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Title: 24-hour sleep-activity rhythms in adolescents with Down syndrome

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Introduction: Very little is known about sleep-wake rhythmicity in individuals with Down syndrome (DS), which is surprising given the high rates of documented sleep problems generally experienced by this population. Sleep fragmentation, obstructive sleep apnea, and low sleep efficiency are present at high rates for infants (Edgin et al., 2015), children (Ashworth et al., 2013; Breslin et al., 2014), and adults with DS (Esbensen & Schwichtenberg, 2016). Although these problems may be associated with lower sleep-wake rhythm integrity, only one human study (Fernandez et al., 2017), to our knowledge, has investigated rhythmicity in the timing of sleeping, waking, and activity levels over a 24-hour period in individuals with DS; and this study included infants only. Sleep-wake rhythmic disruption is well documented in conditions highly comorbid with DS, notably autism (Tordjman et al., 2015) and Alzheimer's dementia (Leung et al., 2020; Videnovic et al., 2014). Therefore, further study of sleep-wake cycles across a wider span of ages in older children and adults with DS may help researchers better understand sleep in this population. The purpose of the current study is to examine sleep-wake activity in teenagers with DS. Specifically, we aim to characterize sleep rhythms in a sample of adolescents with DS and a typically developing (TD) control group using sleep-wake activity profiles and behavioral markers of circadian rhythms. We predict that some teenagers with DS may begin to show signs of reduced circadian strength measured by interdaily stability (IS), intradaily validity (IV), and amplitude. Variance on these measures may occur more for teens who also show greater sleep fragmentation. We also hypothesize that cognitive measures correlated with sleep fragmentation in previous studies (verbal IQ and delayed recall) may be correlated with arhythmic sleep-wake patterns. Finally, we expect to confirm previous findings of differences between individuals with DS and typically developing individuals for the measures of total sleep time (TST), sleep efficiency (SE), and wakes after sleep onset (WASO).

Methods: 30 youth with DS between the ages of 11 and 18 years and a matched group of 30 TD youth were included from two studies between the years of 2014 and 2020. Sleep data were gathered via wrist worn Respironics Actiwatch II actigraphy on 5-7 consecutive nights and were scored in Phillips Actiware 6.0.9 software, and double scored according to laboratory standardized procedures. Actimetrics' ClockLab 6.0 was used for individual analysis of sleep-wake rhythms to yield the phase marker variables: daily onsets, daily offsets, acrophase (averaged time of day of greatest activity), the least active 5 hours of the day (L5) and the most active 10 hours (M10). ClockLab was also used to find the circadian markers: FFT of the 24-hour amplitude, and the non-parametric IS, IV, and relative amplitude as described in Whitehead et al. (2008) and Van Someren et al. (1999). The FFT is used to compute estimates of circadian robustness, IS is defined as a signal-to-noise index of daily circadian strength, IV as an index of rhythm fragmentation, and relative amplitude as a non-parametric measure of amplitude derived from the L5 and M10.

Results: Data for 8 TD youth (ages 13-17) and 8 DS youth (ages 14-17) have currently been analyzed. For the pilot data, t-tests were bootstrapped to estimate group differences in the 24-hour phase markers and measures of circadian robustness. In SPSS, 1000 bootstrapped simulations were run, with replacement, using an alpha level of 0.05 and a 95% confidence interval. Daily onsets, offsets and acrophases did not differ significantly between the groups; the onsets showed a difference in means(SE) of -0.731(0.448), p=.153, offsets of -1.005(0.494), p=.068, and acrophases of -0.733(0.481), p=.164. Amplitudes showed a mean group difference of 224.220(60.402), p=.011; for relative amplitude there was a mean group difference of -0.007(0.015), p=.681. Daily activity rhythms varied between groups with a means difference for L5 of 8.52(2.519), p=.03; and for M10, a means difference of 181.693(48.801), p=.005. For the measures of circadian robustness, IV showed a negligible difference in group means of -0.144(0.089), p=.152; IS a non-significant means differences of 0.138(0.060), p=.071, and the FFT of 0.130(0.025), p=.01. The pilot data also indicate group differences for SE, with a means difference of 97.492(26.53), p=.006; a means difference for WASO of 27.049(7.276), p=.022; and non-significant group differences for total sleep time of -2.466(22.461), p=.909. The cognitive measures are included in the final model with the complete samples.

Discussion: It is surprising that the two groups of teenagers show such similarities for time of waking, falling asleep, and total sleep time. We note that both pilot groups of teens averaged inadequate sleep; the DS group clocked roughly 7 hours per night and the TD group 6 hours 45 minutes, while American Academy of Sleep Medicine guidelines (Paruthi et al., 2016) recommend 8-10 hours per night. Although both groups demonstrated

longer nighttime sleep on the weekends, presumably to compensate for short sleep time during the week, it was not enough to "catch up" for weekday sleep loss. Contrary to our hypothesis, preliminary measures may indicate more robust 24-hour rhythms for teens with DS as measured by amplitude of the 24-hour sine wave and of the FFT of the sine wave, although not by relative amplitudes. Interestingly, IV, as an index of rhythm fragmentation, was no better or worse for individuals with DS despite their significantly increased number of night-time wakings hypothesized to affect it; nor was the index of circadian strength (IS) substantially different. As hypothesized, we replicated prior findings of differences for individuals with DS on SE and WASO, although not for total sleep time, demonstrating fragmented sleep as reported in several studies. These results suggest that the circadian rhythms of teenagers with DS may be intact or possibly stronger than those of control teens. These findings are interesting in relation to the reports of breakdown of daily rhythms in Alzheimer's disease (AD). The tracking of these markers into adulthood may provide one tool to determine when individuals with DS develop preclinical signs of AD.

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