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Aging and sleep in Williams syndrome: Accelerated sleep deterioration and decelerated slow wave sleep decrement

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ABSTRACT

Specific developmental and aging trajectories characterize sleep electroencephalogram (EEG) of typically developing (TD) subjects. Williams syndrome (WS) is marked by sleep alterations and accelerated aging of several anatomo-functional and cognitive measures. Here we test the hypothesis of a premature aging of sleep in WS. Age-related changes of home recorded sleep EEG of 42 subjects (21 WS, 21 age- and gender matched TD subjects, age: 6–29 years) were tested by Pearson correlations and homogeneity-of-slopes analysis. Typical developmental/aging effects of sleep EEGs were observed in TD subjects. Accelerated aging in WS was confirmed by overall sleep/wake measures. Specifically, premature aging was evident in accelerated age-dependent declines in WS subjects' sleep efficiency, as well as in steeper age-related rises in wakefulness and wake after sleep onset (WASO) of the WS group. In contrast, NREM sleep-related measures indicated atypical decelerations of the developmental trends of WS subjects, characterized by the slowing down of the age-related slow wave sleep (SWS) declines mirrored by the lack of age-dependent increase in Stage 2 (S2) sleep. Age-effects in sleep EEG power spectra were not different among the groups. Objectively measured sleep disruption of subjects with WS is age-dependent and increasing with age. Moreover, these data suggest atypical pre- and postpubertal neural development in WS, with sleep/wake balance and REM sleep time indicating accelerated aging while NREM sleep composition revealing signs of an as yet unidentified, perhaps compensatory developmental delay.

1. Introduction

Williams syndrome (WS, also known as Williams–Beuren syndrome) is a genetically determined neurodevelopmental disorder occurring in 1 of 20,000 live births. The syndrome is caused by a hemideletion of 25–28 genes at 7q11.23 and characterized by mild to moderate mental retardation, learning difficulties, cardiovascular abnormalities, high sociability and empathy and a distinctive cognitive-linguistic profile (Järvinen-Pasley et al., 2008; Meyer-Lindenberg, Mervis, &

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Berman, 2006). Attention deficit/hyperactivity disorder (ADHD), specific phobias and generalized anxiety disorder (GAD) are among the particularly frequent comorbid psychiatric syndromes of subjects with WS. The prevalence of GAD in WS was shown to increase significantly with age (Dykens, 2003; Leyfer, Woodruff-Borden, Klein-Tasman, Fricke, & Mervis, 2006).

WS is characterized by atypical development of several anatomical measures as well as physiological and cognitive functions, including neurocognitive aspects of language and social communication (Haas & Reiss, 2012; Laing, Hulme, Grant, & Karmiloff-Smith, 2001), visuospatial processes (Atkinson et al., 2001) and motor performance (Tsai, Wu, Liou, & Shu, 2008). Although pubertal development follows a typical pattern, WS girls reach puberty roughly two years earlier than typically developing (TD) girls (Partsch et al., 1999). The early onset puberty was hypothesized to be linked to premature activation of the hypothalamic–pituary axis (Partsch et al., 1999), although the cause of this precocious activation is not identified yet. Reported findings on multiple organ investigations as well as psychological functions are suggestive for the occurrence of mild accelerated aging of subjects with WS (Cherniske, Sadler, Schwartz, Carpenter, & Pober, 1999; Devenny et al., 2004; Krinsky-McHale, Kittler, Brown, Jenkins, & Devenny, 2005). The list of potential indicators includes graying of hair during adolescence or young adulthood (Lenoff, Wang, Greenberg, & Bellugi, 1997; Pober, 2010), cataracts (Cherniske et al., 2004), senile emphysema (Wan, Pober, Washko, Raby, & Silverman, 2010), high frequency sensorineural hearing loss (Marler, Elfenbein, Ryals, Urban, & Netzloff, 2005), premature wrinkling of the skin (Morris, Demsey, Leonard, Dilts, & Blackburn, 1988; Mari et al., 1995), precipitous age-associated decrease in long-term, episodic memory (Devenny et al., 2004), as well as age related semantic memory performance decline (Krinsky-McHale et al., 2005). However, no evidence for age-related decline in social or adaptive functioning in adults with WS was found by others, at least up to the age of 50–55 years (Elison, Stinton, & Howlin, 2010). Similarly, studying inhibitory processing in older patients with WS Greer and colleagues (Greer, Riby, Hamilitona, & Riby, 2013) found no support for accelerated aging hypothesis.

Sleep of subjects with WS was shown to be altered in several respects. Difficulties in initiating and maintaining sleep, decreases in total sleep, rapid eye movement (REM) sleep and sleep efficiency, as well as increases in intra-sleep wakefulness, slow wave sleep (SWS) and daytime sleepiness are among the common findings (Annaz, Hill, Ashworth, Holley, & Karmiloff-Smith, 2011; Arens et al., 1998; Ashworth, Hill, Karmiloff-Smith, & Dimitriou, 2013; Bódizs, Gombos, & Kovács, 2012; Goldman, Malow, Newman, Roof, & Dykens, 2009; Gombos, Bódizs, & Kovács, 2011; Mason et al., 2011). Sleep cycles were shown to be fragmented and the cyclicity of sleep disorganized (Gombos et al., 2011). Moreover, increases in non-REM (NREM) sleep frontal electroencephalogram (EEG) delta activity, region-independent decreases in alpha and sigma waves, as well as the accelerations of sigma peak frequencies were also reported (Gombos et al., 2011; Bódizs et al., 2012, 2014). These sleep macrostructural and EEG alterations were shown to be present in children and young adults with WS. Most of the reported alterations in sleep are known to be changing during ontogeny and/or affected by physiological aging in TD subjects.

Age is a major determinant of sleep. Almost all of the known sleep architectural or quantitative EEG measures are strongly and reliably depending on the chronological age of the subjects (Carrier, Land, Buysse, Kupfer, & Monk, 2001; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). Reports on both developmental and aging-related changes in human sleep emphasize age-related decreases in the daily amount of sleep, increases in Stage 2 (S2) sleep percentage, and decreases in SWS percentage (Coble, Kupfer, Taska, & Kane, 1984; Colrain & Baker, 2011; Espiritu, 2008; Iglowstein, Jenni, Molinari, & Largo, 2003; Ohayon et al., 2004). In addition the aging of sleep is characterized by decreases in REM sleep time and increases in wakefulness (Coble et al., 1984; Colrain & Baker, 2011; Espiritu, 2008; Iglowstein et al., 2003; Ohayon et al., 2004). The above changes are reflected in age-related decreases in quantitative EEG measures of sleep EEG delta and theta waves during both NREM and REM sleep (Aström & Trojaborg, 1992; Carrier et al., 2001; Darchia, Campbell, Tan, & Feinberg, 2007; Feinberg & Campbell, 2013; Landolt & Borbély, 2001; Ringli & Huber, 2011). In addition age-related declines in sleep spindling (Nicolas, Petit, Rompré, & Montplaisir, 2001) and/or NREM sleep EEG sigma power (Landolt & Borbély, 2001), as well as the increases in the sigma spectral peak frequency (Tarokh, Carskadon, & Achermann, 2011) and/or in the frequency of sleep spindles was supported by several studies (Crowley, Trinder, Kim, Carrington, & Colrain, 2002; Feinberg, Koresko, & Heller, 1967; Nicolas et al., 2001; Principe & Smith, 1982).

In order to shed light on the specific nature of sleep alterations and atypical development in WS as well as to provide further support or disproof of the presumed concept of accelerated aging in WS we report age-related effects in various sleep EEG measures. We hypothesize that the sleep EEG measures which are age-dependently decreasing and increasing in TD subjects are characterized by accelerated age-related decreases and increases in WS subjects, respectively.

2. Methods

2.1. Subjects and genetic investigations

WS participants ($N = 21$, 7 males and 14 females, age range 6–29 years, mean age ± standard deviation: 19.19 ± 7.13 years) were contacted through the Hungarian Williams Syndrome Association (parents were mediating in the case of underage subjects). All WS subjects (including adults) were living with their parents. TD controls ($N = 21$, 6 males and 15 females, age range 6–29 years, mean age ± standard deviation: 19.14 ± 7.14 years) were selected by personal contacts of the authors and matched by age and sex to the WS participants. A twin pair discordant for WS and sex (Bódizs et al., 2014) was considered as a pair case control.