

Short Communication

Altered Sleep-Dependent Motor Learning in Williams Syndrome

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Submitted: 06 November 2015

Accepted: 21 November 2015

Published: 23 November 2015

ISSN: 2379-0822

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Abstract

Williams syndrome (WS) is a genetically determined neurodevelopmental disorder that is characterized by atypical sleep architecture [1-3]. Sequential motor skills are acquired in multiple stages, including a practice-dependent and a sleep-dependent phase of performance improvement [4]. In conditions with disrupted sleep, e.g., in schizophrenia, sequential motor learning is impaired, and has an atypical pattern [5]. The aim of our study was to determine how individuals with WS compare to typically developing (TD) ones in terms of sleep-dependent sequential motor learning. Practice-dependent and sleep-dependent learning was estimated by speed and accuracy in a finger tapping (FT) task. Individuals with WS presented with a lower initial performance, they showed significant practice-dependent improvement, and however, they did not demonstrate any improvement in the sleep dependent stage. Age-matched TD individuals showed both practice and sleep-dependent improvement. This suggests that the characteristic and atypical sleep pattern in WS [1-3] might significantly limit the acquisition of motor skills. Our results also strongly point to the relevance of effective sleep interventions in WS, with a potential outcome of improved motor learning abilities.

Keywords

- Williams syndrome
- Sleep-dependent
- Motor learning
- Finger-tapping

ABBREVIATIONS

WS: Williams Syndrome; FT: Finger Tapping; TD: Typically Developing; ADHD: Attention-Deficit Hyperactivity Disorder; OCD: Obsessive Compulsive Disorder

INTRODUCTION

Williams syndrome (WS) is a genetically determined neurodevelopmental disorder due to a microdeletion on chromosome 7 in the q11.23 region [1-3]. WS is characterized with mild to moderate intellectual disability and a specific cognitive profile [4,5]. The prevalence of sleep problems in developmental disorders vary between 13% and 86% depending on age, physical and sensory impairments, genetic syndromes and medical conditions [6,7], and at least four times higher than for typically developing (TD) subjects [8]. Although sleep problems in children are known to present in 37% of the cases at least in one domain [9], they are more prevalent in WS. When parents of WS children were asked, they reported sleep problems in 97% of the cases [3].

WS sleep studies employ questionnaires [3], actigraphy [10, 11], and/or polysomnography [12]. Atypical sleep pattern was found in several studies, including difficulties in bedtime settling [13], sleep maintenance problems [12,14-16], excessive daytime sleepiness and frequent night-time waking [3,15]. In addition to these, fragmented sleep [14-16], reduced sleep efficiency [12,16] and prolonged sleep latency [15] was also reported. According to

Goldman et al. [15], WS patients spend 9 hours in bed; nonetheless they were sleepy during the day, spent more time awake during the night, with long wake periods and more awakenings [14-16]. Arens et al. [14] found that some WS children presented with periodic limb movement in sleep (PLMS), although Mason et al. [12] found no difference in the PLMS index compared to control subjects. An increased number of leg movements were typically present in WS [15,16]. Studies using EEG showed increased slow wave sleep (non-REM stage 3 and 4 sleep) and decreased time in sleep stages 1 and 2 [12, 14, 16]; decreased REM sleep percentage, reduced cyclicity in the sleep architecture, and decreased total sleep time [16].

In WS, fine motor problems/difficulties are present throughout the lifetime [17], and recently, impairment of fine motor learning was also found [18]. Motor learning, especially learning fine sequences is characterized by multiple phases. Within session (online) gains occur during practice, both in accuracy and in speed. The online phase is followed by a consolidation phase in which motor performance improves off-line, without any further practicing. A number of studies reported that off-line consolidation is brain-state dependent: time spent awake results in retention of performance acquired during practice, while off-line gains are sleep-dependent both in speed and accuracy in adults [19-23]. Several studies suggest that post-sleep improvement correlates with certain sleep parameters.

Offline improvement in the sequential FT task is related to

delta and fast-sigma activity, and sleep spindles in cortical motor areas [20, 24-27]. It has also been shown that altered sleep affects fine motor learning capacity in schizophrenia and obstructive sleep apnea [28-30].

Since WS is characterized by sleep impairment, and also impairment in fine motor learning [18], our aim was to see whether sleep-dependent/offline learning is specifically disturbed. We looked at online and offline learning patterns in WS and in age-matched TD individuals employing a sequential FT task. Our hypothesis was that motor learning impairment in WS is at least partially due to a decreased level of offline gains due to sleep alteration.

MATERIALS AND METHODS

Participants

16 individuals with WS (6 males, 10 females) participated in the study. Age range was 11-27 years, mean age was 18,4 (SD:5,5 years). Three participants with WS were left-handed, two were mixed handed, and eleven were right handed as measured by tool use. These subjects also participated in our earlier polysomnography study, and generally presented with sleep abnormalities [1].

16 TD individuals (6 males, 10 females), age range between 11-29 years (SD: 5,6 years) participated in the study. All TD participants were right handed and reported no sleep disruptions. Handedness could not be fully controlled due to small sample size, and a higher incidence of left and mixed handedness in WS.

Task and design

The motor learning task was a four elements FT task performed with the non-dominant hand. Participants touched their thumb with the index finger, followed by the ring finger, middle finger and little finger, always in this same sequence. Data acquisition started when participants performed three successful sequences consecutively. Ten blocks of 16 repetitions a day were practiced for five days.

Data acquisition

Data were collected using a custom-made data glove, including metal rings placed on each fingertip. The data glove was connected to a laptop computer, where Java based data acquisition software stored and processed the timing and order of finger taps.

Dependent variables

Since the task is characterized by a speed-accuracy trade-off, improvement in speed and accuracy were monitored during acquisition. Speed was defined as the number of finger taps in a second (taps/s). Accuracy (%) was defined as the ratio of the number of finger taps in correctly performed sequences. Baseline was calculated as the mean performance of the first two blocks on the first practice day. Online (practice-dependent) improvement was calculated as a difference between the mean of the first two blocks of a daily session and the mean of the last two blocks of the same session. Offline improvement was calculated as the difference between the last two blocks of a daily session, and the first two blocks on the following day. Baseline performance,

online and offline improvement were calculated with respect to all dependent variables.

Statistical analyses

Two-way repeated measures ANOVA (group baseline/online/offline) was performed on all dependent variables. A p-value of 0.05 was set as significance level for all statistical tests.

To eliminate baseline effect on learning data, ratios of online improvement/total improvement and offline improvement/total improvement were calculated regarding speed and accuracy. Two-way repeated measures ANOVA (group× online/total, offline/total) were performed on the above measures in speed and accuracy.

RESULTS AND DISCUSSION

Accuracy showed a significant main effect of WS and TD groups ($F= 4.985$, $df=1$, $p<0.05$), with a significant main effect of baseline/online/offline improvement ($F= 13.738$, $df=2$, $p<0.01$) with a significant group×baseline/online/offline interaction ($F= 4.49$, $df=2$, $p<0.05$). Regarding speed, there was a significant main effect of WS and TD groups ($F= 67.11$, $df=1$, $p<0.01$), with a significant main effect of baseline/online/offline improvement ($F= 19.43$, $df=2$, $p<0.01$) with significant group×baseline/online/offline interaction ($F= 3.73$, $df=2$, $p<0.05$). After eliminating baseline effect, significant main effect of group ($p>0.05$) and online/offline ($p>0.05$) improvement was not found in accuracy. In speed, significant main effect of group ($F= 1148.28$, $df=1$, $p<0.001$) and significant main effect of online/offline improvement compared to total improvement ($F= 7.199$, $df=1$, $p<0.05$) was still found.

At the beginning of practice, TD participants showed significantly higher baseline performance compared to WS participants with respect to both accuracy ($F= 23.82$, $df=1$, $p<0.001$) and speed ($F= 65.89$, $df=2$, $p<0.01$) (Figure 1A,B). In accuracy, WS and TD participants were not different in terms of online (practice dependent) learning at the group level ($p>0.05$) and offline improvement was not significant either ($p>0.05$). In other words, WS participants had a lower baseline but their online and offline learning was comparable to that of the TD participants in accuracy. This effect remained after eliminating baseline effect from analysis (Figure 1B). In speed, WS participants started at a lower level, they presented practice dependent/online improvement, but offline improvement was lacking (Figure 1D). After correction for baseline, greater online improvement was found with a marginal significance ($F= 3.761$, $df=1$, $p=0.062$) in the WS group. On the other hand, offline improvement showed an opposite pattern between groups. While the TD group improved performance between practice sessions, the WS group deteriorated ($F= 3.17$, $df=1$, $p<0.085$). Decreased speed and lacking improvement in speed was previously found in basal ganglia dysfunction [31]. It may indicate impaired basal ganglia - primary motor cortex network function in control and learning of movement in WS, while improvement in accuracy may involve higher level cortical processing. This may offer explanation for the clear dissociation of speed and accuracy in the present study.

Similar characteristics have been found previously in conditions with disrupted sleep, e.g., in schizophrenia.

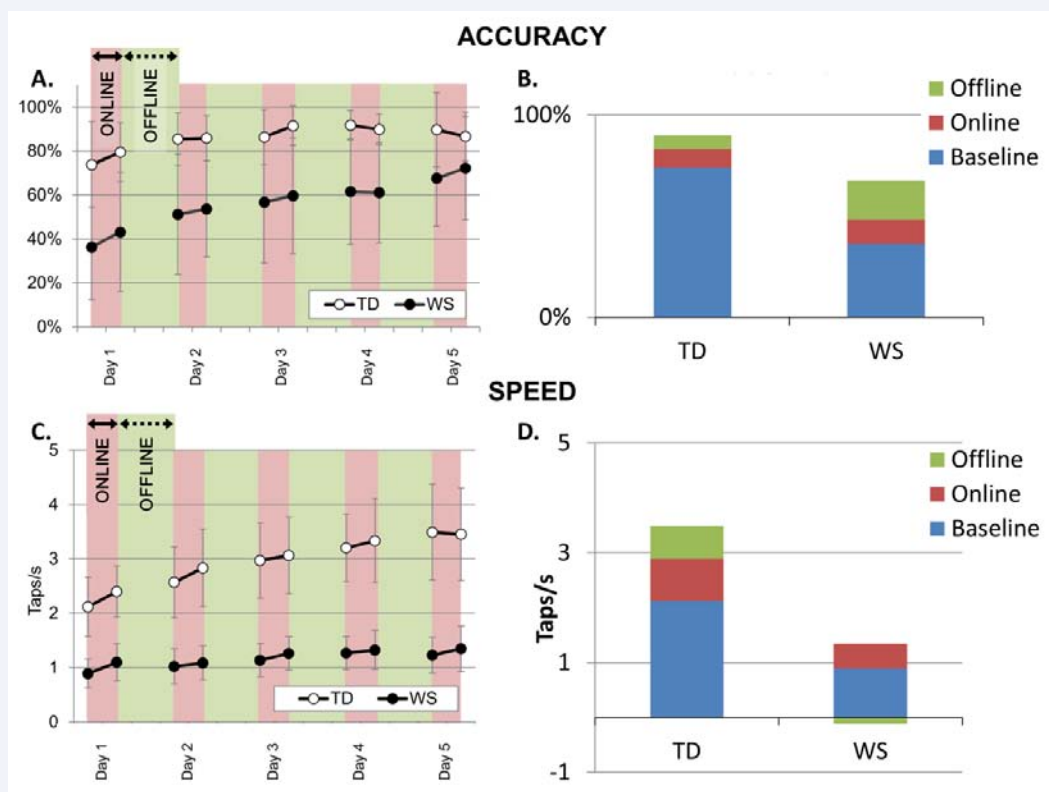


Figure 1 (A) – Five-day practice improvement in accuracy in the sequential finger tapping task. Mean of first and last two practice blocks are plotted for practice day. (B) – Cumulative baseline, online and offline improvement in accuracy, in TD and in WS, respectively. (C) – Five-day practice improvement in speed. (D) – Cumulative baseline, online and offline improvement in speed. Sleep-dependent improvement in speed was not present in WS.

Schizophrenia patients were not different than healthy controls in practice dependent learning but, they lacked offline improvement. Regarding accuracy, schizophrenia patients were different from controls only in sleep-dependent improvement [28,29]. When individuals with attention-deficit hyperactivity disorder (ADHD) were trained on a sequential FT task, within-session improvement in speed was similar to that of healthy controls, and delayed gains were expressed at 24h and 2 weeks retention, but this result was less robust. In accuracy, TD participants showed significant improvement at 24h and 2 weeks after training. On the other hand, participants with ADHD did not improve compared to pre-training level either 24h or 2 weeks after completion of practice [32]. While the above studies found impairment both in speed and accuracy, our study found dissociation between speed and accuracy with respect to sleep-dependent improvement.

In our WS participants, baseline performance was not significantly correlated with online and offline improvement. On the other hand, there was a significant negative correlation between online and offline improvement both in speed ($r = -0.785$, $p < 0.001$) and accuracy ($r = -0.800$, $p < 0.001$). In TD, there was also a significant negative correlation between online and offline improvement in speed ($r = -0.749$, $p < 0.001$) and accuracy ($r = -0.832$, $p < 0.001$). Furthermore, there was a significant negative correlation between baseline and online improvement in accuracy ($r = -0.700$, $p < 0.01$) in TD. Strong negative correlation between

online and offline improvement both in TD and WS participants is not in accordance with previous studies, where practice-dependent and overnight improvement were not significantly correlated in TD and in schizophrenia patients [23, 28, 29].

It has been shown earlier that an atypical sleep pattern has a significant effect on cognitive functioning. Daytime behavior, attention and learning is particularly affected in children and adults with sleep disorders [28,29,32,33], and in individuals with WS [10,12]. Sniecinska-Cooper et al. [11] report abnormalities in cortisol and melatonin levels in WS children, which might be contributing to their altered sleep. Currently, it has been suggested that behavioral treatments targeting the modification of sleep habits might be efficiently applied to manage sleep disturbances in developmental disorders. For example, Sciberras et al. [34] used behavioral sleep intervention in ADHD. They found improved quality of life, daily functioning, and decreased parental anxiety after the extended (2-3 session long) intervention. Ivarsson and Skarphedinsson [35] treated sleep problems in children with obsessive compulsive disorder (OCD) with a 14 week long cognitive behavior therapy. Behavioral treatment (targeting sleep environment, sleep-wake schedule, and parent-child interactions during sleep) was successfully used in another study to manage sleep problems in children with Angelman syndrome [36]. Behavioral factors that can be commonly seen in children with learning disabilities are reported to improve with better sleep hygiene and parental education [37].

Treatment might include parental education focusing on the change of inefficient sleep habits [36], cognitive behavioral therapy of subjects [34], or complementary and alternative medicines (e.g. Melatonin, Valerian, relaxation, autogen training, yoga, and meditation [38]). The importance of sleep quality in maintaining normal cognitive functioning, attention and learning is obvious; on the other hand, it has not directly been addressed how sleep improvements would improve the latter in WS.

CONCLUSION

WS is a neuro developmental disorder accompanied by atypical sleep. The present study showed altered sleep-dependent fine motor learning in WS. In particular, we found a lack of off-line improvement in terms of the speed of movement. Recently, a detrimental effect of atypical sleep on cognitive functioning and motor learning was shown. Interventions improving sleep function such as behavioral treatment have previously been found to be effective in managing sleep problems. Further research shall clarify whether such therapies would be effective in improving sleep-dependent learning in WS.

ACKNOWLEDGEMENTS

This work was supported by the Hungarian National Science Fund (OTKA-NF60806 and OTKA-NK104481 to I.K.). We are grateful to the Hungarian Williams Syndrome Association and to the participating families in the study.

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Cite this article

Berencsi A, László S, Kovács I (2015) Altered Sleep-Dependent Motor Learning in Williams Syndrome. *J Sleep Med Disord* 2(6): 1036.