to children, regardless of their clinical status. As expected,

further analysis showed that both adult groups also had shorter total sleep durations and lower sleep efficiencies compared to children, regardless of clinical status.

A recent study has reported that children with ASD had higher sympathetic and lower parasympathetic activities during slow wave sleep (equivalent to stage N3 sleep) and REM sleep than TD children (Harder et al., 2016). Our results do not replicate these findings, possibly because the ASD children had a poorer sleep quality than subjects in the present study. As a matter of fact, participants in Harder et al. (2016) were drawn from two previous studies in which a large proportion of ASD children had poor sleep according to their parents, lower total sleep time (ranging between 8.15 and 8.22 hours) and lower sleep efficiency (between 84.7% and 88.3%) (Goldman et al., 2009; Malow et al., 2006). In contrast, sleep was not a concern in any of the ASD children included in the present study with a mean total sleep duration of 9.5 hours and sleep efficiency of 97.3%. Moreover, only one night of PSG was performed and the TD children may have suffered from the so-called first-night effect (Coble et al., 1984), displaying a lower sleep efficiency than the TD children in the present study (85% vs. 97%). In another study on HRV in ASD children and contrary to the results of Harder et al. (2016), Pace et al. (2016) found a higher, rather than a lower, parasympathetic activity during sleep in children with ASD compared to TD children. However, as mentioned in the introduction, HRV analysis in this case was performed during a 30-minute continuous period of sleep at home, using a heart rate belt monitor technology that precluded the visual inspection of artifactual waveforms, and sleep was monitored with a problematic actigraphy technology (see introduction). These methodological differences possibly contribute to explain results discrepancies between these two studies and results discrepancies with the present study.

Our results also showed a higher LF/HF ratio in adults than children during REM sleep, regardless of the clinical status. Although the meaning of an increase of LF/HF remains controversial, it is mainly considered as an increase of sympathetic/parasympathetic balance (Malliani et al., 1991; Montano et al., 1994). This increase in sympathetic activity in adults during sleep could potentially be associated to the well-known changes in sleep throughout development. Indeed, both sleep and the autonomic nervous system undergo dramatic changes across the lifespan (Brandenberger et al., 2003; Colten et al., 2006) and PSG results of the present study also show shorter total sleep durations and lower sleep efficiencies in adults compared to children, both in TD and ASD participants.

In the present study, the four groups presented similar mean HR values and levels of sympathetic / parasympathetic activity in the evening before sleep; differences only occurred in the morning, with ASD adults having significantly lower parasympathetic activity than TD adults. Studies show that sleep disorders, short sleep duration and low sleep quality could result in autonomic imbalance in the TD population by increasing the dominance of sympathetic activity over parasympathetic modulation during the day (Lanfranchi et al., 2009; Meerlo et al., 2008; Michels et al., 2013; Spiegelhalder et al., 2011). Higher rates of sleep problems in the ASD population could possibly impact their autonomic functioning and result in lower parasympathetic activity in the morning, as seen in TD population. Further research is needed to explore whether the age-related decline in sleep quality could potentially impact the sympathetic / parasympathetic balance differently in ASD and TD adult individuals at different times of the day, as shown by our results.

5. Study limitations

This study has limitations with regards to the generalization of the results, since the standard selection criteria for ASD induced a bias towards a high proportion of males in the samples of participants. Also, selection criteria required ASD participants to be free from comorbidities and medication. On one hand, our samples of children and adult ASD participants thus represented only a part of the ASD population but, on the other hand, comorbidity (and related medication) would add physiopathological factors that are different from those involved in non-syndromic autism.

Another methodological issue could be that wake segments of ECG were recorded in a semi-recumbent position, not the same position as during sleep. This could have influenced the results since body position has an influence on autonomic measures, but it should be noted that the four groups of participants were recorded in the same position during wake.

The significance of the LF/HF ratio has sometimes been questioned. It has, however, gained wide acceptance overtime as a tool to assess cardiovascular autonomic regulation, where increases in LF/HF are assumed to reflect a shift to “sympathetic dominance” (Malliani et al., 1991; Pagani et al., 1984). This was largely based on the idea that the LF component of HRV reflected the sympathetic activity of the nervous system. Throughout the years some researchers have come to argue that the LF component of HRV does not provide an index of cardiac sympathetic drive but that it reflects a complex mix of sympathetic, parasympathetic, and other unidentified factors [6, 7, 23, 25]. As a consequence, the physiological basis for LF/HF remains controversial [8] and one might argue that our conclusions related to LF and LF/HF may

not necessarily reflect sympathetic activity. However, at the very least, the present results show autonomic modulation of HRV across children and adults as well as between ASD and TD groups. Further research with larger groups of different ages and different clinical profiles should shed more light on how to interpret these limitations.

6. Conclusions

The present study is the first to compare TD and ASD children and adults on HRV parameters during sleep and wake. The findings indicated that ASD adults had lower parasympathetic activity in the morning than TD adults. Moreover, adults had higher sympathetic/parasympathetic balance than children during REM sleep, regardless of their clinical status. Whether these autonomic modulations are linked to a developmental process or to sleep quality should be clarified in further studies.

Acknowledgements

This project was supported by an operating grant from the Canadian Institutes of Health Research (No. 81898, Studies of Sleep, EEG, and Cognitive Performance in Autism), the Natural Science and Engineering Research Council of Canada (No. #1258630, Sleep and Development), the *Fondation Les Petits Trésors de l'Hôpital Rivière-des-Prairies* and the *Fonds de recherche du Québec – Santé*. The authors gratefully acknowledge the skillful assistance of Ms. Élyse Chevrier (polysomnographic recording and scoring), Dr. Laurent Mottron, M.D., Ph.D. (patient evaluation), Jean Paquet, Ph.D. (statistical analysis consultant) and Marjolaine Chicoine, M.Sc. (laboratory coordination and support). Finally, the authors thank the study participants and their families for their invaluable contribution to this project.

Funding

This project was supported by operating grants to RG from the Natural Science and Engineering Research Council of Canada (No. #1258630, Sleep and Development) and the Canadian Institutes of Health Research (No. 81898, Studies of Sleep, EEG, and Cognitive Performance in Autism).

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