Final report on NRDI project 104481

Short title: *Sculpting the Teenage Brain*

Contents

Introduction

We would like to thank NRDI for the support to the "*Sculpting the Teenage Brain*" project. The support resulted in 22 publications, 1 PhD defense, and the development of an enthusiastic research group, determined to continue to study teenage development.

Our project has been included in the **„Impressive results, exemplary achievements"** section of the NRDI homepage. This is particularly honoring, because only two projects have been selected within the Humanities and Social Sciences Panel for such public attention so far: our project, and another one on adolescent addictive behavior.

The main hypothesis of the "*Sculpting the Teenage Brain*" project was that adolescence is a critical period in the protracted course of human brain development, when the cortical networks are going through a transitional destabilization and reorganization phase, just preceding the emergence of established adult cortical networks. According to the Detailed Research Plan, there were three specific aims. First, we will describe these aims, detailing them in terms of the published subprojects (numbers is brackets, e.g., **4, 11, 22,** will indicate the serial numbers of publications in the Publications ("Közlemények") list). Then, we will describe the results with respect to each original aim, and resulting publication.

Specific aims of the "*Sculpting the Teenage Brain*" project

1. **To establish developmental curves of visual, motor and executive function in adolescence.**
    a. There is accumulating evidence, based on morphometric and *in vivo* imaging studies that brain maturation roughly follows a caudal to rostral direction. In order to link this maturational pattern to psychological function, we investigated basic visual integration functions relying on primary visual cortex (V1), motor coordination function related to primary motor cortex (M1), and executive control related to the dorsolateral prefrontal region of the brain **(21)**.
    b. After observing the obvious individual variability in puberty onset times among our teenage subjects, we also asked the question whether this variability should be taken into account more seriously in adolescent studies.
2. **To investigate typical and atypical motor development in adolescence.**
    a. With the hope that motor performance might be a selective indicator of adolescent cortical changes, we have administered different versions of a motor task. The selectivity, in this case, means that the simplest version of the task will address conduction velocity of the corticospinal tract due to myelination, while more complex versions will address cortical function. We asked whether there is any dissociation between these two developmental functions, and whether we can find specific adolescent developmental patterns in those **(4).**
    b. We have also asked whether the above-mentioned dissociation can be found in atypical motor development as well **(5, 6)**. This question was largely motivated by our quest into the understanding of the relationship between sleep and learning, as it is seen in specific aim 3 (**14, 18).**
3. **To find evidence for the hypothesized relationship between sleep and development.**
    a. We have looked at the typical and atypical adolescent development of sleep **(**analysis is in progress on typicals, **1, 17).** As genetically determined developmental disorders are known to bring both sleep disturbances and lags in intellectual development, this is an important issue to clarify before looking at causal links between sleep and development.
    b. The developmental pattern in the sleep EEG carries a lot of information about cortical connectivity at different ages and in different genetic conditions. We developed a method to look at the development of large scale connectivity of the brain based on sleep EEG synchronization (analysis is in progress in typicals, **7, 20**).
    c. We investigated specific sleep correlates of intellectual development **(2, 3, 11, 12, 15, 16, 19, 22).**
    d. Investigations with respect to the causal role of specific sleep parameters in learning and development are the most demanding ones even at the current technological and theoretical level of development. We have implemented a novel paradigm including polysomnography, quantitative EEG analysis and a thorough investigation of behavioural functions for both typical and atypical development. Our first published results clearly show a link between sleep and learning, potentially determining developmental pathways (analysis in progress in typicals, **8, 9, 10, 13, 18).**

Results

1. Establishing developmental curves of visual, motor and executive function in adolescence.

a. Developmental trajectories

There is accumulating evidence, based on morphometric and *in vivo* imaging studies that brain maturation roughly follows a caudal to rostral direction. In order to link this maturational pattern to psychological function, we investigated basic visual integration functions relying on primary visual cortex (V1), motor coordination function related to primary motor cortex (M1), and executive control related to the dorsolateral prefrontal region of the brain **(21)**.

We addressed three distinct functions and brain regions with a perceptual (contour integration, CI), motor (finger tapping, FT), and executive control (Navon global–local) task. We investigated basic visual integration functions relying on primary visual cortex (V1) in CI; motor coordination function related to primary motor cortex (M1) in FT, and the executive control component, switching, related to the dorsolateral prefrontal region of the brain in the Navon task. **122 volunteer subjects** were recruited to participate in this study between the **ages of 10 and 20** (females n = 63, males n = 59). Employing conventional statistical methods, we found that 10 and 12 year olds are performing significantly weaker than 20 year olds in all three tasks. In the CI and Navon global–local tasks, even 14 years old perform poorer than adults. We have also investigated the developmental trajectories by fitting sigmoid curves on our data streams. The analysis of the **developmental trajectories of the three tasks showed a posterior to anterior pattern** in the emergence of the developmental functions with the earliest development in the visual CI task (V1), followed by motor development in the FT task (M1), and cognitive development as measured in the Navon global–local task (DLPC) being the slowest. Gender difference was also present in FT task showing an **earlier maturation for girls in the motor domain**, see **Figure 1**.

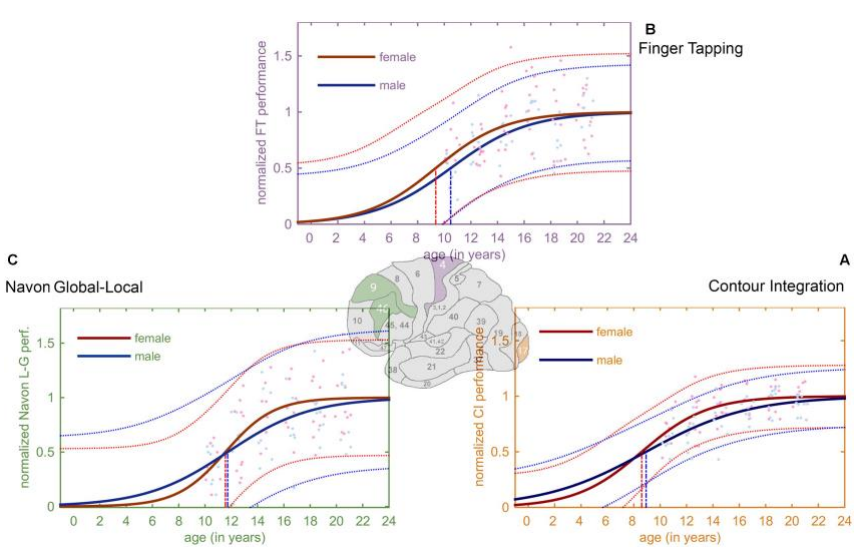

Figure 1. *The derived developmental trajectories for the three tasks. Red and blue stands for females and males, respectively. Lighter, dotted lines depict the 95% prediction bounds. (A) Fitted sigmoid curves for normalized CI performance (B) Fitted sigmoid curves for normalized FT performance (C) Fitted sigmoid curves for normalized Navon global–local task.*

b. **individual variability in puberty onset times**

Looking at the data-points in Figure 1., it is obvious that there is very large individual variability. Although recent studies show that the adolescent brain continues to mature well into the 20s, with neural circuitry underlying executive functions among the last to mature, there is actually no consensus on the developmental pace of different cognitive functions because of the extremely large individual variability. In other words, puberty onset times probably affect the results of most of the studied adolescent cohorts in the published literature.

A usual pitfall of all adolescent studies is that individual differences in puberty onset time (biological age) are difficult to take into consideration against the amount of experience in one's life (chronological age). Cross-sectional studies that take separate chronological age-groups, and compare their functioning, will lead to very noisy data if neuroendocrine maturation is playing any role in the given function. Longitudinal studies will also face the problem of different onset times of puberty even if the onset is defined precisely: teenagers coming of age at different times will have different amounts of experience; thus, comparisons are also very noisy. In addition to imprecisions in the derived developmental curves, there is a great uncertainty in both cross-sectional and longitudinal studies about the sheer contribution of genetically preprogrammed maturation versus experience. The trade-off between biological maturity and life-time experience is clear, however, it has not been clearly addressed before.

Based on the behavioural studies of the "*Sculpting the Teenage Brain*" project, we have come up with a solution to the above mentioned serious problem. We have found a proper way to dissociate biological and chronological age, and investigate their role independently in adolescent cognitive functioning and in the development of large-scale functional cortical networks. We believe that the question whether adolescent reorganization of cortical networks is determined by the onset of puberty or by experience can now be answered with the help of our novel paradigm. A proposal based on the proposed paradigm has been submitted to NKFI (entitled "*Maturation and Experience*") and to HAS for support. After receiving news that HAS provides five-year support, starting in 2017, for this follow-up study, we have withdrawn our NKFI proposal. However, the new **HAS-PPCU Research Group on Adolescent Development** is obviously a result and a continuation of the support from NKFI for the "*Sculpting the Teenage Brain*" project.

BETA
Biological & Experience-based
Trajectories in Adolescent brain
& cognitive development

In addition to the financial support from the HAS, PPCU has also substantially contributed to the funding of the new project. With the help of this generous funding, our new research group – that we call **BETA Lab** – is currently taking the ideas and results of the "*Sculpting the Teenage Brain*" project further.

2. Motor development

a. Pubertal trajectory of fine motor development

Puberty involves marked changes in the musculoskeletal and nervous systems and shows gender-based behavioural and morphological differences. The present study aimed to investigate developmental changes in ne motor function and map sex-related differences using a finger tapping (FT) paradigm. Age-dependent improvement of finger movements in terms of speed mainly depends on the maturation of the brain, corticospinal (CS) tract, spinal cord circuits, and periphery; while improvement in accuracy is mainly attributed to brain maturation. Speed and accuracy show a trade-off during performance.

118 typically developing participants (male n=56, female n=62) were assigned to six age groups (10, 12, 14, 16, 18, 20 years), ages counterbalanced. Repetitive (index FT with dominant and non-dominant hand) and serial (four-elements-sequence with non-dominant hand) tasks were performed **(4).** We found unexpected gender-differences, and we conclude that those reflect developmental changes of the nervous system, such as earlier maturation of white matter in females, and a male advantage in CS tract myelination/ axonal diameter.

b. Impaired motor learning in WS

Following up on our previous **NRDI (OTKA NF 60806)** project on typical and atypical procedural development and learning, we have also asked whether we can find the above-mentioned dissociation in atypical motor development as well **(5, 6)**. This was also motivated by our quest into the understanding of the relationship between sleep and learning, as it is seen in specific aim 3 (**14, 18).**

Williams syndrome (WS) is a rare neurodevelopmental disorder due to microdeletion on chromosome 7 in the q11.23 region. In WS, motor problems have an early onset and persist into adulthood. The present study aimed to investigate whether individuals with WS differ from their age-group in a sequential finger tapping (FT) task, and whether they are able to improve their performance during a five-day-learning session.

14 participants with Williams syndrome (6 males and 8 females, age range: 11 to 26 years, 10 right-handed, 2 left- handed, 2 mixed-handed), and **80 typically developing** (TD) controls (age-range: 7-30 years, divided into 8 age-groups) took part in the study. WS learning performance lagged behind TD, although some task specific learning took place both in terms of speed and accuracy, as it is shown in Figure 2. Based on our data, we hypothesize a possible dysfunction in motor cortex-basal ganglia networks during motor performance and learning in WS. The individual results also show a **lack of sleep-dependent learning, which suggests the potential involvement of sleep disorders.**

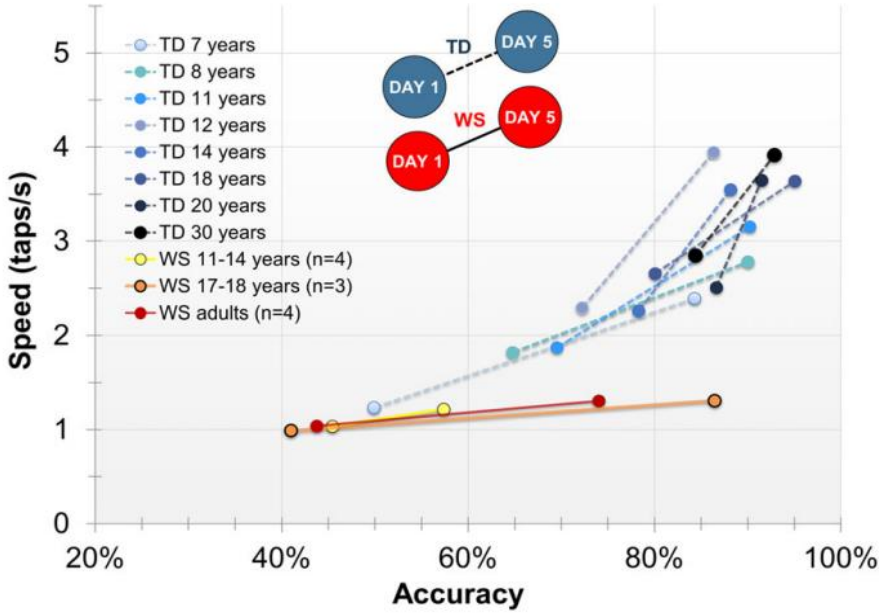

Figure 2. *Day 1 to Day 5 improvement in speed/accuracy in WS and in TD. Each bar represents a Day 1 (first data point) to Day 5 (second data point) improvement in speed and accuracy. In spite of the fact that learning took place in WS at a group level, characteristics of baseline and learning performance were different from that of TD participants. Results showed that initial performance lagged behind TD age-group level both with respect to speed and accuracy, and none of the WS participants provided better performance than the TD baseline.*

3. Sleep and development

a. Typical and atypical adolescent development of sleep

As genetically determined developmental disorders are known to bring both sleep disturbances and lags in intellectual development, this is an important issue to clarify before looking at causal links between sleep and development. **(1, 17).**

Aging and sleep in Williams syndrome: Accelerated sleep deterioration and decelerated slow wave sleep decrement (1)

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 anatomical, functional and cognitive measures. The present study confirmed the hypothesis of a **premature aging of sleep in WS**.

Sleep EEG of 42 subjects (21WS, 21age-and gender matched TD subjects, age: 6–29years) was recorded in this study. 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. Objectively measured sleep disruption of subjects with WS is age-dependent and increasing with age. NREM sleep-related measures indicated atypical decelerations of the developmental trends of WS subjects revealing signs of an as yet unidentified, perhaps compensatory developmental delay, as it is shown in Figure 3.

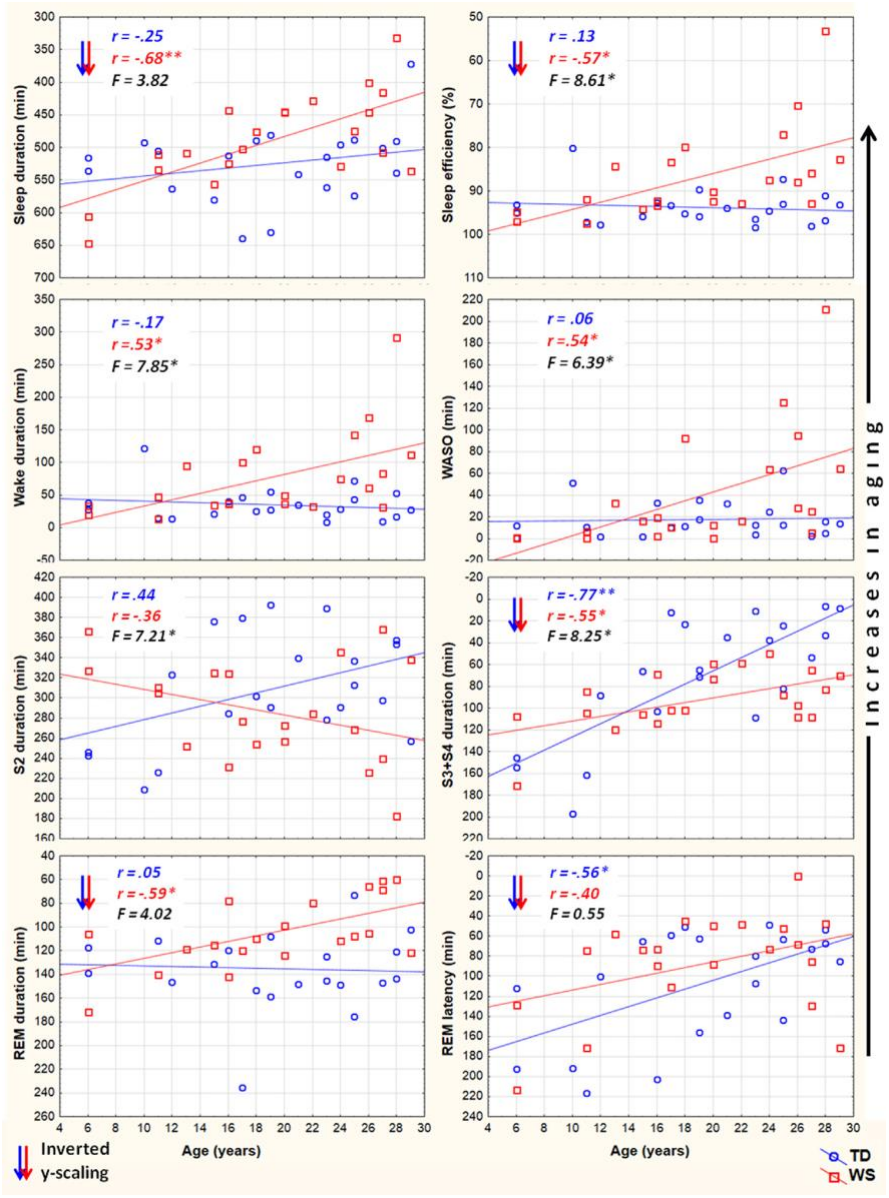

Figure 3. *Aging and sleep architecture in typically developing (TD) and Williams syndrome (WS) subjects. Upward changes depict increasing aging. Inverted scaling for sleep duration, sleep efficiency, S3+S4duration, REM duration and REM latency was used. Inserts depict linear relationships as expressed by Pearson correlation coefficients (r), as well as the interaction effects revealed by the homogeneity of slopes analyses (F). *p < .05; **p < .01; ***p < .001.*

EEG spectral power in phasic and tonic REM sleep: different patterns in young adults and children (17)

Rapid eye movement sleep is composed of phasic and tonic periods, two distinguishable microstates in terms of arousal thresholds and sensory processing. Background electroencephalogram oscillations are also different between periods.

Phasic and tonic spectral power differences within a group of 4–8-year-old children (n=18) were examined based on the polysomnographic data of 20 young adults. The results underscore the heterogeneity of rapid eye movement sleep, and point to **marked differences between young adults and children regarding phasic/tonic electroencephalogram spectral power**. These results suggest that the differentiation between phasic and tonic rapid eye movement periods undergoes maturation.

Topographic and spectral sleep EEG changes in adolescent-adult transition (HD-EEG analysis in progress)

20 young adults (mean age: 21.4 ± 0.6 years; 10 males) and 20 adolescent (mean age: 15.9 ± 0.5 years; ten males) underwent full-night polysomnography in our sleep laboratory. Sleep EEG was recorded with a 128 channel HD-EEG device. We analyzed the topographic and spectral sleep EEG changes in adolescent-adult transition.

Our results related to age changes are in line with earlier findings. In the NREM state, the absolute spectrum of the low frequency bands (slow oscillations, delta and theta) shows a large decrease on the entire scalp surface, whereas the high sigma band shows a centrally increasing activity with age. The relative spectra show decrease in the delta band in the parietal, occipital and left temporal regions, while alpha, sigma (mainly high sigma) and beta bands are increased mostly in parietal and temporal regions.

In REM, the absolute spectrum of the delta and the theta frequency ranges are decreased with age, while the relative delta activity is decreasing in parietal parieto-occipital regions and the high sigma activity is increasing in the whole scalp with age (Figure 4.).

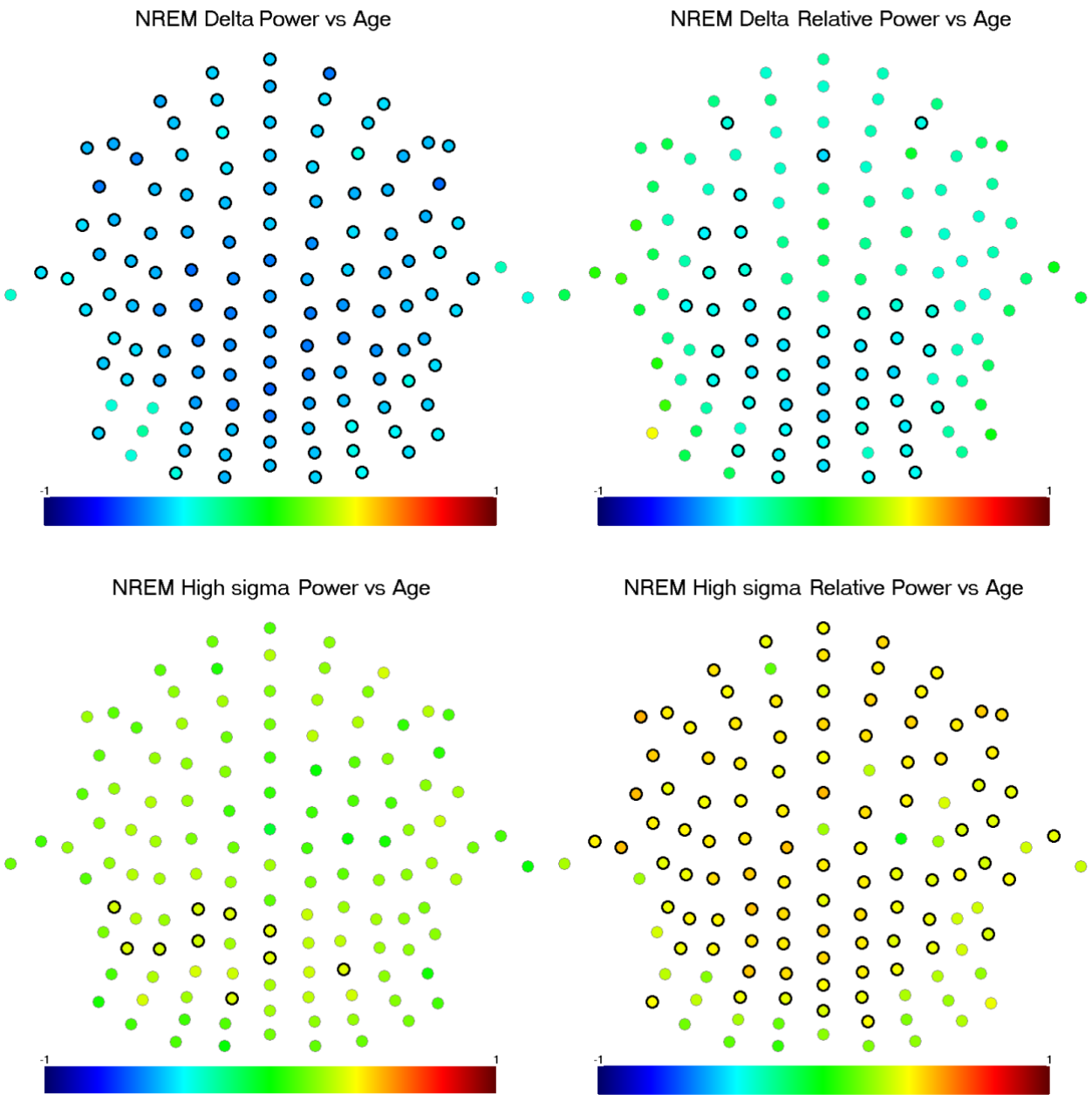

Figure 4. *NREM delta EEG absolute and relative power vs. Age. Circles denotes electrodes on the scalp. Green color means no correlation, blue means negative and red means positive correlations. Circles with thick outline denotes areas where the correlation is significant.*

b. **Sleep EEG synchronisation**

The developmental pattern in the sleep EEG carries a lot of information about cortical connectivity at different ages and in different genetic conditions. We developed a method to look at the development of large scale connectivity of the brain based on sleep EEG synchronization (analysis is in progress in typicals, **7, 20**).

Increased overall cortical connectivity with syndrome specific local decreases suggested by atypical sleep-EEG synchronization in Williams syndrome (7, 20)

The region, sleep state and frequency-specific EEG synchronization of whole night sleep recordings of 21 Williams syndrome and 21 typically developing age- and gender-matched subjects was analyzed by calculating weighted phase lag indexes.

We found broadband increases in inter- and intrahemispheric neural connectivity for both NREM and REM sleep EEG of Williams syndrome subjects. These effects consisted of increased theta, high sigma, and beta/low gamma synchronization, whereas alpha synchronization was characterized by a peculiar Williams syndrome-specific decrease during NREM states (intra- and interhemispheric centro-temporal) and REM phases of sleep (occipital intra-area synchronization). We also found a decrease in short range, occipital connectivity of NREM sleep EEG theta activity (Figure 5. and 6.).

The striking increased overall synchronization of sleep EEG in Williams syndrome subjects is consistent with the recently reported increase in synaptic and dendritic density in stem-cell based Williams syndrome models, whereas decreased alpha and occipital connectivity might reflect and underpin the altered microarchitecture of primary visual cortex and disordered visuospatial functioning of Williams syndrome subjects.

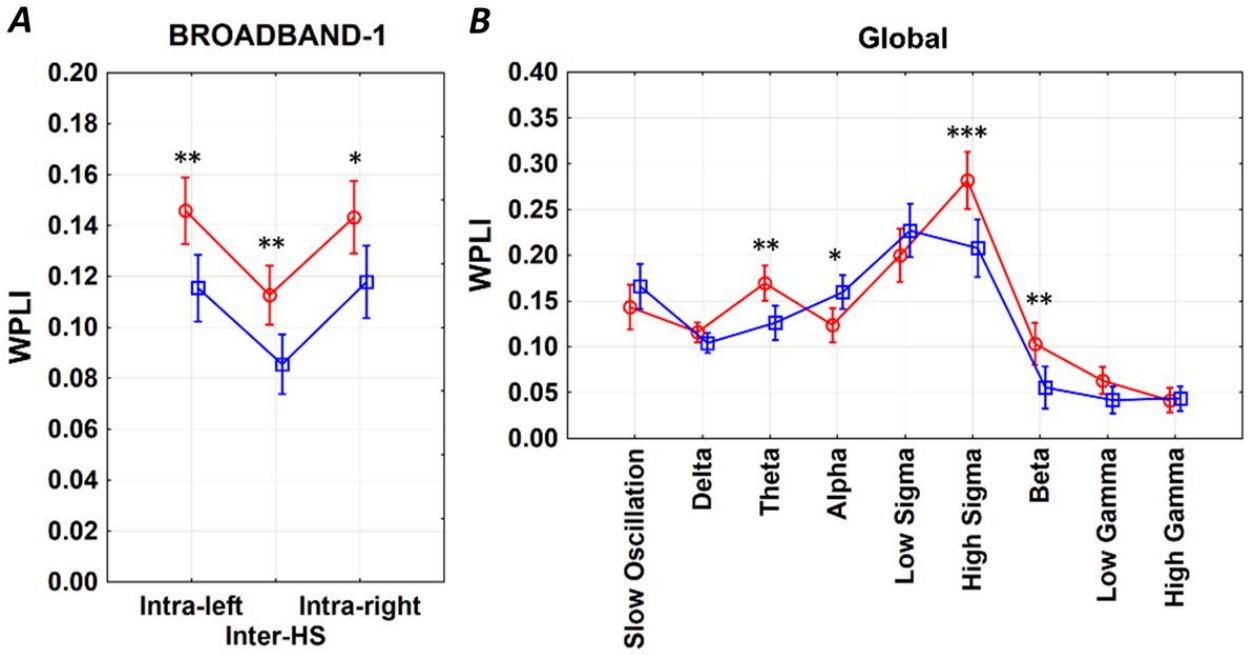

Figure 5. *NREM sleep EEG WPLI means. (A) Intra- and interhemispheric NREM sleep EEG broadband-1 and broadband-2 WPLI means of Williams syndrome and typically developing subjects (means and 95% confidence intervals). Intra-left – left intrahemispheric, Inter-HS – interhemispheric, Intra-right – right intrahemispheric. *p < 0.05, **p < 0.01. (B) Band-limited global WPLI means of Williams syndrome and typically developing subjects' NREM sleep EEG recordings (means and 95% confidence intervals). *p < 0.05, **p < 0.01, ***p < 0.001.*

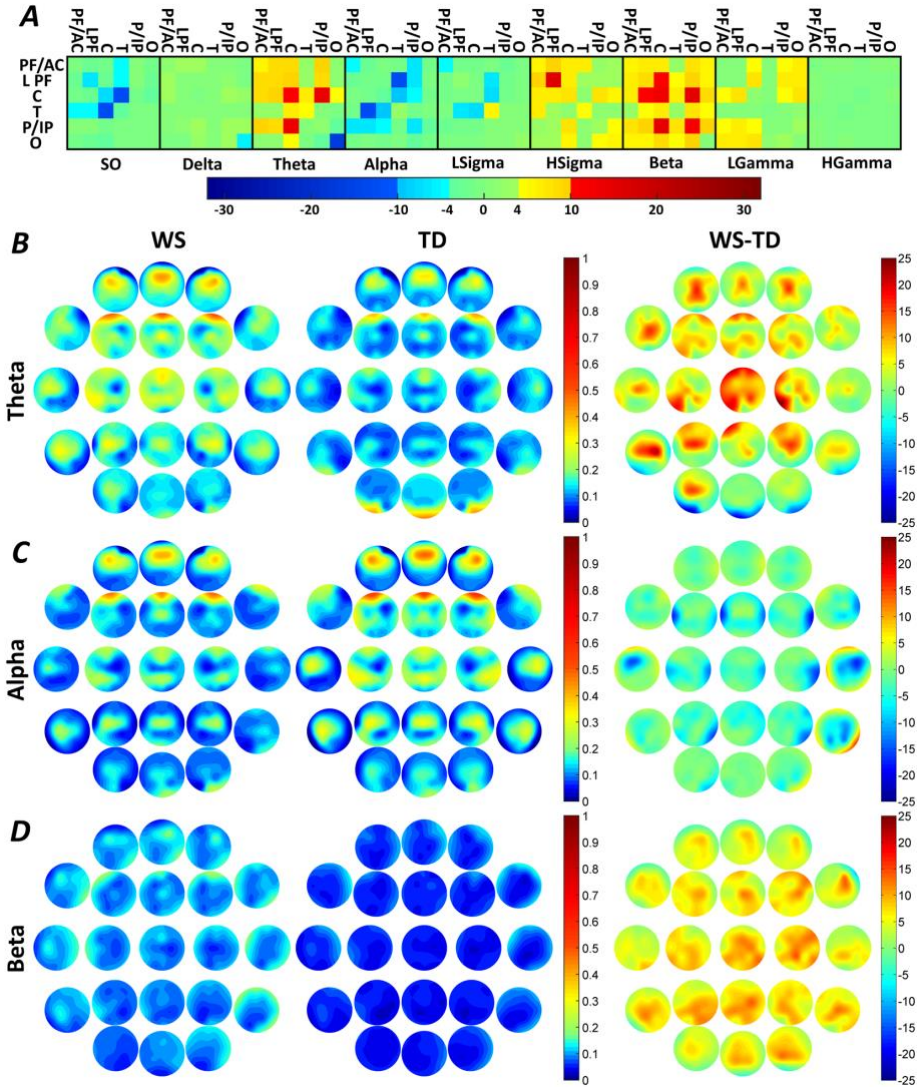

Figure 6. *Region-specific and band-limited NREM sleep EEG connectivity differences. Decreased WPLI was evidenced in the slow oscillation range for the C-T inter-regional pairing, as well as in the intra-regional O theta and LPF-T alpha synchronizations. Several Williams syndrome-specific increases in WPLIs were found in the theta, high sigma and beta ranges. Frequency range codes: SO = Slow oscillation, LSigma = Low sigma, HSigma = High sigma, LGamma = Low gamma, HGamma = High gamma. Color codes: Red = Williams syndrome > typically developing (B-H corrected), Yellow-orange = Williams syndrome > typically developing (uncorrected), Green = Williams syndrome ≈ typically developing, Light blue = Williams syndrome < typically developing (uncorrected), Blue = Williams syndrome < typically developing (B-H corrected). B-D. Theta, alpha and beta WPLI maps highlighting the patterns of absolute group means (left: Williams syndrome; middle: typically developing) and Williams syndrome-typically developing differences (right). Positions of the maps represent the seed derivation of the synchronization analyses (according to the 10–20 system), while the color patterns are the representations of the variable strengths in the synchronization (WPLI) between the respective region and the seed derivation.*

c. Sleep and sleep spindles vs. intelligence

We investigated specific sleep correlates of intellectual development **(2, 3, 11, 12, 15, 16, 19, 22).**

Sleep spindles are thalamocortical oscillations in nonrapid eye movement sleep, which play an important role in sleep-related neuroplasticity and offline information processing. Sleep spindle features are stable within and vary between individuals, with, for example, females having a higher number of spindles and higher spindle density than males. Sleep spindles have been associated with learning potential and intelligence; however, the details of this relationship have not been fully clarified yet.

In a series of studies, we analyzed the specific correlation between sleep and intelligence: we analyzed the age-related changes of sleep (16), the sexual dimorphism of the correlation of sleep spindles and intelligence (2, 3, 22) and the lateralization of sleep spindles (15, 19). Beyond the full night polysomnography studies, we analyzed sleep spindles and intelligence in a napping study also (11). Furthermore, in a methodological study we investigated the automated sleep spindle detection methods (12).

Age-related changes in sleep EEG are attenuated in highly intelligent individuals (16)

Non-rapid eye movement (NREM) sleep EEG delta power reflects neural plasticity and, in line with age-related cognitive decline, decreases with age. Individuals with higher general intelligence are less affected by age-related cognitive decline or other disorders and have longer lifespans.

We investigated the correlation between age and EEG power in 159 healthy human subjects (age range: 17-69 years), and compared an average (IQ<120; N=87) with a high (IQ≥120; N=72) intelligence subgroup. We found less age-related decrease in all-night relative NREM sleep EEG delta power in the high intelligence subgroup.

Our results suggest that highly intelligent individuals are less affected by the sleep-related effects of biological ageing, and therefore potentially less at risk for age-related cognitive deficits and other diseases.

Sleep Spindles and Intelligence: Evidence for a Sexual Dimorphism (3)

In a sample of 160 adult human subjects with a broad IQ range, we investigated the relationship between sleep spindle parameters and intelligence.

In females, we found a positive age-corrected association between intelligence and fast sleep spindle amplitude in central and frontal derivations and a positive association between intelligence and slow sleep spindle duration in all except one derivation. In males, a negative association between intelligence and fast spindle density in posterior regions was found.

Our results demonstrate that, although there is an association between sleep spindle parameters and intellectual performance, these effects are more modest than previously reported and mainly present in females. This supports the view that intelligence does not rely on a single neural

framework, and stronger neural connectivity manifesting in increased thalamocortical oscillations in sleep is one particular mechanism typical for females but not males.

Sleep spindling and fluid intelligence across adolescent development: sex matters (2, 22)

Adolescent development of sleep spindle oscillations were studied in a home polysomnographic study focusing on the effects of chronological age and developmentally acquired overall mental efficiency (fluid IQ) with sex as a potential modulating factor.

Subjects were 24 healthy adolescents (12 males) with an age range of 15–22 years (mean: 18 years) and fluid IQ of 91–126 (mean: 104.12, Raven Progressive Matrices Test). A significant age-dependent increase in average FS density was found. Moreover, fluid IQ correlated with FS density and amplitude. The latter effects were entirely driven by particularly reliable FS-IQ correlations in females. The only positive spindle-index of fluid IQ in males turned out to be the frequency of FSs.

Increases in FS density during adolescence may index reshaped structural connectivity related to white matter maturation in the late developing human brain. The continued development over this age range of cognitive functions is indexed by specific measures of sleep spindling unraveling gender differences in adolescent brain maturation and perhaps cognitive strategy.

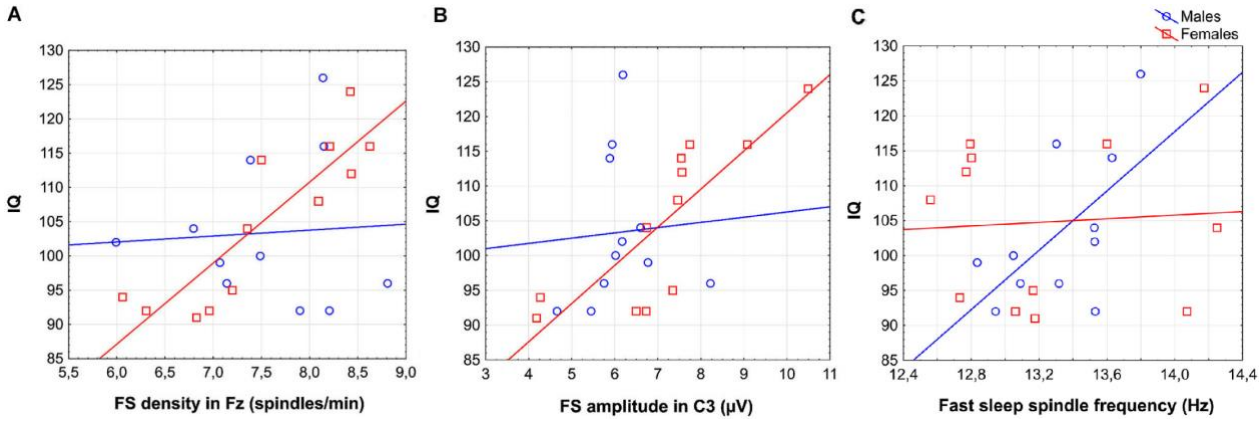

Figure 7. *Gender-specific sleep EEG fast spindle (FS) attributes vs. IQ relationship in adolescents. (A) Frontal midline FS density vs. IQ relationship. (B) Frontal midline FS amplitude vs. IQ relationship. (C) Correlation between sleep EEG FS frequency and IQ in males.*

The hemispheric lateralization of sleep spindles in humans (15, 19)

Females and males differ in several features of their spindle oscillations, as well as in the hemispheric lateralization of their neurocognitive processes. In addition, the hemispheric lateralization of cognitive functions was shown to vary in an age-dependent manner.

The aim of the present study was to fill this gap by the description of the hemispheric lateralization of sleep spindles in healthy human subjects. Data sets from three research groups were unified (N

= 251, age range: 4−69 years, 122 females) in this retrospective multicenter study. The amplitude, density, and duration of slow (frontally dominant) and fast (centroparietally dominant) spindles were analyzed using the individual adjustment method.

Orbitofronto-temporo-occipital and parietal fast sleep spindle measures are left lateralized, while prefrontal spindle amplitude is characterized by right hemispheric dominance. Left lateralization of fast spindle density and duration in the temporal and orbitofrontal regions, respectively, increases as a function of age in males, but not in females. In turn, females are characterized by higher left hemispheric dominance in occipitally measured fast spindle durations as compared with males.

Sleep spindles are asymmetrically distributed over the two hemispheres. This phenomenon is sexually dimorphic and region-specific perhaps indexing sex differences in neurocognitive architectures.

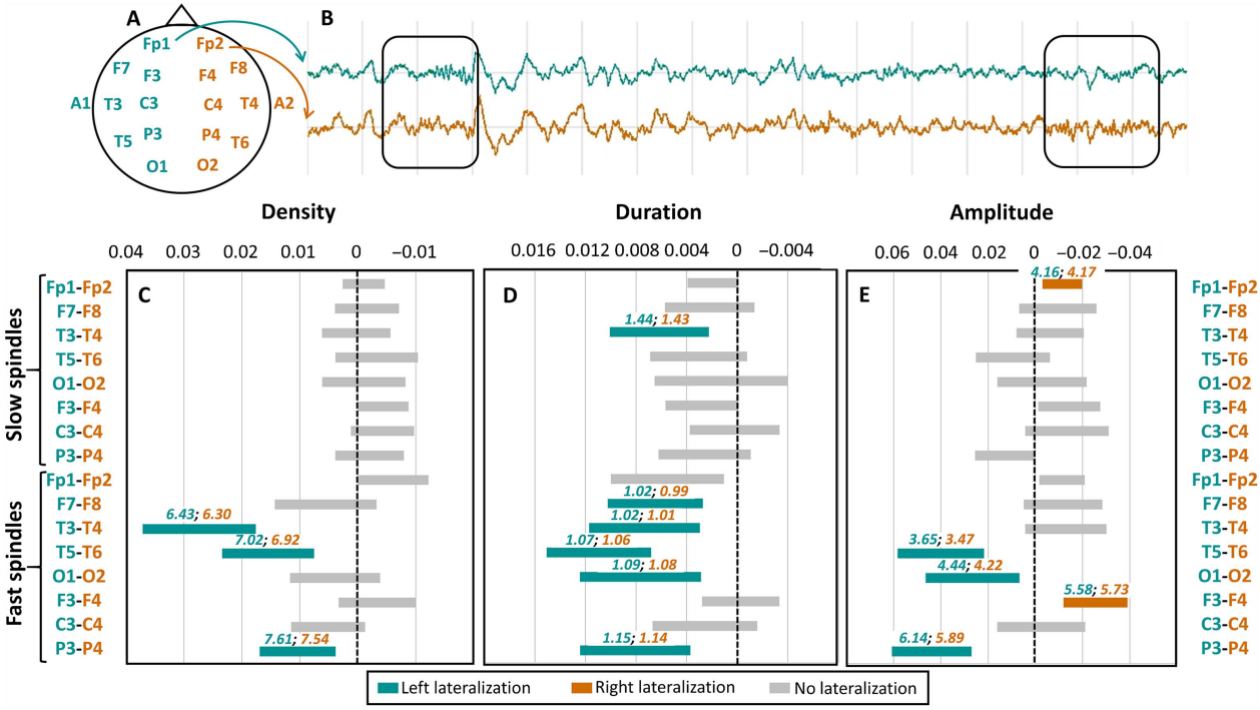

Figure 8. *The hemispheric lateralization of different sleep spindle features in healthy human subjects. A: EEG locations (dark teal – left, tawny – right). B: Left (Fp1) and right (Fp2) frontopolar samples of stage 2 sleep EEG traces. Highlighted periods (black rectangles) exemplify hemispheric asymmetries in sleep spindles. Vertical gray lines indicate seconds. C: The hemispheric lateralization of sleep spindle densities. D: The hemispheric lateralization of sleep spindle durations. E: The hemispheric lateralization of sleep spindle amplitudes. Horizontal bars denote 95% confidence intervals of the mean hemispheric lateralization indices: (Left − Right)/mean (Left, Right). Vertical dotted black lines indicate zero values (0 = no hemispheric lateralization). Overall means of absolute left and right values are seen over the horizontal bars indicating significant lateralization effects.*

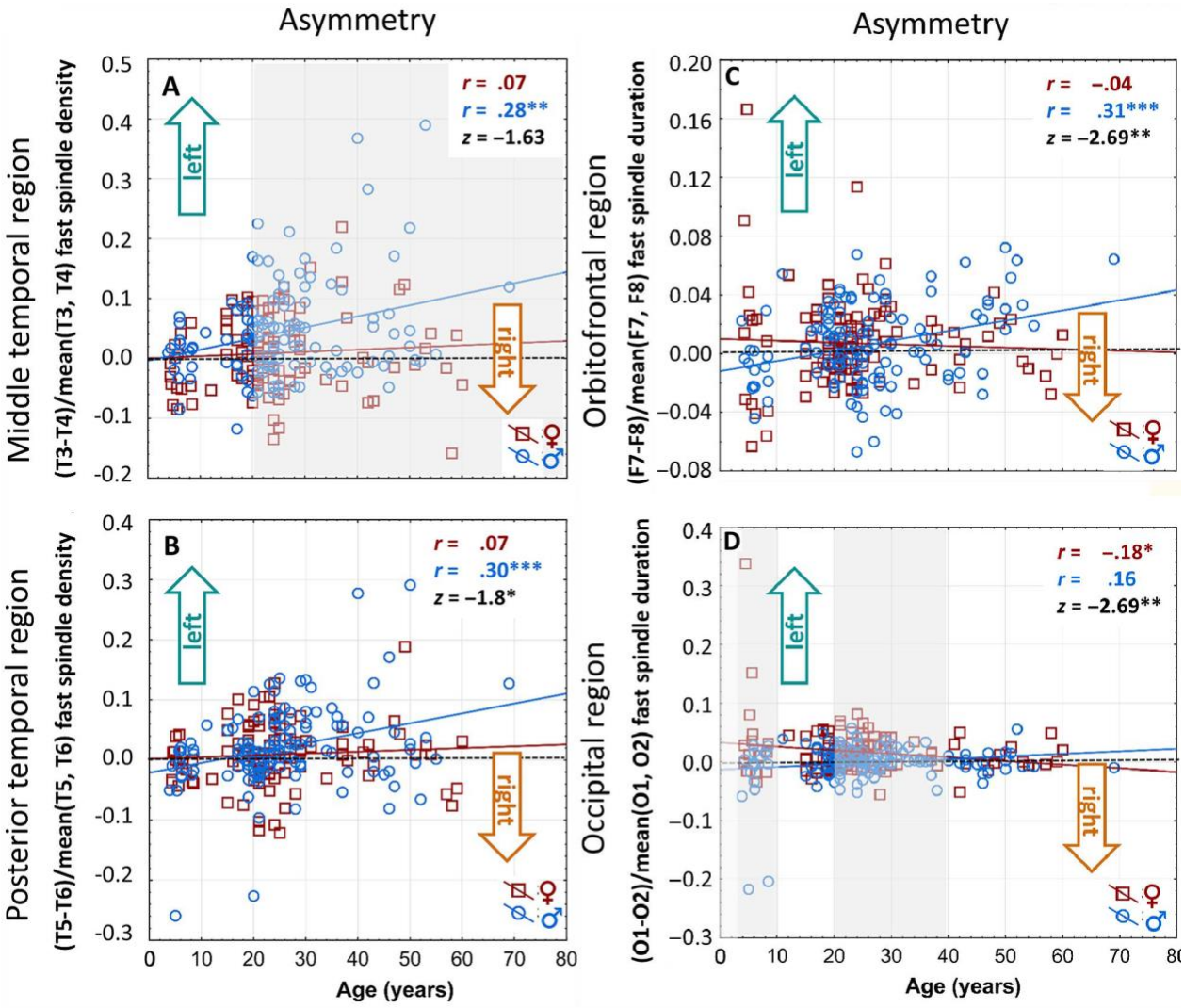

Figure 9. *Hemispheric asymmetry of temporally recorded fast sleep spindle densities and durations as a function of age, sex, and left/right absolute values. A: Age-related changes in the left hemispheric dominance of middle temporal fast sleep spindle densities in females (♀, red) and males (♂♂, blue). Horizontal dotted line indicates 0 value (no lateralization). Gray area indexes the age range (≥20 years) characterized by significant male > female left hemispheric asymmetry. Note the age-dependence of left hemispheric dominance in males, but not females. B: Age-related changes in the left hemispheric dominance of posterior temporal fast sleep spindle density. Note the age-dependence of left hemispheric dominance in males, but not females. C: Age-related changes in the left hemispheric dominance of orbitofrontal fast sleep spindle durations. Note the age-dependence of left hemispheric dominance in males, but not females. D: Age-related changes in the left hemispheric dominance of occipital fast sleep spindle durations. Note the age-dependence of left hemispheric dominance in females, but not males. Gray areas indicate the age ranges (<10 years and 20–40 years) characterized by significant group effects (females > males).*

Nap sleep spindle correlates of intelligence (11)

Sleep spindle regulation underlies a circadian rhythm, however the association between spindles and intelligence has not been investigated in daytime nap sleep so far. In a sample of 86 healthy male human subjects, we investigated the correlation between fluid intelligence and sleep spindle parameters in an afternoon nap of 100 minutes.

Mean sleep spindle length, amplitude and density were computed for both slow and fast spindles. A positive association was found between intelligence and slow spindle duration, but not any other sleep spindle parameter.

A comparison of two sleep spindle detection methods based on all night averages: individually adjusted vs. fixed frequencies (12)

Due to their frequent occurrence in NREM sleep, the detection of sleep spindles is only feasible using automatic algorithms, of which a large number is available. We compared a fixed frequency (FixF) (11–13 Hz for slow spindles, 13–15 Hz for fast spindles) automatic detection algorithm and the individual adjustment method (IAM), which uses individual frequency bands for sleep spindle detection.

Fast spindle duration and amplitude are strongly correlated in the two algorithms, but there is little overlap in fast spindle density and slow spindle parameters in general. The agreement between fixed and manually determined sleep spindle frequencies is limited, especially in case of slow spindles. This is the most likely reason for the poor agreement between the two detection methods in case of slow spindle parameters.

Our results suggest that while various algorithms may reliably detect fast spindles, a more sophisticated algorithm primed to individual spindle frequencies is necessary for the detection of slow spindles as well as individual variations in the number of spindles in general

Intelligence vs. sleep EEG spectral parameters in typically developing adolescents and adults (HD-EEG analysis in progress)

The local character and effectiveness of sleep is not only relevant to the performance of a learning situation, but also from the perspective of learning ability, which depends on the effectiveness of the attention and execution functions and the working memory, which mainly show frontal localization.

In the present study, 20 young adult (mean age: 21.4 ± 0.6 years; 10 males) and 20 adolescent (mean age: 15.9 ± 0.5 years; ten males) subjects underwent full-night polysomnography in our sleep laboratory. Sleep EEG was recorded with a 128 channel HD-EEG device.

Learning ability was tested by the Raven Standard Progressive Matrix Test, whose scores showed a strong positive correlation in the central and fronto-central areas with the NREM absolute delta activity in the adult group, which refers to more efficient and more sustained delta homeostasis

(Figure 10.). However, in the group of adolescents, we could not find any correlations which is consistent with the literature data (Tarokh, L., Carskadon, M.A., and Achermann, P. ,2010) and indicates that these functions are less mature.

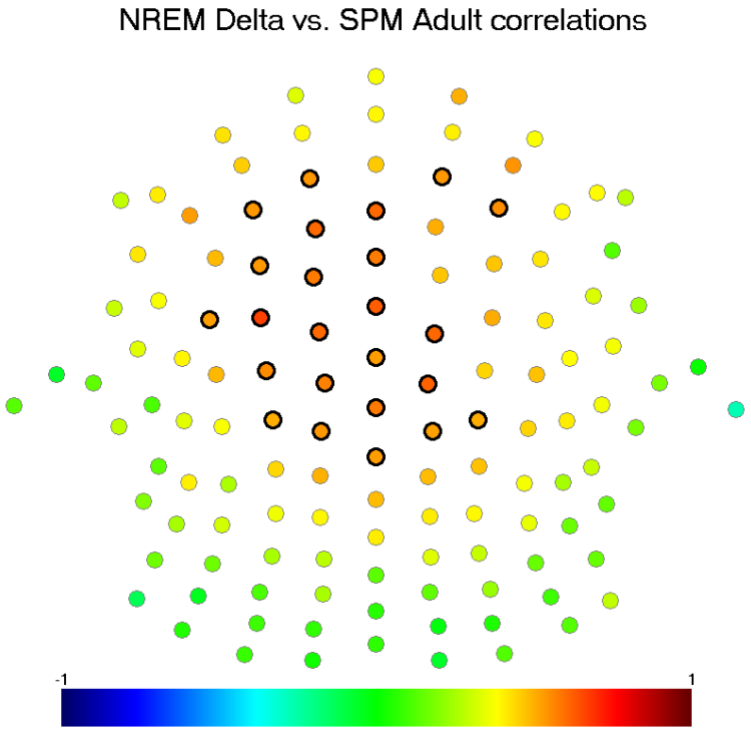

Figure 10. *NREM delta EEG power vs. Raven Standard Progressive Matrix Test scores. Circles denotes electrodes on the scalp. Green color means no correlation, blue means negative and red means positive correlations. Circles with thick outline denotes areas where the correlation is significant.*

d. **Sleep and learning!**

Investigations with respect to the causal role of specific sleep parameters in learning and development are the most demanding ones even at the current technological and theoretical level of development. We have implemented a novel paradigm including polysomnography, quantitative EEG analysis and a thorough investigation of behavioural functions for both typical and atypical development. Our first published results clearly show a link between sleep and learning, potentially determining developmental pathways (analysis in progress in typicals, **8, 9, 10, 13, 18).**

The most exciting hypothesis with respect to sleep parameters relevant in learning processes is the suggestion that sleep spindles might play a major role. Sleep spindle or sigma band characteristics affect motor learning in typically developing individuals. We asked whether the earlier found, altered sigma activity in a neurodevelopmental disorder (Williams syndrome, WS, see Figure 11.)

predicts motor learning. 16 TD and 16 WS participants practiced in a sequential finger tapping (FT) task for two days. Although WS participants started out at a lower performance level, TD and WS participants had a comparable amount of online and offline learning in terms of the accuracy of movement. Spectral analysis of WS sleep EEG recordings revealed that motor accuracy improvement is intricately related to WS-specific NREM sleep EEG features in the 8–16 Hz range profiles: higher 11–13.5 Hz z-transformed power is associated with higher offline FT accuracy improvement; and higher oscillatory peak frequencies are associated with lower offline accuracy improvements – see Figure 12. **These findings indicate a fundamental, potentially causal relationship between sleep spindle (or sigma band) activity and motor learning in WS.**

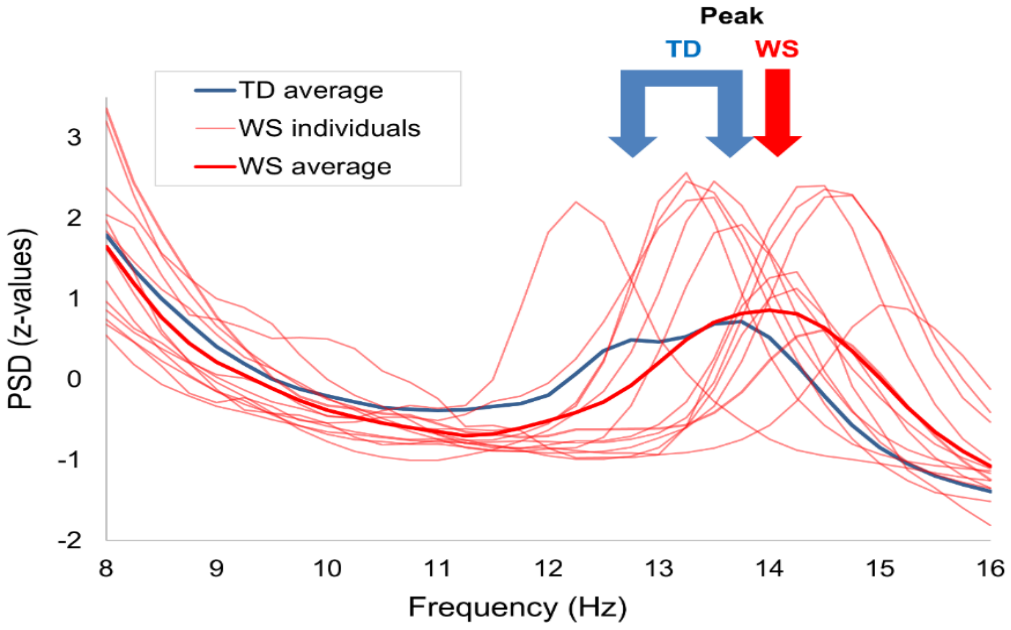

Figure 11. *Focus of the present study: the broadband sigma range (8–16 Hz) in NREM sleep. Normalized sigma power as expressed in z-scores of EEG activity in WS subjects and group averages (WS and TD) at derivation Cz. Spectral power densities of artifact-free, Hanning-tapered 4 second EEG epochs were calculated via the Fast Fourier Transformation method and averaged for all-night NREM sleep (data from15)/TD data shown as a reference from21. The 8–16 Hz range was normalized in a derivation- and individual-specific manner by z-transformation19. TD sigma activity typically has two peaks (it is also true for the individual subjects) which could be referred to as the slow and fast sleep spindle peak frequencies, correspondingly. The slow spindle peak is usually missing or greatly reduced in WS patients and generally the second (fast spindle) peak is at a higher frequency in WS than in TD subjects21.*

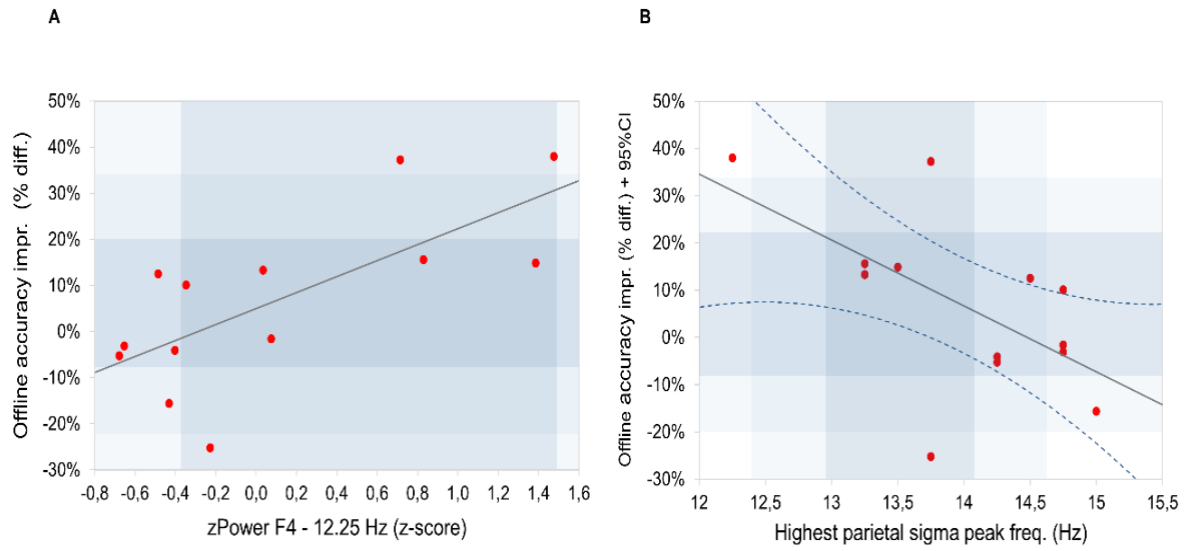

Figure 12. *Positive correlation between z-scores of 12.25 Hz NREM sleep EEG power, and Day 1 to Day 2 offline motor accuracy improvement in WS participants. The z-score of the 12.25 Hz power is based on the individual-specific normalization of 8–16 Hz spectra20 in the right frontal derivation (F4). Offline FT accuracy improvement is expressed in terms of percent change from Day 1 to Day 2. Light and dark grey indicates ±1 and ± 2SD of the corresponding variable in TD participants, respectively. SD of TD spectral data are from ref.21. Note that higher 12.25 Hz power is associated with higher offline FT accuracy improvement. (B) Negative correlation between parietal sigma peak frequency and Day 1 to Day 2 offline motor accuracy improvement in WS participants. Highest parietal sigma peak frequency is the frequency at which the highest observable local maxima are found in the 8–16 Hz NREM sleep EEG power spectra of WS participants. Offline FT accuracy improvement is expressed in terms of percent change from Day 1 to Day 2. Light and dark grey indicates ±1 and ±2 SD of the corresponding variable in TD participants, respectively. SD of TD spectral data are from ref.21. Note that higher oscillatory frequencies are associated with lower offline accuracy improvements.*

Summary

Adolescence is a relevant period in human development, not only in terms of identity- forming life-events, but also in terms of the transition of cortical neural networks into an adult pattern of connectivity and function. Our purpose has been to map the puberty induced changes in the maturation and development of the "canonical circuits" of sensory, motor and frontal cortices, and to delve into the unresolved issue of how sleep might determine development in this age-group. This is a short summary of our main results detailed in the Results section, and organized according to the Specific Aims of the "Sculpting the Teenage Brain" project. Numbers in brackets refer to our published papers as they are enlisted in the List of Publications.

1. **To establish developmental curves of visual, motor and executive function in adolescence.**
    a. We have shown that the known pattern of posterior-anterior anatomical brain maturation is reflected by the developmental trajectories of visual, motor and executive function **(21)**.
    b. We consider our new project, supported both by the HAS and PPCU a major result of the "Sculpting the Teenage Brain" project.
2. **To investigate typical and atypical motor development in adolescence.**
    a. The most interesting result was an unexpected gender-difference reflecting earlier maturation of white matter in females, and a male advantage in CS tract myelination/ axonal diameter **(4).**
    b. We found that WS subjects show deteriorated sleep-dependent learning, which suggests the potential involvement of sleep disorders **(5, 6)**.
3. **To find evidence for the hypothesized relationship between sleep and development.**
    a. We found premature aging of sleep in WS, (**1**), and marked differences between young adults and children regarding phasic/tonic electroencephalogram spectral power in TD (**17**). HD-EEG analysis of topographic and spectral sleep EEG changes in the TD adolescent-adult transition is still in progress.
    b. We found an increased overall cortical connectivity with syndrome specific local decreases suggested by atypical sleep-EEG synchronization in Williams syndrome **(7, 20).** HD-EEG analysis of sleep-EEG synchronization changes in the TD adolescent-adult transition is still in progress.
    c. We found specific sleep correlates of intellectual development **(2, 3, 11, 12, 15, 16, 19, 22).**
    d. We found a causal relationship between sleep spindle (or sigma band) activity and motor learning in WS **(8, 9, 10, 13, 18)**. HD-EEG analysis of sigma band sleep EEG activity as it is related to learning in the TD adolescent population is still in progress.

To recapitulate the specific results, we found that **posterior-anterior anatomical brain maturation is reflected by the developmental trajectories of visual, motor and executive**

function, providing a link between neuroscientific and behavioural data. Studying hundreds of teenage subjects helped us to develop **a novel paradigm that takes puberty onset times into real account for the first time**. We have recently received HAS and PPCU support to apply this new paradigm.

In terms of finding the exact developmental role of sleep in adolescence, there are three major results of the project. First, with our newly developed technique to analyze sleep-EEG synchronization, we found **relevant typical and atypical developmental trends in large-scale cortical connectivity**. Second, we found **specific sleep correlates of intellectual development**. And third, we found a **causal relationship between sleep spindle activity and motor learning**. Taken together, these findings point to the fact that sleep is the Achilles' heel of brain development – detailed in the **„Impressive results, exemplary achievements"** section of the NRDI homepage.

List of Publications

This list is identical to the one in the projects online publications ("közlemények") list. Papers are listed in the temporal order of publications. The serial numbers are referred to in the text of this Final Report.

1. Bódizs R, Gombos F, Gerván P, Szőcs K, Réthelyi J, Kovács I: ***Aging and Sleep in Williams Syndrome: Accelerated Sleep Deterioration and Decelerated Slow Wave Sleep Decrement***, RESEARCH IN DEVELOPMENTAL DISABILITIES 35:(12) pp. 3226-3235., 2014
   Teljes dokumentum»
2. Bódizs R, Gombos F, Ujma PP, Kovács I: ***Sleep spindling and fluid intelligence across adolescent development: sex matters.***, FRONTIERS IN HUMAN NEUROSCIENCE 8: Paper 952., 2014
   Teljes dokumentum»
3. Ujma PP, Konrad BN, Genzel L, Bleifuss A, Simor P, Pótári A, Körmendi J, Gombos F, Steiger A, Bódizs R, Dresler M: ***Sleep spindles and intelligence: evidence for a sexual dimorphism***, THE JOURNAL OF NEUROSCIENCE 34(49):16358-68, 2014
   Teljes dokumentum»
4. Berencsi A, Gerván P, Filep O, Kovács I.: ***Gender differences in the pubertal trajectory of fine motor development***, Progress in Motor Control X.: Program and Abstracts. p. 88., 2015
   Teljes dokumentum»
5. Berencsi A, Kovács I.: ***Impaired fine motor learning in Williams syndrome***, Progress in Motor Control X.: Program and Abstracts. p. 87., 2015
   Teljes dokumentum»
6. Berencsi A, László S, Kovács I: ***Altered Sleep-Dependent Motor Learning in Williams Syndrome***, JOURNAL OF SLEEP MEDICINE AND DISORDERS 2(6): 1036, 2015
   Teljes dokumentum»
7. Gombos F, Bódizs R, Kovács I: ***Atypical NREM sleep EEG synchronization in Williams syndrome***, Worldsleep 2015 - 7th World Congress of the World Sleep Federation, p. 98., 2015
   Teljes dokumentum»
8. Kovács, I: ***Sleep, the Achilles' Heel of brain development***, 1º Workshop Internacional de Síndrome de Williams, Brasil, meghívott előadás, 2015
   Teljes dokumentum»
9. Kovács, I: ***Adaptability in atypical human development***, Adaptive Brains and Machines, Downing College University of Cambridge, meghívott előadás, 2015
   Teljes dokumentum»
10. Kovács, I: ***Sleep, the Achilles' Heel of brain development***, Neurosciences Cognitives séminaire du LNC, UMR 7291 CNRS, Fédération de Recherche 3C - Comportement Cerveau Cognition Aix-Marseille Université, meghívott előadás, 2015
11. Ujma PP, Bódizs R, Gombos F, Stintzing J, Konrad BN, Genzel L, Steiger A, Dresler M: ***Nap sleep spindle correlates of intelligence***, SCIENTIFIC REPORTS 5:17159, 2015
    Teljes dokumentum»

12. Ujma PP, Gombos F, Genzel L, Konrad BN, Simor P, Steiger A, Dresler M, Bódizs R: ***A comparison of two sleep spindle detection methods based on all night averages: individually adjusted versus fixed frequencies***, FRONTIERS IN HUMAN NEUROSCIENCE 9: Paper 52, 2015
    Teljes dokumentum»
13. A Berencsi, F Gombos, S László, R Bódizs, I Kovács: ***Sigma frequency dependent motor learning in Williams syndrome.***, International Conference on Sleep Spindling, May 12-14, 2016, Budapest, Hungary, 2016
    Teljes dokumentum»
14. Berencsi A, Gombos F, Kovács I: ***Capacity to Improve Fine Motor Skills in Williams Syndrome: Motor learning in Williams syndrome.***, JOURNAL OF INTELLECTUAL DISABILTY RESEARCH, 2016 Oct;60(10):956-68. doi: 10.1111/jir.12317. Epub 2016 Aug 3., 2016
    Teljes dokumentum»
15. Bódizs R, Ujma PP, Gombos F, Szakadát S, Sándor P, Simor P, Pótári A, Konrad BN, Genzel L, Steiger A, Dresler M, Kovács I.: ***Sex differences in the hemispheric lateralization of sleep spindles in humans.***, JOURNAL OF SLEEP RESEARCH 25:(S1) p. 293. (2016). 23rd Congress of the European Sleep Research Society. Bologna, Olaszország: 2016.09.13 -2016.09.16, 2016
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16. Pótári A, Ujma PP, Konrad BN, Genzel L, Simor P, Körmendi J, Gombos F, Steiger A, Dresler M, Bódizs R.: ***Age-related changes in sleep EEG are attenuated in highly intelligent individuals.***, Neuroimage. 2016 Sep 23. pii: S1053-8119(16)30519-5. doi: 10.1016/j.neuroimage.2016.09.039, 2016
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17. Simor P, Gombos F, Szakadát S, Sándor P, Bódizs R: ***EEG spectral power in phasic and tonic REM sleep: different patterns in young adults and children***, JOURNAL OF SLEEP RESEARCH Jan 14. doi: 10.1111/jsr.12376. [Epub ahead of print], 2016
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18. A Berencsi, R Bódizs, F Gombos, S László, I Kovács: ***Sigma frequency dependent motor learning in Williams syndrome***, SCIENTIFIC REPORTS - NATURE 7: Paper 16759. 9 p., 2017
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19. Bódizs R, Gombos F, Ujma PP, Szakadát S, Sándor P, Simor P, Pótári A, Konrad BN, Genzel L, Steiger A, Dresler M, Kovács I: ***The hemispheric lateralization of sleep spindles in humans***, SLEEP SPINDLES & CORTICAL UP STATES 1:(1) pp. 42-54., 2017
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20. F Gombos, R Bódizs, I Kovács: ***Increased overall cortical connectivity with syndrome specific local decreases suggested by atypical sleep-EEG synchronization in Williams syndrome***, SCIENTIFIC REPORTS 7:(1) p. 6157., 2017
    Teljes dokumentum»
21. Gerván P, Soltész P, Flep O, Berencsi A, Kovács I: ***Posterior-anterior brain maturation reflected in perceptual, motor and cognitive performance***, FRONTIERS IN PSYCHOLOGY,8: Paper 674. 10 p., 2017
    Teljes dokumentum»

22. Róbert Bódizs, Ferenc Gombos, Péter P. Ujma, Ilona Kovács Christian O'Reilly, Simon C. Warby, Tore Nielsen (ed.): ***Sleep spindling and fluid intelligence across adolescent development: sex matters***, Lausanne: Frontiers Media S.A., 2017. 165 p. (Frontiers in Human Neuroscience) SLEEP SPINDLES: BREAKING THE METHODOLOGICAL WALL, 2017