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Sleep EEG fingerprints reveal accelerated thalamocortical oscillatory dynamics in Williams syndrome

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ABSTRACT

Sleep EEG alterations are emerging features of several developmental disabilities, but detailed quantitative EEG data on the sleep phenotype of patients with Williams syndrome (WS, 7q11.23 microdeletion) is still lacking. Based on laboratory (Study I) and home sleep records (Study II) here we report WS-related features of the patterns of antero-posterior 8–16 Hz non-rapid-eye-movement (NREM) sleep EEG power distributions. Participants in Study I were 9 WS and 9 typically developing (TD) controls matched for age (14–29 years) and sex, and sleeping for two consecutive nights in the laboratory. WS participants were characterized by region-independent decreases in 10.50–12.50 Hz and central increases in 14.75–15.75 Hz EEG power. Region-independent decreases and increases in *z*-scores of the spectra were observed in the 10.25–12.25 Hz and 14–16 Hz ranges, respectively. Moreover, in the EEG spectra of participants with WS a lower probability for the emergence of a frontally dominant peak was observed. Parietal fast sigma peaks and the antero-posterior shifts in power distributions were of higher frequencies in WS (~1 Hz difference). A 1 year follow-up of 9 WS and 3 TD participants, as well as their inclusion into larger samples (20 WS and 20 TD, age: 6–29 years) of a two-night ambulatory home polysomnography study confirmed the WS-specific decrease in alpha/low sigma power (8–11.75 Hz) and the pattern of *z*-score differences (decreases: 8.50–11.25 Hz; increases: 13.5–14 Hz), including the antero-posterior shifts in power distribution (0.5 Hz) and some features of the spectral peaks. Altogether these data suggest a decrease in alpha/low sigma power, as well as a redistribution of NREM sleep 8–16 Hz EEG power toward the higher frequencies and/or a higher frequency of NREM sleep thalamocortical oscillations in WS.

1. Introduction

Evidence supports the robustness and stability of individual differences in non-rapid eye movement (NREM) sleep EEG spectra with a special emphasis on the 8–16 Hz range corresponding to alpha and sigma activity (Buckelmüller, Landolt, Stassen, & Achermann, 2006; De Gennaro, Ferrara, Vecchio, Curcio, & Bertini, 2005; De Gennaro et al., 2008; Tan, Campbell, Palagini, & Feinberg, 2000; Tarokh, Carskadon, & Achermann, 2011). Data supporting this stability were provided by period and amplitude analysis measures of several EEG bands including sigma activity, which were shown to be highly consistent across nights (Feinberg, Fein, & Floyd, 1980). The particularly high inter-night correlation in the sigma band power reported

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by Tan et al. (2000) was attributed to the marked and stable individual differences in phasic spindle activity (Gaillard & Blois, 1981; Silverstein & Levy, 1976). A substantial genetic influence on spectral composition of NREM sleep in humans, in particular with respect to alpha and sigma frequencies was also reported (Ambrosius et al., 2008). Furthermore, the unique profile of the 8–16 Hz EEG spectra of NREM sleep was considered as the EEG fingerprint of sleep (De Gennaro et al., 2005), and found to be the one of the most heritable human traits, characterized by a heritability estimate of 96%, not influenced by sleep need and intensity (De Gennaro et al., 2008). A similar invariance of EEG power distribution during human NREM sleep has also been suggested by a full-scalp recording (Finelli, Achermann, & Borbély, 2001). The NREM sleep EEG spectral profiles and their topographical distributions were hypothesized to reflect genetically determined traits of functional neuroanatomy rather than sleep-dependent mechanisms (De Gennaro et al., 2005; Finelli et al., 2001). Given the increasing evidence for the robustness of this trait-like feature of NREM sleep EEG, further studies unravelling the distinct phenotypes peculiar to specific developmental disabilities are of potential interest. Indirect evidence for the promising nature of this approach comes from the studies reporting alterations in sleep EEG spindling of patients with Asperger syndrome (Godbout, Bergeron, Limoges, Stip, & Mottron, 2000), developmental dyslexia (Bruni et al., 2009) or malformations of cortical development (Selvitelli, Krishnamurthy, Herzog, Schomer, & Chang, 2009). Although, several phasic spindle features were shown to be inherently related to the individual shape of the power spectra in the alpha/sigma band (Bódizs, Körmendi, Rigó, & Lázár, 2009), no study focusing on developmental disorders characterized the fine structure of the genetically determined 8–16 Hz NREM sleep EEG. However, some distinct features of sleep spindling were characterized in patients with malformations of cortical development (Selvitelli et al., 2009).

Williams syndrome (WS) is a genetically determined developmental disorder linked to a microdeletion of 25–28 genes in chromosome 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, & Berman, 2006). Perhaps this latter aspect is the most interesting for cognitive research: severe visual-spatial deficits and relative strength in expressive language (Bellugi, Lichtenberger, Jones, Lai, & St George, 2000; Karmiloff-Smith et al., 1997). As overactivity and short attention span is typical in WS more than 50% of WS individuals are diagnosed with attention deficit hyperactivity disorder (Leyfer, Woodruff-Borden, Klein-Tasman, Fricke, & Mervis, 2006; Morris & Mervis, 2000). Available data on the sleep of children with WS suggest decreases in sleep time, sleep efficiency, and REM time as well as increased slow-wave sleep (SWS) and periodic leg movements during sleep (PLMS) (Arens et al., 1998; Mason, Arens, Sharman, Pack, & Kaplan, 2008). Actigraphic and polysomnographic studies support the persistence of some of these early age sleep-features in groups of adolescents and young adults with WS, including increased SWS, decreased REM sleep and sleep efficiency, but not the diagnosis of PLMS (Goldman, Malow, Newman, Roof, & Dykens, 2009; Gombos, Bódizs, & Kovács, 2011).

Given the genetic determination of both WS and the 8–16 Hz NREM sleep EEG, as well as the relevance of studying polygraphic sleep in neurodevelopmental disabilities, our aim is to unravel the peculiarities of the individual sleep EEG fingerprints of WS participants. Results of these analyses might shed light on both the neural correlates of WS and the genetic factors determining sleep EEG in general. We hypothesize that there are specific features of the individual sleep EEG fingerprint in WS and that the distribution of NREM sleep 8–16 Hz EEG power along the antero-posterior cortical axis distinguishes WS from typically developing (TD) participants.

2. Study I: sleep EEG fingerprints according to laboratory sleep recordings of participants with WS

2.1. Methods

2.1.1. Participants

Nine WS and 9 age- and gender matched TD control participants were enrolled in the study. WS participants were recruited from the Hungarian Williams Syndrome Association. WS diagnosis was based on the fluorescence in situ hybridization test of the absence of an elastin gene from chromosome 7. Exclusion criteria for TD participants were medical diagnosis of sleep problems or psychiatric, neurological or other medical disorder. Body mass index (BMI) was in the normal and under the normal range in the WS group (between 13.9 and 26 with an average of 19.4) and in the normal range in the TD group (between 17.4 and 23.3 with an average of 20.5). The research protocol was approved by the Ethical Committee of the Budapest University of Technology and Economics. Adult participants or the parents of the underage participants signed informed consent for the participation in the study according to the Declaration of Helsinki. Participants were free of drugs except for 1 WS patient who was on stable medication with clonidine (150 mg/day), enalapril (5 mg/day), acetylsalicylic acid (500 mg/day), betaxololi hydrochloridum (20 mg/day), and amlodipine (15 mg/day). Those patients not on medication were not withdrawn from any pharmacological treatment prior to the study. Age- and sex-matching of TD participants were performed in a case-controlled manner: every WS subject had a TD pair with similar age (within the limits of ± 2 years, but usually less than 1 year difference) and sex. One except in sex-matching was intentionally introduced in the case of a 16 years old dizygotic twin pair discordant for WS and sex, the non-WS 16 year old girl serving as a TD control of her WS brother. Age range of the whole sample was 14–29 years, the mean age being 20.44 years. Five males and 13 females participated in the study.

2.1.2. Procedures and recordings

Participants underwent polysomnographic examinations on two consecutive nights during their sleep in the laboratory. The timing of lights off was determined by participants' habit, and the awakenings were spontaneous. If participants needed