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Individual Characteristics of the Sleep Electroencephalogram as Markers of Intelligence– Effects in a Broad Age and Intelligence Range

Doctoral thesis

Péter Przemyslaw Ujma

Semmelweis University
Doctoral School of Mental Health Sciences

Advisor: Róbert Bódizs, PhD, chief research fellow

Official Reviewers: Gábor Csukly, MD, Ph.D., lecturer
Kristóf Kovács, Ph.D., chief research fellow

President of the Qualification Committee: István Bitter, MD, DSc, professor
Members of the Qualification Committee:Pál Czobor, MD, Ph.D., associate professor
Dezső Németh, Ph.D., associate professor

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Table of Contents

DOI:10.14753/SE.2016.1895

DOI:10.14753/SE.2016.1895

List of abbreviations

APM – Advanced Progressive Matrices

BA – Brodmann area

CPM – Coloured Progressive Matrices

DTI – diffusion tensor imaging

EEG – electroencephalography

FDR – false discovery rate

FFT – Fast Fourier Transform

fMRI – functional magnetic resonance imaging

IAM – individual adjustment method

IQ – intelligence quotient

MRI – magnetic resonance imaging

NREM – non-rapid eye movement

PET – positron emission tomography

PTSD – post-traumatic stress disorder

REM – rapid eye movement

RPMT – Raven Progressive Matrices Test

SD – standard deviation

SWS – slow wave sleep

WASO – wake after sleep onset

1. Introduction

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A typical human being spends approximately one third of his life sleeping, which is hardly matched by any other activity typical for our lives. Despite its prominence, sleep has been an elusive subject to study, and its functional importance has not been known until the second half of the last century. Once a subject of religious speculations, a source of mystery and prophetic dreams, sleep has been revealed to be a very particular neurobiological state in which the central nervous system enters a drastically altered state of functioning compared to wakefulness. While not all questions regarding the functions and mechanisms of sleep have been completely elucidated, by now it is certain the changes in the functioning of the central nervous system sleep brings about are crucial for optimal functioning in wakefulness.

Individual characteristics of sleep variables have also been revealed to correlate with intelligence. Single-factor intelligence has been repeatedly confirmed as a valid and reliable psychometric tool for over a century, and its importance is increased even further in new theories of its interpretation which stress that based on intelligence reliable predictions can be made not only of cognitive functioning or social status, but also about health and longevity. Therefore, the study of the relationship between sleep and intelligence links two fields – one from a neurobiological and one from a psychometric domain – which are of exceptional importance for human life.

The introduction section of this thesis briefly presents the most important morphologic and functional aspects of sleep – particularly NREM sleep – and the mechanisms by which it can contribute to cognitive functioning. Sleep spindles – NREM oscillations often implicated in the relationship between cognition and sleep – will be described in detail. The introduction also reviews some of the most important theoretical and empirical results related to intelligence, demonstrating that intelligence, on the one hand, can be conceptualized as a single-factor construct and on the other hands its importance extends beyond the cognitive domain into basic aspects of life strategies. Furthermore, the introduction reviews previous studies about the relationship between sleep and cognition, and it also comments on some important methodological details which were considered in the studies presented in the Methods and Results section.

Our investigations were performed on over two hundred subjects with a wide age range (4-70 years) and a similarly wide IQ range (85-160). Our results confirm the

relationship between individual EEG characteristics in sleep and intelligence, but they also point out the sexually dimorphic nature of this relationship.

1.1. Sleep as a Biological State

1.1.1. Basic Features and Regulation of Sleep

The profound biological importance of sleep is supported not only by the fact that humans spend a significant time of their lives sleeping, but also by the fact that sleep is present in virtually all animals as well, some of which spend even more time sleeping than humans(Cirelli and Tononi, 2008), and sleep deprivation generally leads to serious impairment in cognitive abilities and other biological functions. Despite these facts, our current knowledge of the functions of sleep is far from complete (Rosen, 2006). Some features and characteristics of sleep, however, may help highlight its significance for physiological and cognitive functioning.

Sleep is characterized by changes in hormone levels and it affects the functioning of the immune system, thus contributing to ’regeneration’ in a broad sense. After sleep deprivation, immune responses are attenuated due to a lower white blood cell count (Zager et al., 2007). On the other hand, slow-wave sleep increases growth hormone level(Van Cauter et al., 2000), which enables regeneration, wound healing and physical restorative processes of the body. Reduced restorative capacity was found in sleep-deprived rats(Gümüstekin et al., 2004), albeit this effect appears to originate rather from NREM sleep deprivation and it is not present in case of selective REM deprivation (Mostaghimi et al., 2005). A higher amount and better quality of sleep is correlated with higher levels of melatonin in diurnal species, a hormone heavily involved in restorative processes (Bubenik, 2002; Odaci and Kaplan, 2009), suggesting that better sleep quality may be both a cause and an index of the increased ability of the body to heal itself.

The effects of sleep deprivation are certainly more immediate and perhaps even more dramatic in the cognitive domain. The most common and immediate effects of sleep deprivation are sleepiness, the slowing of mental processes as well as the lack of the ability to concentrate. These effects can partially reversed voluntarily, such as by being motivated by rewards (Horne and Pettitt, 1985; Monk, 1991), but they never completely

disappear. Sleep deprivation reduces performance in working memory tasks to a particularly striking degree(Turner et al., 2007), in line with increased hemodynamic responses inthe prefrontal cortex, a sign of compensatory recruitment (Drummond et al., 2000; Drummond et al., 2005). However, similarly to the more basic physiological effects of sleep deprivation, alterations in the cognitive domain also appear to rather stem from NREM than REM sleep. REM sleep causes disturbances in emotional regulation(Ellman et al., 1978; Rosales-Lagarde et al., 2012), but it appears to be less involved in sleep-related cognitive processing (Siegel, 2001) and individuals with chronic pharmacological or traumatic REM deprivation are able to live without serious cognitive impairments (Vertes and Eastman, 2000). Thus, sleep cannot be treated as a monolithic process in terms of its effects and functions.

Sleep can be broadly defined as two very distinct states: rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep (Rechtschaffen et al., 1968; Iber et al., 2007). At the same time NREM and REM sleep are two alternating phases of the ultradian oscillation serving the basis of the cyclical nature of sleep. Furthermore, subdivisions of these states can be made, reflecting the different depths or electrophysiological states. The following basic description of the most important features of normal sleep – when no other sources are noted – arepresented based on these two classification system (Rechtschaffen et al., 1968; Iber et al., 2007) and one book chapter (Billiard, 2008). Typical EEG features of different sleep stages are illustrated on Figure 1, whileFigure 2 shows a typical hypnogram of all-night sleep..

DOI:10.14753/SE.2016.1895

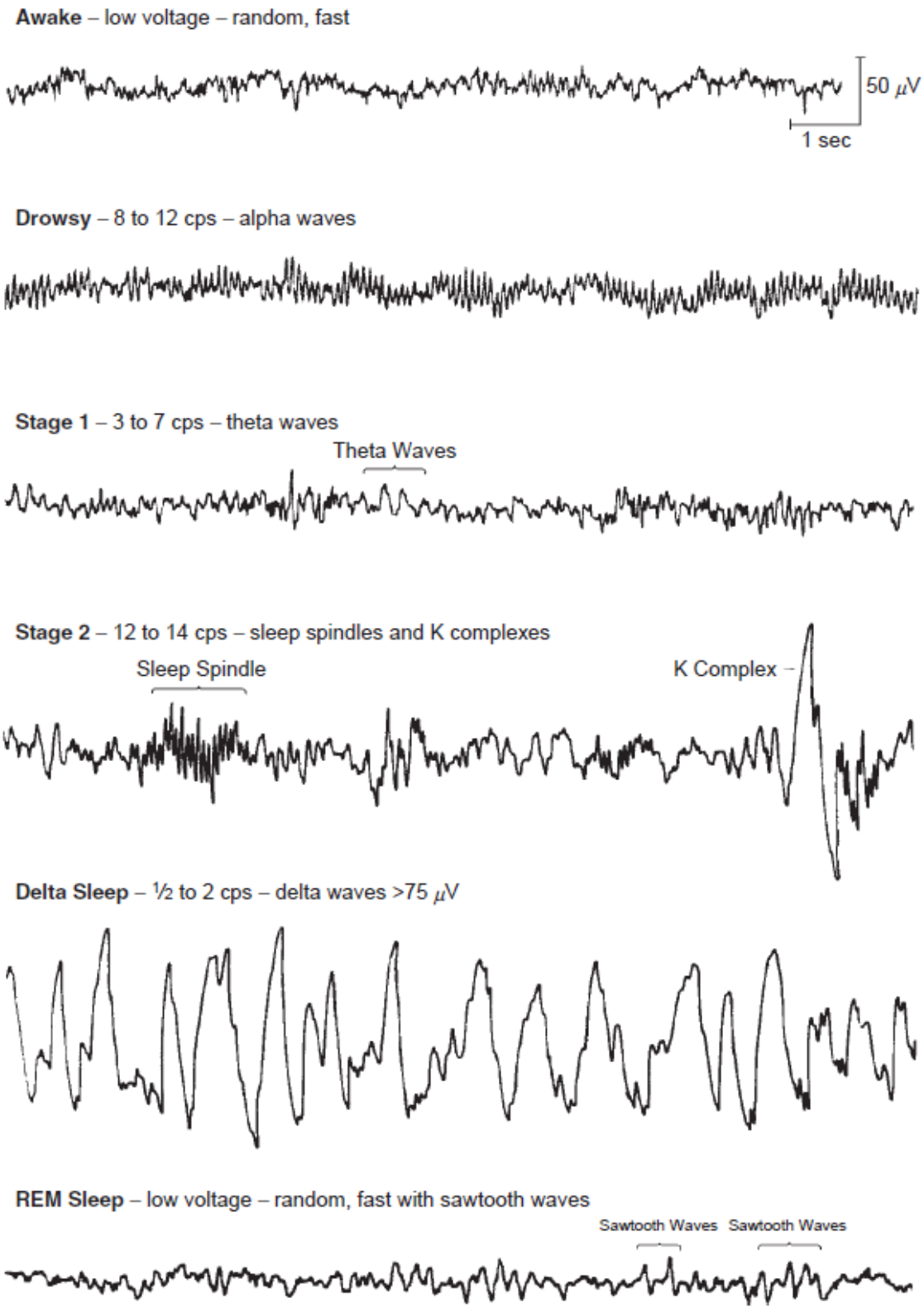

Figure 1. "EEG patterns of human sleep states and stages". Figure and caption from(Billiard, 2008)

DOI:10.14753/SE.2016.1895

The onset of sleep is characterized by the disappearance of alpha wave trains which are prominent in the resting wakeful EEG signal. There is an increase in theta power, as well as vertex waves and occipital sharp transient waves. This intermediate state is Stage 1 sleep. Stage 1 sleep rarely lasts for more than a few minutes, and instead gives way to either deeper NREM sleep or, if sleep pressure is low (typically in the last periods of night sleep) an awakening.

Stage 2 sleep is characterized by an increased power int he delta band (<4 Hz) and the appearance of its main features, K-complexes and sleep spindles. K-complexes are transient, low-frequency waves which appear spontaneously but can also be elicited by stimulation. Sleep spindles are waxing and waning sinusoidal waveforms which appear all over the scalp but mainly in central and frontal midline derivations, reflecting specific neuronal firing patterns in thalamocortical circuits, mediated by reticular thalamic interference (Steriade, 2003; Lüthi, 2013). Sleep spindles are heavily implicated in the effect sleep exerts on cognition, which is why they will be described in greater detail in later chapters of this thesis.

Stage 3 sleep – together with what is called Stage 4 sleep in an earlier classification system (Rechtschaffen et al., 1968) – is also called slow wave sleep (SWS). Consequently, this sleep stage is characterized by the proliferation of low-frequency, high-amplitude slow waves, generated by synchronous firing (and silence) in cortical assemblies (Csercsa et al., 2010).

Importantly, slow wave activity in Stage 2 sleep and SWS does not appear in a symmetrically distributed manner, but they are instead organized into cyclic alternating patterns (CAPs) (Terzano et al., 1985; Terzano et al., 2001). Sometimes, slow waves are uniformly distributed for several minutes (Non-CAP), but at other times they appear in sudden, high-amplitude burst series (CAP A1), preceded and followed by a flattened EEG signal devoid of prominent low-frequency, high-amplitude activity (CAP B). Apart from the CAP A1 subtype, consisting of a transient burst of slow waves, other types of CAP activity are known. CAP A3 is characterized by arousal, reflected by a transient increase in alpha or beta activity and/or muscle tone, while the CAP A2 subtype is characterized by mixed (slow and fast) transient activity. While a detailed description of cyclic alternating patterns is beyond the scope of this thesis, they

certainly deserve mention due to many results (Aricò et al., 2010; Esposito and Carotenuto, 2010; Drago et al., 2011) linking them to individual differences in waking cognitive ability. Figure 3 shows EEG recordings from NCAP sleep as well as CAP sequences.

The stages of NREM sleep are typically organized into 90-120 minute long sleep cycles with alternating sleep depth, which continue until awakening. Typically, the deepest stage (reflected by the amount of slow wave activity) of sleep is shallower in each successive sleep cycle.

Rapid eye movement sleep (REM) typically occurs between sleep stages, with increased prominence towards the end of the night. Regarding its appearance and physiological characteristics, REM sleep is radically different from NREM sleep. While reduced muscle tone is typical in all sleep stages, physiological REM sleep is characterized by complete atonia in the skeletal muscles, except for the facial muscles responsible for eye movements. However, REM stage is characterized by increased activity in every other regard, reflected by increased EEG activity in the beta and gamma band (with the complete disappearance of slow waves and sleep spindles), eye movements and prominent – albeit very chaotic – mental activity, which is evident from the fact that dreams are more frequently reported after awakenings from REM sleep. Importantly, however, dreams also occur in NREM sleep.

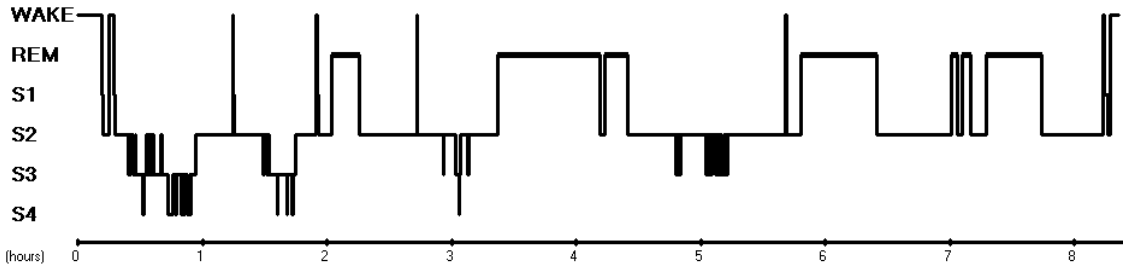

Figure 2. Night sleep hypnogram of a healthy young male subject. Note the decreased depth and increased REM prominence in later parts of the night.

The existence and alternation of NREM and REM phases has been explained in numerous ways. One theory (Rial et al., 1993; Rial et al., 2010) proposes that sleep in mammals evolved from reptilian waking states, while mammalian waking is a phylogenically new phenomenon related to the development of a greater and more

specialized telencephalon. Based on similarities in EEG patterns and reactivity, these authors proposed that human NREM sleep is analogous to reptilian basking behavior, while REM sleep is analogous to the post-basking behavior of reptiles which is characterized by an observation of the environment and the initiation of new goals. Another – not necessarily contradicting – theory suggests that sleep phases are tools of energy conservation (Schmidt, 2014). Since thermoregulation is suspended in sleep – especially REM sleep – longer sleep periods are adaptive since they contribute to energy efficiency. This, however, comes at the price of less time available to achieve goals and also a longer time of exposure to predation and other potential dangers. In line with this theory, longer REM phases are observed in larger animals (which have greater thermal inertia) and extremely long periods of continuous waking are observed in niche exploiting animals, such as artic birds with very short mating periods.

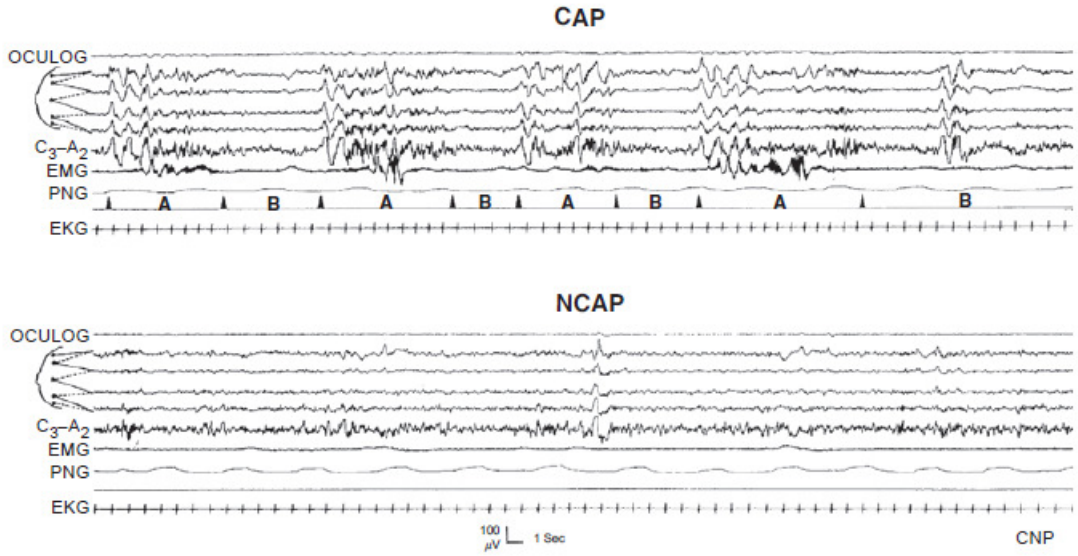

Figure 3. "CAP time and non-CAP time in stage 2 NREM sleep. CAP time: alternance of arousal-related phasic events (A) and of the background EEG activities (B). EMG, electromyogram; PNG, pneumogram; EKG, electrocardiogram; CNP, Clinica Neurologica Parma". Figure and caption from (Terzano and Parrino, 1992) and (Billiard, 2008)

Sleep is frequently investigated using polysomnography for both clinical and research purposes. Polysomnography is the use of multiple electrophysiological exploration methods to accurately determine physiological activity (including and beyond neural activity) during sleep.

DOI:10.14753/SE.2016.1895

A very important part of polysomnography recordings is electroencephalography (EEG). EEG recordings are usually performed on multiple channels, typically referenced to contralateral mastoids in order to ensure an even distribution of signal voltage.

Eye movements in sleep are investigated using electrooculography (EOG). EOG recordings are sensitive to eye movements by recordings the changes in the potential fields of the moving eyes. The most prominent use of EOG is in sleep stage scoring, since large eye movements are typical features of REM sleep.

Electromyography (EMG) is a measurement of muscle activity by electrophysiological measures. The applications of EMG include sleep stage scoring as well as the exclusion of muscle movement artifacts from EEG channel data using automatic noise rejection algorithms.

Electrocardiography (ECG) detects the electrical signals generated by the beating heart. In polysomnography settings, ECG recordings are performed with less electrodes than in clinical practice, and their role is typically limited to the investigation of basic features – such as heart rate and its variability in relation to sleep events – and the removal of cardiac artifacts from EEG channels.

Most of the research cited or described in this thesis was done according to the sleep staging and recording methodology described in this subsection.

1.1.2. Potential Functions of Sleep, Slow Waves and Spindles

Slow waves – Synaptic homeostasis

Slow waves are perhaps the most prominent and mostly sleep-related oscillations, which led to their early recognition as important electrophysiological features of sleep. Early theories, however, identified delta waves as basically pathological, reflecting ‘death, decay and disease’(Walter, 1936), mostly due to the occurrence of slow waves in brain areas which were damaged due to physical lesions or strokes. While the visually salient nature of slow waves is by no means misleading in the sense that they continue

to be among the most widely researched features of NREM sleep, these early claims about their pathological nature have proven to be unfounded.

Theories about the function of slow waves can be generally traced back to the general characteristics of these waves in relation to environmental and psychological variables. Slow wave activity follows an inverted U-shaped maturational curve, peaking in early childhood, dropping significantly during maturation, especially in adolescence (Jenni and Carskadon, 2004; Feinberg and Campbell, 2010; Feinberg and Campbell, 2013), but continuing to diminish throughout adulthood (Landolt et al., 1996; Carrier et al., 2001). In elderly adults, more retained slow wave activity is a marker of better neurocognitive functioning (Anderson and Horne, 2003; Mander et al., 2013) and it was recently directly linked to reduced mortality (Mazzotti et al., 2014).

Another maturational feature of slow waves is that changes in slow wave activity follow a very distinct postero-anterior pattern (Feinberg et al., 2011), much like cortical maturation itself (Tamnes et al., 2010), obviously hinting at a possible direct relationship between the two. The fact that maturational changes in the slow wave activity of young subjects are a direct function of cortical maturation has been demonstrated (Ringli and Huber, 2011; Feinberg and Campbell, 2013), suggesting that slow wave activity decreases in a region-specific manner when the cortical regions in question undergo maturation. Cortical maturation in children and adolescents generally means cortical thinning and an overall decrease in synaptic density (Tamnes et al., 2010; Herting et al., 2015), reflecting the formation of ‘mature’, that is, functionally efficient networks and a loss of plasticity since it is no longer required. Of course, this coupling between cortical maturation (that is, synaptic density) and slow wave activity suggests that slow waves are the hallmarks of synaptic plasticity in sleep, which is why they diminish in the absence of highly plastic cortical networks.

A further point that was considered in early theories of slow wave function is that slow wave activity (spectral power) is increased after sleep deprivation, in line with a general deepening of NREM sleep, generally at the expense of stages 1 and 2, REM sleep and wakefulness(Borbely et al., 1981). This suggests that slow waves are not stand-alone elements of the sleep EEG, but they are related to waking neural activity.

One of the first theories to systematically address these features of slow waves and suggest an explanatory model was the two-process theory by Alexander Borbély (Borbély, 1982). Borbély proposed that slow wave activity is ultimately a function of time spent awake: if wakefulness is longer, sleep pressure increases, and slow wave activity in sleep is a direct function of sleep pressure. During sleep, sleep pressure decreases, followed by the characteristic decrease in slow wave density, until it is so low that an awakening occurs. The (non-linear) relationship between time spent awake and sleep pressure (practically equivalent to slow wave pressure) was hypothesized to be regulated by a time-dependent Process S, while a sinusoidal Process C (corresponding to the circadian regulation) was proposed to regulate sleep and waking thresholds. Some EEG activity – most prominently sleep spindling – was also demonstrated to be regulated by both circadian and homeostatic processes rather than sleep pressure (Dijk and Czeisler, 1995), and some new evidence suggests that slow (slow) wave activity also depends on circadian phase too (Lazar et al., 2015).In sum, according to Borbély's theory Process S mainly regulates sleep (slow wave) pressure as a function of time spent awake, while Process C regulates whether a given amount of sleep pressure implies sleep or wakefulness in the organism as a function of the phase of the circadian clock.

Borbély's theory was solidly proven by the fact that he was able to create equations which accurately predicted sleep pressure (measured by slow wave activity) as a function of time spent awake(Achermann et al., 1993; Borbely and Achermann, 1999). This suggested that – as proposed by the theory – sleep pressure is indeed the result of time spent in wakefulness.

However, Borbély's theory treated sleep and sleep pressure as an essentially global phenomenon, which was challenged by later studies. Slow wave activity was subsequently found to be regulated by waking activity in a region-specific manner: increased use (Kattler et al., 1994) or immobilization (Huber et al., 2006) of an arm during wakefulness elicited increased and decrease slow wave activity, respectively, but only over the contralateral motor cortices, suggesting that slow wave regulation occurs within local networks instead of the entire cortical structure of the brain. This is in line with the theories which envisage sleep as a local process (Krueger and Obál, 1993;

Krueger and Tononi, 2011), generated in small functional networks of the brain as a result of the long term potentiation (LTP) caused in the network by events in wakefulness. In these models, an asymmetric wakefulness-related change of slow wave activity is possible in different brain regions as a function of their prior use.

All the above findings are summarized in the synaptic homeostasis hypothesis (SHY) of Giulio Tononi and Chiara Cirelli (Tononi and Cirelli, 2003, 2014), which is arguably the best account of slow wave function currently available, as well as possibly the most significant description of NREM sleep function in general. The SHY proposes that the main function of NREM sleep is to compensate for plastic changes occurring in wakefulness, and this takes place through the generation of slow waves – that is, "sleep is the price the brain pays for plasticity" (Tononi and Cirelli, 2014). Ultimately, SHY proposes that the downregulation of synaptic strength is impossible in wakefulness, but slow waves perform this function in sleep in a manner that does not eliminate synaptic changes which reflect the learning of meaningful information.

SHY is supported by ample evidence. The density of GluA1-containing AMPA receptors (Vyazovskiy et al., 2008), synaptic strength (Liu et al., 2010), the number of synapses and synaptic spines (Bushey et al., 2011; Maret et al., 2011) and the slope and amplitude of electrophysiological evoked responses (Huber et al., 2013) increase during wakefulness and decrease during sleep, suggesting corresponding changes in synaptic strength.The time course of these variables is strikingly similar to that of slow wave activity, which is also strongest after prolonged wakefulness, but decreases during sleep. In fact, the slope of evoked responses in wakefulness was found to correlate positively with slow wave activity in later sleep(Vyazovskiy et al., 2008).

The intrinsic synaptic downscaling properties of NREM sleep are thought to be mediated among others by the upregulation of calcineurin and the inhibition of the protein kinase CamKII (Cirelli et al., 2004; Tononi and Cirelli, 2014). However, these downscaling effects are not symmetrical: very strong new synapses may be protected, for example by the inhibition of CamKIIN function by high calcium levels or the exclusion of downregulation-evoking genes from highly potentiated synapses (Tononi and Cirelli, 2014). Thus, the strong new synapses potentially encoding meaningful new information from a previous period of wakefulness can be protected even in an

environment which heavily favors synaptic downscaling and elimination, increasing the signal-noise ratio of neuronal activity through the elimination of randomly formed new synapses. Protein synthesis is also increased during NREM sleep(Ramm and Smith, 1990), enabling the transformation of the strongest synaptic connections into a more permanent structure (Frey et al., 1988; Reymann and Frey, 2007; Poe et al., 2010). These sleep-related plastic changes, mainly induced by slow waves, increase the energetic efficiency of synapses and save extracellular space (Xie et al., 2013; Tononi and Cirelli, 2014). On a behavioral level, it promotes the forgetting of irrelevant information but enhances gist extraction, may bring forward new insights and consolidate memories through the elimination of synaptic noise(Tononi and Cirelli, 2014).

To summarize the previous sub-section, the maturational, daily and overnight course of slow wave activity, together with structural, molecular and electrophysiological evidence suggests the main function of slow waves is to compensate for the increases in synaptic strength in functional units of the cortex caused by their use during wakefulness. As a result of slow wave activity, synaptic strength decreases to normal levels, but due to the selective protection of certain new synaptic connections most relevant new information from the previous episode of wakefulness is successfully retained.

As provided before, there is very strong empirical evidence for these statements, but the picture about NREM sleep function – let alone the function of sleep in general – is not yet complete. In fact, the concept of improving the information encoded in neural networks by *decreasing* synaptic strength – as proposed by the SHY – is somewhat counter-intuitive. While synaptic downscaling is certainly a very important part of NREM sleep, and it is also generally absent from wakefulness (Vyazovskiy et al., 2008; Liu et al., 2010), the opposite – increased synaptic strength in sleep – may be possible, complementing the downscaling properties of slow waves.

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Ripples, hippocampal replay and long-termpotentiation

The previously discussed hypothesis of synaptic homeostasis relies on evidence about the fact that sleep – especially NREM sleep – is characterized mainly by decreasing synaptic strength, and it contributes to sleep-related enhancements of cognitive abilities by using this downscaling to eliminate noise and make synaptic assemblies more efficient. However, other theories about the functions of sleep also exist, which take into account the possibility of synaptic potentiation during sleep.

NREM sleep is generally characterized by an absence of acetylcholine, which makes LTP impossible(Leonard et al., 1987; Bramham and Srebro, 1989) as well as a lack of the expression of LTP-related genes(Poe et al., 2010; Ribeiro, 2012). There is, however, some evidence that LTP might still be possible if specific conditions are met during sleep.

NREM sleep is characterized by co-occurring sleep spindles and hippocampal sharp-wave ripples, which are thought to play a role – among others - in sleep-related memory consolidation(Inostroza and Born, 2013; Genzel et al., 2014). Sharp-wave ripples initiate a cellular influx of calcium which may provide excellent conditions for LTP(Sejnowski and Destexhe, 2000; Steriade and Timofeev, 2003), while sleep spindles can demonstrably induce LTP if the right conditions are met(Rosanova and Ulrich, 2005). While the idea that ripples and spindles generally induce LTP is not decisively supported (see(Tononi and Cirelli, 2014) for review), it provides the framework for an alternative theory to SHY, which also takes into account the properties of REM sleep. It is notable that sleep spindles – while they occur in NREM sleep – are preceded by a drop in noradrenergic activity from the locus coeruleus(Aston-Jones and Bloom, 1981) which may provide unique neurochemical conditions different from the rest of NREM sleep and more similar to REM sleep(Poe et al., 2010).

The theory of systems consolidation during sleep (Inostroza and Born, 2013; Rasch and Born, 2013) assumes that NREM and REM sleep work in tandem in order to consolidate memories acquired during wakefulness. In NREM sleep, a – generally accelerated – replay of waking activity takes place. Such a replay of waking activity has actually been found in NREM sleep in the hippocampus(O'Neill et al., 2010) as well as

neocortical structures (see(Inostroza and Born, 2013) for review). This replay happens in order to move episodic memories (that is, memory traces with a strong binding to specific circumstances and personal experience) from their initial, fast-learning hippocampal store to a more permanent but less episodic and more declarative (that is, less experience-related and more encyclopedic) neocortical memory store. This serves both to 'reset' the limited hippocampal memory storage capacity in order to enable the acquisition of more information and also to allow for the creation of memories which have less to do with individual experiences and provide more information about the general characteristics of the environment. The hippocampal-neocortical replay during NREM sleep 'tags' synapses for transformation during a subsequent REM sleep episode(Rasch and Born, 2013).

The contribution of REM sleep to sleep functions is admittedly less clear that in case of NREM sleep(Tononi and Cirelli, 2014). However, the neurochemical environment in REM sleep, with the presence of acetylcholine but the absence of noradrenaline is drastically different, and LTP is readily induced in the hippocampus during REM sleep(Bramham and Srebro, 1989; Poe et al., 2010). While hippocampal reactivations – that is, the replay of prior waking activity – are generally observed in NREM sleep, they were also observed in REM sleep(Poe et al., 2000; Booth and Poe, 2006). Hippocampal REM sleep reactivations in these studies were structured by the hippocampal theta rhythm, and their effects were synaptic strength depended on the phase of the theta oscillation on which they occurred. Reactivations at theta peaks led to synaptic potentiation while reactivations at theta troughs led to synaptic depotentiation, allowing a bidirectional change in synaptic strength. In rats, the preferred direction of the change of synaptic strength varied as a function of familiarity with the environment: after initial exploration, LTP was more prevalent, but synaptic depotentiation prevailed after the environment became familiar, suggesting that an episodic-declarative transformation of memory traces indeed took place(Poe et al., 2000).

It is notable, however, that hippocampal reactivations in REM sleep were not universally found(Kudrimoti et al., 1999). Furthermore, REM sleep – in contrast to NREM sleep – does not appear to contribute to the sleep-related consolidation of hippocampal memory systems, being instead rather involved in amygdala-related

functions(Genzel et al., 2015). It is therefore not clear whether REM sleep indeed plays a role in hippocampal-neocortical memory transformations as a time of general synaptic strengthening of selected synapses.

An elegant and interesting alternative theory of NREM and REM function was recently put forward (Vyazovskiy and Delogu, 2014), drawing inspiration from both SHY and the systems consolidation hypothesis. This hypothesis considered NREM sleep to be a time of synaptic downscaling which is necessary because of the effects of the previous wakefulness, and which takes place during cortical slow waves. However, in line with the local and region-specific nature of these slow waves (Nir et al., 2011), slow wave activity is thought to reflect local synaptic homeostasis processes. Sleep spindles – which generally appear after slow waves have dissipates – indicate a 'tagging' of networks which have previously undergone synaptic homeostasis by slow waves. In subsequent REM sleep, the functionality of these 'tagged' networks is tested in a safe environment where skeletal muscles are paralyzed (preventing accidents due to sub-optimally functioning cortical networks) and the 'simulation' of cortical activity may be what is experienced in dreams. As an increasing time is spent in sleep, the number of cortical networks still in need for synaptic homeostatic regulation decreases, which is reflected in turn by the decreasing number and increasingly regional occurrence of slow waves and the increasing prevalence of sleep spindles and REM sleep. Finally, when the process is completed and no more synaptic homeostatic regulation is necessary, awakening occurs.

Vyazovskiy and Delogu's account is far from resolving every issue surrounding the functions of NREM and REM sleep, but it provides a framework which is a novel and logical addition to previous theories.

In sum, the functions and mechanisms of sleep cannot be limited to a single process, especially where REM sleep is also considered. Competing theories generally agree about the importance of synaptic changes that occur during sleep, but they disagree about the importance – or even the presence – of synaptic potentiation and depotentiation. Currently, empirical evidence seems to point in the direction that synaptic depotentiation occurs in sleep in a unique manner, in response to the synaptic potentiation that took place during the previous episode of wakefulness, and that this

depotentiation, occurring during slow waves, is perhaps the most important mechanism involved in NREM sleep function. The importance of synaptic potentiation by sleep spindles or spindle-ripple complexes is less completely delineated. The functions (and the mechanisms thereof) of REM sleep appear to be even more elusive.

It is probable that the most prominent electrophysiological characteristics of NREM sleep – slow waves, sleep spindles and hippocampal ripples – play similar or complementary functional roles. Of these three, only two – slow waves and sleep spindles – are observable on the scalp EEG. The importance of slow waves for synaptic homeostasis has been previously elaborated in this subsection. However, sleep spindles have been shown to be especially closely associated with cognitive functioning and they have been thoroughly investigated in the studies later presented in this thesis.

Sleep spindles

Sleep spindles are prominent features of NREM sleep, particularly of more shallow stages (Iber et al., 2007). Sleep spindles arise as a result of reduced cholinergic activation which is typical in NREM sleep, and they are generated a network which encompasses thalamocortical, corticothalamic and (thalamic) reticular neurons (Steriade and Deschenes, 1984; Amzica and Steriade, 2000; Steriade, 2000; Fogel and Smith, 2011).

At the descriptive level, sleep spindles are mainly observed throughout the scalp but mainly in midline derivations (frontal, central and parietal) with greater prevalence in the second half of the night where sleep is more shallow (Fogel and Smith, 2011). While spindles are characterized by a clear topographical prevalence in the aforementioned midline derivations – in line with distribution of the main outputs of their thalamic generators – they are essentially local phenomena (Nir et al., 2011) and much like slow wavesthey were shown to respond to learning involving well-delimited brain areas with locally increased activity at the corresponding sites (Tamaki et al., 2009; Johnson et al., 2012).

The circadian regulation of sleep spindles is, however, quite different from that of slow waves. Unlike slow waves which are regulated in a principally homeostatic manner, sleep spindles generally follow both a circadian and an inverted S process,

appearingmost prominently during a clear-cut period of the day, with maximum prevalence achieved during the second half of the night (Dijk and Czeisler, 1995; Dijk et al., 1995). Sleep spindles are profoundly affected by melatonin levels (which also peak during the night), which affects mainly their peak frequency and density (Dijk et al., 1995; Knoblauch et al., 2003), while amplitude and duration are less affected (Knoblauch et al., 2003; Knoblauch et al., 2005).

At the microstructural level, sleep spindles are synchronized to the up-states of cortical slow oscillations (Steriade, 2003; Staresina et al., 2015). This synchronization may contribute to the efficacy of spindle function, as a correlation between intelligence and the coupling strength of sleep spindles to slow oscillations was found (Bodizs et al., 2005).

The main features of sleep spindle generation are well understood and were reviewed recently by (Lüthi, 2013). The thalamic reticular nucleus (TRN), a diffuse structure enveloping most thalamic nuclei is a key element of sleep spindle generation (Fuentealba and Steriade, 2005). The TRN receives inputs from cortical neurons, but it only projects to other thalamic structures (with GABAergic inhibitory synapses) and does not have cortical projections. TRN neurons are active and functionally important both during wakefulness and sleep, but in sleep – due to the absence of ascending monoaminergic (and possibly cholinergic (Steriade, 2003)) inputs – their firing properties change drastically, since in the absence of such inputs their resting membrane potential decreases, leading to the activation of a certain type of voltage-gate Ca^{2+} channels (T-channels) (McCormick and Bal, 1997; Saper et al., 2010; Lüthi, 2013). T-channels are expressed along the dendrites of TRN cells, where corticothalamic projections terminate. In NREM sleep, these projections are able to provide very strong bursting activity from TRN cells through the T-channels (Fuentealba and Steriade, 2005). In case of cortico-TRN input, TRN-thalamic inhibitory synapses generate burst inhibitory postsynaptic potentials in thalamocortical cells (McCormick and Bal, 1997; Lüthi, 2013). This in turn leads to a similarly burst-like re-excitation of TRN cells via thalamocortical-reticular connections, inducing a ‘back-and-forth excitation cycle… like two ping-pong players’ (Lüthi, 2013) in thalamocortical and TRN neuron populations. Thalamocortical cells induce similar rhythms in cortical cell populations as well, which

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is what scalp EEG recordings are ultimately able to detect as sleep spindles. The self-sustaining neural firing patterns which underlie sleep spindles ultimately terminate due to several limiting mechanisms, including lateral inhibition between TRN cells, inhibitory inputs from lower brainstem areas, the activation of hyperpolarization-activated cation-nonselective channels and the desynchronization of cortical activity (Lüthi, 2013). Sleep spindle oscillations are possibly generated by the same or similar mechanisms as cortical oscillations, and their occurrences are related (Steriade, 2003) and may reflect the strength of cortical connections (Werk et al., 2005). Figure 4. illustrates the role of thalamocortical networks in spindle generation, as well as the generation of other rhythms in sleep and wakefulness.

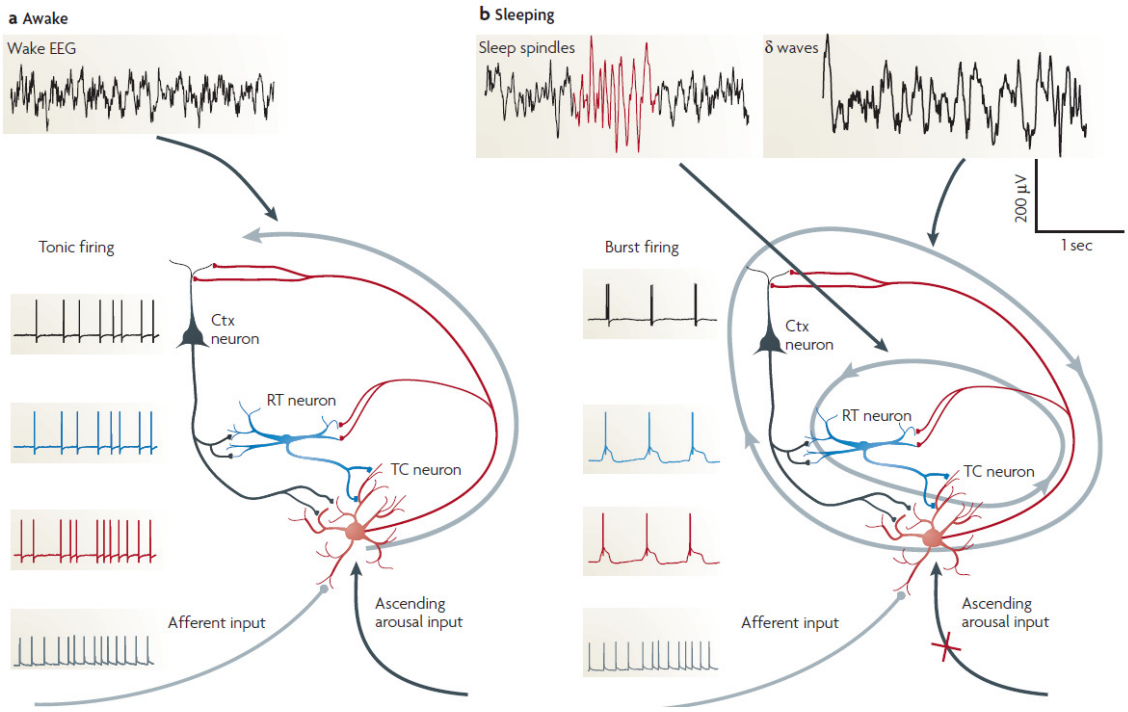

*Figure 4. "**a** |During wakefulness, ascending excitatory input from arousal nuclei to thalamocortical (TC) neurons (red) provides a depolarizing drive that causes thalamocortical neurons and reticular (RT) neurons (blue) to exhibit single-spike tonic firing and allows a more-or-less faithful transfer of information from the periphery up to cortical (Ctx) neurons (black). During wakefulness there is also a descending depolarizing drive onto TC neurons from Ctx neurons. **b** | During deep non-rapid-eye-movement (NREM) sleep, the thalamic relay neurons switch into a burst-firing mode which they adopt by default in the absence of external input. The intrinsic ionic conductances of TC neurons favour a rhythmic burst-firing pattern, which is generated following a hyperpolarizing drive. Because of the extensive connectivity that*

exists among and between thalamic and Ctx neurons, large populations of neurons are induced to fire in synchrony; this is the origin of the slow delta (δ) waves that are the electroencephalographic signature of deep sleep. During this burst-firing mode, ascending information through the thalamus is blocked. The transition from waking to sleeping also involves thalamic oscillations. In the electroencephalogram (EEG) these are called sleep spindles (highlighted in red on the left-hand EEG trace); they are generated when a burst of spikes from a TC neuron impinges on a GABA (γ-aminobutyric acid)-ergic RT neuron which then sends a robust inhibitory postsynaptic potential back to the same TC neuron. This hyperpolarizes the cell, which then fires another barrage of spikes on rebound, establishing an oscillation. The length of theinhibitory potential (which is mediated by GABA type A receptors) determines the time until another burst of spikes is generated by the TC neuron103,106 and sets the frequency at ~7–14 Hz. Although the TC–RT loop is necessary for spindle oscillations, isolated RT neurons can also oscillate with a natural frequency in the same frequency range, and this property might aid spindle generation." Figure and caption from (Franks, 2008).

Probably due to their effect on thalamocortical communication, sleep spindles play a key role in the reduced behavioral responsiveness which is generally observed is sleeping animals and humans (Lüthi, 2013). It requires more intensive stimulation to wake up a person during sleep spindles (Yamadori, 1971), and both event-related potentials and fMRI BOLD responses to stimuli are reduced during sleep spindles (Schabus et al., 2012). The activation of GABAergic interneurons including, but not limited to reticular thalamic areas (which are also implicated in spindle generation) underlies the gating of sensory information in the thalamus in general (Bokor et al., 2005; Groh et al., 2014; Rovo et al., 2014). Therefore, the very particular thalamocortical communication pattern during spindle oscillation reflects a mechanism which also regulates the flow of sensory information towards cortical areas in other physiological states.

Still, the most prominent candidate mechanism through which sleep spindles might contribute to cognitive function is not the protection of sleep, but their ability to induce long-term plastic changes in cortical and thalamocortical circuits. The rhythmic activity of TRN cells observed during sleep spindles induces long-term potentiation (LTP) in thalamocortical synapses (Astori and Luthi, 2013). Perhaps even more importantly, the

rhythmic cellular firing patterns observed during spindles constitute optimal conditions for long term synaptic changes in the cortex in general (Buzsaki, 1989; Fogel and Smith, 2011), and such synaptic changes – including LTP – were successfully induced experimentally (Rosanova and Ulrich, 2005). Another – but not unrelated – function of sleep spindles is that they are able to coordinate hippocampal ripple activity, which also contributes to long-term plastic changes in the cortex (Siapas and Wilson, 1998; Inostroza and Born, 2013; Genzel et al., 2014; Staresina et al., 2015). In line with the systems consolidation hypothesis, sleep spindles are thought to be involved in the deafferentation of the cortex from the hippocampus, providing a mechanism to consolidate memory traces (Peyrache et al., 2009; Wierzynski et al., 2009; Genzel et al., 2014).

In line with these physiological characteristics and involvement in LTP generation (and plastic processes in general), sleep spindles were especially frequently implicated in cognitive functioning,that is, memory consolidation and trait intelligence.Evidence about the relationship between sleep spindling and cognition is presented in subsection 1.3.

1.1.3. Methodological Problems – Measuring Spectra and Sleep Spindles

Most contemporary research intended to investigate sleep oscillations, such as spectral components or sleep spindles, uses mathematical algorithms to quantify these oscillations. The precise methodology chosen by such a study is not a trivial question, as the detection or analysis of most sleep oscillations does not have a ‘gold standard’ method which is accepted by all or almost all studies. Visual detection of sleep spindles is sometimes considered as a gold standard (Warby et al., 2014), however, this method is subjective and time consuming. This problem is particularly pervasive in the study of sleep spindles and EEG spectral components, and in our studies much attention was paid to choosing the right methodology.

Sleep spindles are very frequently detected using automatic algorithms. Early automatic detection methods implemented phase-locked loop devices, and they were reported to have sufficient agreement with visual detection to warrant their use in research (Broughton et al., 1978; Campbell et al., 1980). Another early implementation

of an automatic spindle detector was built as a combined software-hardware system(Ferri et al., 1989), which was also able to reliably reproduce visual detections.

Pure software solutions of sleep spindle detections were developed only somewhat later (Schimicek et al., 1994) with a specificity of 70% at a specificity point of 90%, with even better results in an altered implementation (Devuyst et al., 2006). Further modern automatic sleep spindle detections use neural networks (Acır and Güzeliş, 2004; Ventouras et al., 2005) and decision trees (Duman et al., 2009).

There are at least two very important pitfalls in automatic sleep spindle detection which must be avoided by automatic detectors. First, sleep spindles can be either slow and fast spindles, reflecting different generating structures and networks. Slow spindles have a lower frequency and a frontal maximum and they are generally restricted to frontal areas, whereas fast spindles have a higher frequency and a centro-parietal maximum, albeit they are also present in the frontal cortex (Andrillon et al., 2011). Also, slow and fast spindles have different hemodynamic correlates (Schabus et al., 2007), further reinforcing the concept of two superficially similar, but at their core quite different oscillations.Second, a very important feature of sleep spindle oscillations is that they are characterized by prominent intra-individual stability and inter-individual variability (De Gennaro et al., 2005), with individual parameters heavily affected by age and sex (Driver et al., 1996; Carrier et al., 2001; Huupponen et al., 2002; Genzel et al., 2012). As a result, sleep spindle detector parameters should be expected to take into account that sleep spindles may have different characteristics in different individuals.

The Individual Adjustment Method (IAM, (Bódizs et al., 2009; Ujma et al., 2014)) , developed in our laboratory based on the electrophysiological fingerprint theory of human sleep (De Gennaro et al., 2005; De Gennaro et al., 2008) is an automatic sleep spindle detector specifically designed to account for such individual differences in spindle parameters and take into account the separation of slow and fast spindles. The IAM relies on the shape of the individual NREM sleep EEG spectrum (from frontal and centro-parietal electrodes for slow and fast spindles, respectively) to extract individual sleep spindle frequencies which are used for filtering the EEG data for sleep spindle detection. A slow or fast spindle is detectedif the envelope of the filtered signal exceeds an amplitude threshold, which is determined using the average value of the amplitude

spectrum at the edges of the previously determined sleep spindle peaks. This way, both the threshold frequency and the amplitude of sleep spindles is determined in an individually adaptive manner.

Another very common approach in automatic sleep spindle detection is the SIESTA method or its modifications (Anderer et al., 2005). These methods use a generic frequency band (usually 11-16 Hz) to filter EEG data for sleep spindle detection, as well as a generic threshold amplitude (usually 11 μV). Sleep spindles are detected when the amplitude of the filtered signal exceeds this amplitude threshold. Slow and fast spindles are sometimes separated using the peak frequency of the detected signal as a classification parameter: slow spindles have a peak frequency below 13 Hz whereas fast spindles have a frequency over 13 Hz.

A third very common – and perhaps most intuitive – approach of sleep spindle detection is a fixed-frequency, adaptive-amplitude method (FixF)(Schabus et al., 2007; Ujma et al., 2015a). In this implementation, the EEG signal is filtered to a slow (11-13 Hz) and a fast (13-15 Hz) frequency band, and a sleep spindle is detected when the root mean square of the amplitude of this filtered signal exceeds the 95% percentile. While this method has the merit of separating slow and fast spindles and using an adaptive amplitude criterion – that is, taking into account individual differences in baseline spindle amplitude – the determination of these frequency bands and the 95% percentile as the amplitude cutoff point is not based on empirical data. In fact, a comparison of individual sleep spindle features computed either from IAM or FixF (Ujma et al., 2015a) revealed that while fast spindle parameters can be reliably estimated using the 13-15 Hz frequency window, the 11-13 Hz slow spindle frequency window did not correspond well to empirically determined slow spindle frequencies, with many subjects having even lower peak frequencies and almost all having a much narrower slow spindle frequency window. Consequently, IAM and FixF slow spindle parameters were very different, pointing out the importance of choosing the right detection method.

The approach of using individual frequency bands, adaptive amplitude criteria and an explicit separation of slow and fast spindles is surprisingly rare in the scientific literature, and different studies investigating the relationship between sleep spindling and cognition use quite diverse sleep spindle detection methods. Many studies did not

separate slow and fast spindles, instead analyzing sleep spindle events or spectral power from a broader sigma frequency band (Clemens et al., 2005; Fogel and Smith, 2006; Fogel et al., 2007; Tucker and Fishbein, 2009; Lustenberger et al., 2012; Gruber et al., 2013). Studies which did separate slow and fast spindles generally used a post-hoc classification of spindles based on their central frequency, usually with 13 Hz as the split point (Schabus et al., 2006; Schabus et al., 2008; Chatburn et al., 2013). Occasionally another separation of slow (11.5-12.5) and fast (13.5-14.5) sigma power bands was also used (Bang et al., 2014). Only a few studies used individually determined sleep spindle frequencies, either by using the IAM method (Bodizs et al., 2005; Bódizs et al., 2008) or by computing individual relative sigma power defined as power ± 2Hz around a single maximal spectral peak relative to the otherwise exponentially declining (as a function of frequency) background EEG spectral power(Gottselig et al., 2002; Geiger et al., 2011). Our results (Ujma et al., 2015a) show that while fast spindles are fairly robust to the implemented specific detection method, with different methods yielding quite similar results, slow spindles are much more sensitive to the correct selection of frequency bands. Empirically determined slow spindle bands are lower than 11 Hz in many subjects, while in others they extend beyond the 13 Hz window, potentially confounding slow and fast spindle detections. It is notable that in studies with fixed detection frequencies (Schabus et al., 2006; Schabus et al., 2008) both slow and fast spindles were correlated with cognitive abilities, while in studies with individually determined frequencies (Bodizs et al., 2005; Ujma et al., 2014) only fast spindles were correlated.

Thus, sleep spindle detection may be affected by an incorrect choice of frequency (and potentially amplitude) thresholds and the lack of separation between slow and fast spindles is a significant potential methodological problem. In order to avoid such errors, we used the IAM method in all the studies reported in this thesis.

Another mathematical tool frequently used in the study of sleep oscillations is spectral analysis. Spectral analysis transforms signals from the time domain to the frequency domain: that is, it determines how much is present in a signal of a sinusoid signal of a given frequency(Keil et al., 2014). The ratio of sinusoidal and cosinusoidal components determines the phase of the oscillation, but this distinction is irrelevant for spectral

power, which is determined as the sum of the squared sinusoidal and cosinusoidal components. The importance of spectral components in EEG analysis is that oscillations of a given frequency are thought to reflect the functioning of well-determined brain networks (Nir et al., 2011; Piantoni et al., 2013; Saletin et al., 2013). The shape of the sleep EEG spectrum is stable within individuals but variable between individuals(Finelli et al., 2001; De Gennaro et al., 2005), showing genetic determination (Buckelmuller et al., 2006; Ambrosius et al., 2008; De Gennaro et al., 2008; Landolt, 2011) and a direct relationship with the physical anatomy of the brain (Piantoni et al., 2013; Saletin et al., 2013), which is why sleep EEG spectral components have long been considered candidate markers of cognitive functioning as well as mental status.

While the computation of EEG spectral components is arguably more straightforward than sleep spindle detection, selecting the correct measure of EEG spectral power is still an important methodological feature of any study. The raw spectral power of EEG signals – whether in wakefulness or sleep – follows a pink noise-like power law distribution, with the vast majority of power present in the lowest frequencies (Ferree and Hwa, 2003). Baseline power law trends are sometimes removed from the EEG spectrum by a procedure called detrending.Given the squared amplitudes in the formula of the FFT (serving the basis of power spectral estimation), the logarithmization of the raw spectrum is frequently performed to provide a more linear distribution and enable the use of standard parametric statistics which do not work well with power law distributions. It is notable that the voltage of the EEG signal is first and foremost affected by features not related to neural processes, such as the thickness of the skull and connective tissues (Chauveau et al., 2004), introducing a large amount of noise into the inter-individual differences in the spectral power of the EEG signal. This issue can be avoided by computing the relative spectrum, usually by dividing the spectral power of every frequency bin by the sum of power in all frequency bins, effectively removing the differences in the baseline amplitude of the spectrum and thus correcting for the effect of the default individual EEG voltage. An even more specialized method of assessing the shape (and not the amplitude) of the individual EEG spectrum is to compute z-transformed spectra. The z-transformation of spectral power does not only remove the effects of baseline voltage, but it is particularly sensitive to individual differences in the shape of the spectrum. This method – due to its sensitivity – works

best if it is applied to a relatively narrow frequency range, such as the broadly defined sigma (spindle) frequency range, where it has been frequently used to investigate the sleep EEG fingerprint (De Gennaro et al., 2005; Bódizs et al., 2012).

When a sample of subjects is relatively homogeneous – especially in terms of age, sex and physical build – results with absolute (logarithmized) and relative spectra are expected to be similar. If this is not the case, however, then the use of relative spectra may be necessary in order to correct for baseline individual differences in EEG voltage. In the studies elaborated in this thesis, while absolute logarithmized power was also computed, it was done so in addition to z-transformed spectral power. Just like in case of sleep spindle detection, this combination of methods was chosen in order to use a reliable and unbiased method and avoid common sources of potential error.

1.2. Intelligence

A frequently used – albeit somewhat cynical – definition of intelligence is that it is "what intelligence tests measure"(Thorndike, 1921). The reason for this seemingly tautological definition is that intelligence – or more precisely, IQ – is a statistical abstraction, a factor. That is, its existence is confirmed by the consistent multicollinearity of several well-observable variables – such as school grades, socioeconomic status or the level of education – which are characterized by a large degree of common variance, also referred to as the g-factor (Spearman, 1927; Carroll, 1997).

While a variable like IQ, arising as a stable amount of common variance in easily observable and psychosocially relevant variables, is less intuitively understandable than many other concepts used in psychology, it is arguably stronger as a construct. Psychological concepts which are derived from a human language – that is, practically invented as statistical constructs – are frequently easy to grasp, but it is unclear if they are honest to their true meaning. A very strong case is made about 'emotional intelligence', where the tests which it is measured by may rather be measuring 'conformity'(Roberts et al., 2001). That is, just because a psychological concept exists

in our language, it is absolutely not certain that it can be translated into a measurable mathematical reality, or that its measurable properties in relation with other psychological concepts will follow what we intuitively consider reasonable. Intelligence as a psychological construct was formed the other way around: the common variance ('positive manifold') of many cognitive and socioeconomic variables was discovered (Spearman, 1927), and this common variance was matched with a linguistic concept ('intelligence') to help grasp its meaning.

That is, to refer to the positive manifold, the g-factor or IQ (which concepts have no meaning outside the research of intelligence, and therefore accurately reflect the nature of this concept as a mathematical abstraction) as 'intelligence' is just an attempt to express an intuitivemeaning of this factor. As with all statistical factors, its naming is subjective and it may be improved by a more careful consideration of the factor structure. That is, the true nature of IQ is best discovered by examining the easily observable and socially, psychologically and culturally important variables it correlates with.

1.2.1. Traditional Views of Intelligence

The concept of a unified and objectively measurable intelligence was first put forward by Galton(Atkinson et al., 2014) who proposed in the late 19th century that a correlation between cognitive ability and reaction time may exist (albeit this was not proven). Spearman's studies in the early 20th century(Spearman, 1904; Williams et al., 2003) revealed a correlation between socioeconomic status, cognitive ability and biological variables. Spearman also demonstrated that while different persons may excel in different subdomains of cognitive ability and lag behind in others, their abilities are not uncorrelated: there is a strong presence of a 'general ability' which manifests itself in very different areas of cognition.

Spearman's studies of school-age children also revealed a strong correlation between school grades, subjective peer ratings of intelligence as well as sensory discrimination (Spearman, 1904, 1927), further supporting the view of a 'general ability' behind many apparently different domains of cognition. Spearman's idea of intelligence was that for every cognitive task a general ability (g-factor) as well as a task-specific skill (s-factor)

is used in tandem: that is, while a significant degree of individual differences is explainable by differences in general ability, there is of course room for individual excellence in or preference for a specific task as well as skill training. The measurement of school-age children was very important in early studies of intelligence: in fact, the first tests for measuring intelligence were developed to measure mental age(Binet and Simon, 1908), that is, the proportion of biological age and the age at which the level of competence demonstrated by the child are usually typical. Spearman's idea of a general cognitive ability and Stanford and Binet's ideas about measuring it are the precursors of modern intelligence measurement. While later theories of intelligence do not necessarily agree with all or any aspects of these frameworks, they frequently involve some concept which resembles or can be demonstrated to resemble the g-factor, and tests with very high g-factor-loadings such as Raven's Progressive Matrices(Neisser et al., 1996; Gray and Thompson, 2004b) continue to be used to explore the biological underpinnings of cognitive ability.

Most later theories of intelligence differed from Spearman's in that they assumed multiple intelligences instead of the single g-factor proposed by Spearman. One of the earliest of the alternative theories is Cattel's idea of fluid and crystallized intelligence (Cattell, 1963; Cattell, 1987). In Cattel's theory, fluid intelligence corresponds to the ability to rapidly recognize patterns, process novel information and adjust behavior accordingly. On the other hand, crystallized intelligence is the explicit knowledge of information, regardless of its ease of access or relationship to novel situations. These two abilities (often abbreviated as Gf and Gc, respectively) are subdivisions of the g-factor. Cattel's theory of a dual intelligence is very valuable as it can account for the changes in human cognitive abilities across the lifespan: in older individuals, fluid intelligence decreases but crystallized intelligence increases(Horn and Cattell, 1967; Lee et al., 2005). Stuart-Hamilton (Stuart-Hamilton, 2012) argues that this shift between different domains of intelligence is crucial in understanding the changes in human cognition which are typically encountered during ageing. On the other hand, Cattel's theory is not bulletproof regarding its statistical postulates and construct validity. Intelligence tests with a high g-loading, such as Raven's Progressive Matrices or the Woodcock-Johnson Tests of Cognitive Abilities typically correlate strongly with fluid, but not crystallized intelligence(Kline, 2014), which is more sensitive to tests of explicit

knowledge or text comprehension. Furthermore, fluid intelligence is often drastically impaired after brain injury, while crystallized intelligence is retained(Suchy et al., 2007). This is very similar to the dissociation of working memory and long-term memory, which are similarly impaired and retained, respectively, after traumatic injury to the brain. The notion that fluid intelligence and working memory are very similar constructs is supported by the fact that tasks which train working memory (such as the n-back task) boost performance in tests of fluid(Jaeggi et al., 2008; Feiyue et al., 2009)but not crystallized(Yuan et al., 2006) intelligence. Overall, Cattel's theory of fluid and crystallized intelligence is not impossible to reconcile with Spearman's g-factor. In the light of research, it seems that fluid intelligence, the g-factor and working memory are very similar constructs (Geary, 2005), probably reflecting the functioning of the same frontal, prefrontal and cingular areas. On the other hand, crystallized intelligence and long-term memory seem to be part of a different functional unit with a more diffuse neocortical neural substrate. In real life situations the explicit knowledge of situations cannot always be compensated for with great cognitive flexibility, and the concept of intelligence as understood by most non-scholars arguably entails a significant level of explicit knowledge, which is why Cattel's idea of a crystallized intelligence is an important addition to Spearman's original g-factor. However, it seems that the g-factor is not composed of Gc and Gf, but nearly synonymous with just the latter. Crystallized intelligence can be rather considered a system of consolidated knowledge and skills.

Robert Sternberg(Sternberg, 1985, 2000) took a more drastic approach to developing a theory of multiple intelligences by proposing his framework of a triarchic intelligence. Sternberg differentiates analytical thinking (metacomponents) from the ability to carry out strategies (performance components) and the ability to acquire new information (knowledge-acquisition components) which together constitute intelligence. Sternberg's view admittedly steered away from a psychometric view of intelligence in the process of separating performance in abstract intelligence tests from real-life success of adaptation, which is the ultimate test of intelligence. However, there is little empirical evidence for the existence of the triarchic intelligence proposed by Sternberg(Gottfredson, 2002), while there is plenty of evidence supporting the

predictive power of traditional IQ tests with a high g-loading for educational success, income, or other measures of adaptation (these are demonstrated later in detail).

Perhaps the most frequently quoted theory of multiple intelligences is the framework proposed by Howard Gardner(Gardner, 2011). Gardner's theory proposes seven different 'intelligences' (with more added later), which involve linguistic, logical-mathematical, musical, spatial, bodily-kinetistic, intrapersonal and interpersonal intelligences. The foundation of Gardner's theory is the idea that the spectrum of human abilities is too wide to be squeezed into a single measurement of intelligence, especially one (as in Sternberg's original g-factor) which relies very heavily on performance in abstract pseudo-mathematical operations while remaining uninfluenced by individual excellence in domains like language or music. Gardner's theory, however, did not receive support from empirical research. First, Gardner's selection of abilities which are classified as an intelligence is subjective and arbitrary(Waterhouse, 2006). Second, Gardner's claim of multiple intelligences, as opposed to a single g-factor is unsubstantiated as most of the proposed intelligences correlate strongly with the g-factor (Visser et al., 2006b, a). Therefore, while it may seem attractive to have a theory which appreciates the diversity of human cognitive abilities, research results are overwhelmingly weighed against multiple intelligences (Geake, 2008).

Most of the socioeconomic neurobiological correlates of intelligence were measured using single-factor test of intelligence, typically either Raven's Progressive Matrices or the Wechsler's Adult Intelligence Scale (although this latter provides a verbal and a performance IQ score, both of which were sometimes used and which can be considered different aspects of IQ, even if not as multiple intelligences). IQ is devised as a concept mainly measuring cognitive performance and, from a broader perspective, educational success and also socio-economic status as its result. Results show that IQ is generally correlated to all these variables.

Neisser's seminal work (Neisser et al., 1996) provided invaluable results about the correlates of IQ and socio-economic variables. This study found a correlation of about 0.5 between IQ scores and school grades, and a correlation of a similar magnitude between IQ and social status. Income itself was generally found to be positively

correlated with IQ, with correlation coefficients in the range of 0.4-0.5 (Seligman, 1992; Jensen, 1998; Murray, 1998), heavily mediated by other variables.

Work productivity was also found to be positively correlated to IQ, though the strength of this link depended on the type of work in question(Hunter and Hunter, 1984), varying between 0.2 and 0.6.

Criminality, as an indicator of low socio-economic status and failure to comply with the standards of society, was found to be negatively correlated with IQ (Neisser et al., 1996). Bartels et al. (Bartels et al., 2010) reported negative correlations between the average IQ scores measured in different US states and these states' respective crime rates. This is, however, not the only indication of a connection between IQ and a the socio-economic status of an entire society instead of an individual: in their book, Lynn and Vanhanen (Lynn and Vanhanen, 2012) report the correlation between the per capita GDP levels of the countries of the world and their average measured IQ scores to be 0.62.

Some of the most sensitive correlates of IQ in this field are school tests such as the Scholastic Aptitude Test (SAT) and the General Certificate of Secondary Education (GCSE). Frey and Detterman(Frey and Detterman, 2004) found the correlation between IQ and SAT to be 0.82. Deary et al. (Deary et al., 2007) reported a correlation of 0.81 between IQ and GCSE.

It is debatable how much the neural correlates of g differ from other, more precisely defined but conceptually similar psychometric concepts, such as working memory or fluid reasoning. Very similar frontal (Duncan et al., 2000; Gray and Thompson, 2004b) and frontal and parietal (Jung and Haier, 2007) areas have been implicated in g and working memory, while other studies (Conway et al., 2003) warn against blurring the boundaries between (fluid) intelligence and working memory or executive functioning. Since it is not the purpose of this thesis to present this debate in detail, only the neural correlates of intelligence test scores will be considered, with a note that the neural processes implicated in many of these studies may in fact be similar or synonymous in more precisely defined higher-order cognitive processes.

It is long known that intelligence correlates not only with head size (Gignac et al., 2003), but with brain volume as well (Andreasen et al., 1993; Witelson et al., 2006; Luders et al., 2009). Since these correlations are relatively modest – typically in the 0.3-

0.4 range – it has long been considered an attractive line of research to identify specific brain areas which are particularly important for intelligence, reflected by a correlation with their structural or functional characteristics. Haier and Jung (Jung and Haier, 2007) put forward the theory of parieto-frontal integration theory (P-FIT) of intelligence, suggesting that high scores on standard intelligence tests are attainable using mainly higher-order sensory integration areas in the parietal cortex, executive functions in the frontal cortex, and the anterior cingulate for decision-making. In their review of several dozen studies which sparked a very long list of commentaries (Jung and Haier, 2007) they found that among the many studies investigating cerebral structural and functional correlates of intelligence, the most frequently implicated brain areas were BA 7 and BA 40 in the parietal lobe, BA 6, BA 46 and BA 9 in the frontal lobe as well as BA 19 in the occipital lobe (particularly if fMRI studies were considered). All of their results are shown on Figure 5.

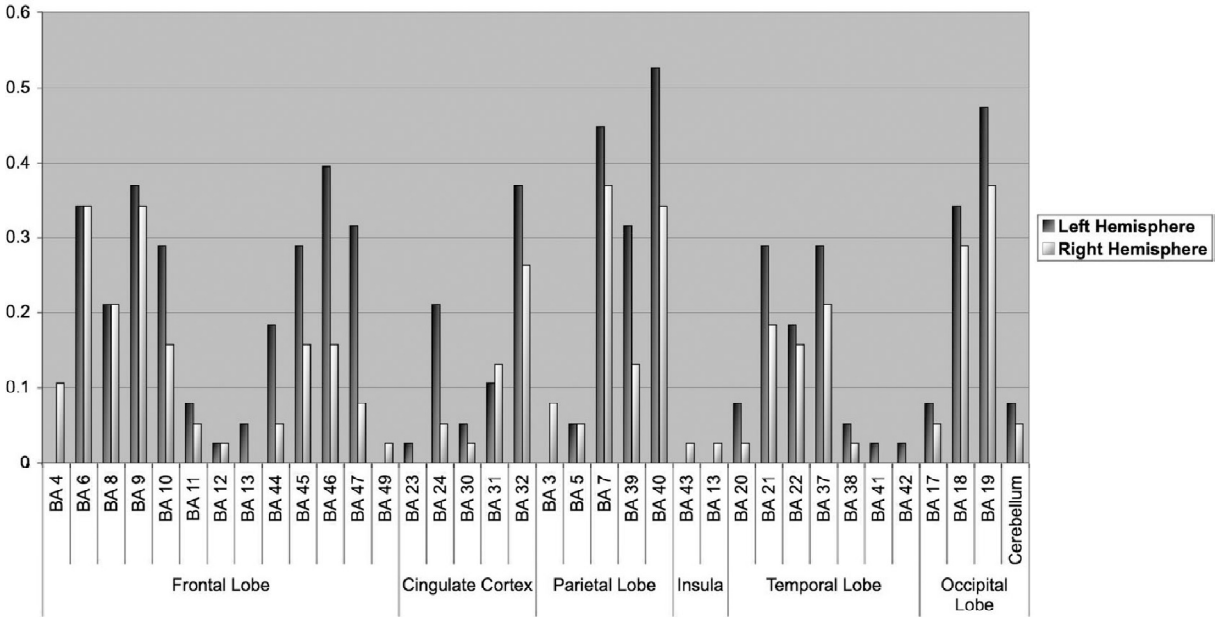

Figure 5. „Graphical representation of the proportion (Y-axis) of all reviewed structural, PET, and fMRI studies describing relationships between intelligence and/or reasoning and discrete Brodmann areas by lobe (X-axis). These studies represent 1,557 subjects. Brodmann areas (BAs) in which greater than 25% of studies found significant relationships between intelligence/reasoning and neuroimaging measures were included as comprising the P-FIT. Furthermore, within a given BA that met this threshold, if hemispheric asymmetry

ratio exceeded 10:7, then predominantly left hemisphere asymmetry was assumed. In BAs where the hemispheric asymmetry ratio wasless than 10:7, bilateral symmetry was assumed." Figure and caption from (Jung and Haier, 2007).

This was interpreted as supporting evidence for P-FIT, albeit these areas were found to be implicated in intelligence in a relatively small proportion of studies (the strongest proportions being around 50-70%), with several other areas also implicated in many studies, which suggests that P-FIT may not be a complete account of the neural underpinnings of intelligence (Colom, 2007). Another review (Luders et al., 2009) confirmed that intelligence correlates with a relatively wide array of brain areas and cerebral metrics, including various measures of gray and white matter structure. While the strongest correlates of the common variance of many tests of intelligence and higher-order cognitive processes were found in the frontal lobe in one study (Colom et al., 2013), the converging evidence suggests that intelligence is supported by a wide range of structural and functional properties of the brain. It is true that no IQ test is a true measure of g: for example it can be said about Raven's Standard Progressive Matrices that "SPM measures g plus spatial and reasoning abilities plus SPM specificity" (Colom et al., 2010). However, the broadly distributed neural correlates of IQ do not appear to be an artifact of poor psychometric practices, since structural correlates of intelligence in fact become *more widespread* when tests with higher g-loadings are used (Colom et al., 2006).It has been explicitly studied of how different lower-level neural mechanisms – more similar to clear-cut neuropsychological constructs – contribute to intelligence (Choi et al., 2008). In this research of over a hundred subjects a clear distinction between crystallized intelligence (Gc, measured by the verbal subscale of the WAIS) and fluid intelligence (Gf, measured by Raven's Progressive Matrices) was found. Anatomical properties of the brain – mainly cortical thickness in temporal areas – correlated positively and more strongly with Gc, while functional properties (fMRI BOLD signal during a reasoning task) correlated positively and more strongly with Gf. Importantly, functional imaging correlates of Gf were found in prefrontal and parietal cortices without significant lateralization, very much in line with the P-FIT model of intelligence (Jung and Haier, 2007) and the idea that prefrontal functioning is an important core feature of both executive functions and general (fluid) intelligence (Gray and Thompson, 2004b).

A large – albeit perhaps somewhat less extensive – body of research was conducted to reveal the functional correlates of intelligence. Early pioneering PET studies(Haier et al., 1988; Haier et al., 1992a) revealed that task-related increases in cerebral glucose uptake is reduced in highly intelligent subjects, suggesting that the brains of these individuals is able to perform the same tasks more efficiently. However, glucose uptake measured by PET decreased dramatically after learning (Haier et al., 1992b), suggesting that task difficulty and familiarity may confound lower task-related increases in glucose uptake in highly intelligent individuals.

Many waking EEG studies used event-related desynchronization (ERD) primarily in the alpha band as a measure of task-related activation of the brain. A high level of ERD suggests a strong engagement of neural circuits which is reflected by more profound changes in the EEG signal. (Grabner et al., 2006) found an independent effect of task familiarity and intelligence on the level of ERD, suggesting that while neural efficiency may be observed in more intelligent individuals, it is also affected by task familiarity. An interaction between sex and task content has also been found (Neubauer et al., 2005): females expressed neural efficiency in verbal tasks while males expressed neural efficiency in spatial tasks. A recent review of the neural efficiency theory (Neubauer and Fink, 2009)acknowledges that while this theory may be true in relatively easy and familiar tasks, task type, task difficulty and sex may have a strong confounding effect.

Many other waking EEG studies were performed partially or fully diverging from the neural efficiency theory. Generally, resting EEG power and frequency were modestly or not correlated with cognitive ability (Marosi et al., 1999; Jausovec and Jausovec, 2000; Thatcher et al., 2005). More evidence was found for current density measured by LORETA (Jausovec and Jausovec, 2001; Thatcher et al., 2007), coherence (Jausovec and Jausovec, 2000; Thatcher et al., 2005) and especially phase locking and phase delay (Thatcher et al., 2005; Thatcher et al., 2008). The study which to date analyzed the most waking EEG parameters(Thatcher et al., 2005) found that the relative effect sizes for IQ-EEG correlations were the following: “EEG phase > EEG coherence > EEG amplitude asymmetry > absolute power > relative power and power ratios”.

Given the limited convergence of the results obtained from imaging or waking electroencephalographic studies of intelligence, it is arguable that the correlation between sleep spindling in NREM sleep is one of the most frequently reproduced neural

correlates of intelligence. Studies demonstrating this relationship are reviewed under subsection 1.3 of this thesis.

It is notable that both structural and functional correlates of intelligence were frequently reported to be sexually dimorphic. Despite this fact, not all studies investigated potential sex differences in the biological correlates of IQ, perhaps adding to the apparent lack of consensus which is evident from these studies. As for structural studies, two MR volumetric studies (Gur et al., 1999; Haier et al., 2005) reported stronger correlations between intelligence and white matter volume in women. A study using magnetic resonance spectroscopy (MRS) (Jung et al., 2005) revealed that N-acetylaspartate levels (which is a metabolite that is indicative of neural density) in white matter correlated with intelligence only in women. fMRI connectivity (indicated by BOLD time course) was found to be correlated with intelligence in older, but not younger girls, while in boys a correlation was found in younger children but not in older ones (Schmithorst and Holland, 2006), suggesting not only sex differences in the neural underpinnings of IQ, but also an increased importance of connectivity in girls towards adulthood. In a recent study it was confirmed that gray matter parameters were more strongly correlated with cognitive ability in men (Escorial et al., 2015). In fact (Jung and Haier, 2007) reported that “it does appear that, across several studiesand groups, the relationship of intelligence to white mattervolumes, chemical composition, and perhaps water diffusivity may be higher in women than in men”. Interestingly, a single recent DTI study (Dunst et al., 2014) found an opposite pattern and a correlation between callosal white matter fractional anisotropy and radial diffusivity in men but not in women. The correlation in men was positive with FA and negative with RD.

Functional correlates of intelligence were also frequently reported to be sexually dimorphic. Glucose metabolic rate was found to correlate with mathematical ability only in men (Haier and Benbow, 1995). Highly intelligent males showed greater event-related alpha decoupling in the waking EEG, while highly intelligent females showed the opposite pattern and greater decoupling (Jausovec and Jausovec, 2005). Results about the apparently divergent neural efficiency in men and women as a function of task content (Neubauer et al., 2002; Neubauer et al., 2005) have already been mentioned. It is notable that this pattern is not caused or affected by a possible stereotype threat (Dunst et al., 2013), suggesting the existence of truly biological reasons. To our

knowledge, however, no previous study investigated the potential sex differences in the correlates of intelligence in sleep.

Overall, structural parameters of many brain areas (including gray and white matter) as well as a large number of functional imaging results (PET or fMRI) and waking EEG parameters were reported as candidate markers or correlates of intelligence. Some of these were replicated more often than others, but the true neural framework of intelligence is far from being understood. In fact, it must be considered that intelligence is mainly a psychometric and sociological and not a neurological construct: it is not meant to reflect the functioning of a single organ or cerebral subregion, but rather a possibly very complex and redundant array of neural networks and abilities, which are however very important for the social and cognitive adaptation of an individual.

One could argue that IQ is an artifact (Schlinger, 2012) and use the lack of a clear-cut and sublime neural framework behind as an evidence. However, while IQ tests are not designed to measure a single ability or the functioning of a singular cerebral network (unlike neuropsychological tests, which are sometimes superficially similar) they are able to provide predictions about a very large and diverse are of life outcomes far beyond the realm of cognition or neuropsychology. The following subsection (1.2.2) reviews some of the non-cognitive correlates of intelligence in order to show that intelligence truly is "a unifying construct for the social sciences" (Lynn and Vanhanen, 2012): a concept with an unquestionable importance for human beings, the neural underpinnings of which are certainly worth researching even if a consensus on such underpinnings is hard to find.

1.2.2. Non-Cognitive Correlates of IQ

While a large body of socioeconomic and biological evidence confirms the existence and practical importance of the g-factor and highlights the importance of some neural mechanisms behind it, it does not completely clarify the *meaning* of g. Given that g typically correlates with cognitive performance, school performance and educational attainment as well as social status, it is compelling to refer to it as 'intelligence'. However, performance on IQ tests with high g-loadings correlates with variables vastly outside the cognitive domain.

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Health and longevity are generally positively associated with IQ (Deary, 2008). A follow-up study (Hauser and Palloni, 2011) found significantly positive correlations between adolescent IQ recorded from 1957 onward and survival to at least 69 years old. (Marmot and Kivimäki, 2009) reported similar results using a large Swedish sample. Similar results were obtained in a Scottish study (Whalley and Deary, 2001)as well. A frequently coined (Gottfredson and Deary, 2004; Hauser and Palloni, 2011) explanation for this association is that people with higher IQs are more conscious of their health behavior, and they are less likely to have harmful habits or dangerous jobs. While socioeconomic variables undeniably mediate the health outcomes related to IQ, IQ was found (Gottfredson and Deary, 2004; Batty et al., 2006) to have an effect on overall mortality which is independent from common risk factors.

Specifically, IQ was found to be negatively associated with the probability of developing heart conditions (Batty et al., 2008), even if controlled for socioeconomic variables. A similar negative association was found with cancers (Batty et al., 2009) in an American study, where there was an effect of both IQ which was independent from common risk factors, such as smoking. However, a research group under the leadership of the same first author failed to find such an association in a Swedish cohort (Batty et al., 2007). Results about the inverse association between IQ and heart disease or cancer are especially important given that these diseases are among the leading causes of death in developed societies.

IQ is also often found to be negatively correlated with the prevalence of psychiatric disease.(Batty et al., 2005) found that childhood IQ was in itself negatively correlated with later psychiatric hospitalization. The effect was independent from socioeconomic variables and birth weight. More specifically, an inverse relationship between the risk of schizophrenia (David et al., 1997; Zammit et al., 2004)and major depression, as well as other nonaffective psychoses (Zammit et al., 2004) and IQ was found. In a follow-up study (Breslau et al., 2006) found that children with higher IQ were more successful in coping with traumatic life events, as expressed by a lower incidence of PTSD.

Fertility – expressed as the number of children de facto born, not as a biological potential for procreation – has been long thought to be related to intelligence (Graff, 1979). However, while the correlation between IQ, effective functioning of the brain

and educational success may not seem odd as all of these things may generally be perceived as positive, correlations between IQ and measurements of fertility have generally been demonstrated to be negative.

A large and relatively modern (post-WW2) sample of several thousand people yielded extremely high negative correlations between fertility rates and IQs of American women (Vining, 1982). In fact, these correlations were so high (0.8-0.9) that they approached test-retest and inter-test correlation rates of IQ tests themselves. These results – although with more modest correlations – have been replicated using the same cohort (Vining Jr, 1995). Similarly, (Lynn, 1999) found negative correlations between IQ and fertility, albeit with more modest correlation levels. Significant negative correlations between IQ and both the number of children and the number of siblings (Meisenberg, 2010) have been found by another study. A more recent study (Lynn and Van Court, 2004) confirmed this tendency, also with modest, but significant correlations. A large-scale review(Van Court and Bean, 1985) found consistently negative correlations between IQ and fertility in the American population between 1912 and 1982.

There are fewer such studies from countries outside the United States or other Western countries. However, a study (Vining et al., 1988) found negative correlations between IQ and the number of siblings in a Japanese sample – however, not surprisingly knowing the high correlation of IQ and educational success – this relationship did not survive controlling for the father's level of education. In the same study, however, no significant correlations were found in a Swedish cohort.

There is even less data available for developing countries. However, there were attempts to measure 'national IQ', by using non-standardized IQ score averages recorded in different countries as indicators (Lynn and Vanhanen, 2012). While such measurements certainly do not reach the psychometric excellence ordinary IQ tests do, it is certainly notable that using such an approach(Lynn and Harvey, 2008)a strong (-0.73) correlation between national IQ and the average fertility rates of the countries in the study has been found. Once again, the strength of this correlation approaches the test-retest and interest correlations observed in actual IQ tests. Another study (Meisenberg, 2009) used a multiple regression method and revealed that both GDP and national IQ had an independent, significantly negative effect on the average fertility

rate. The negative relationship between national IQ and fertility has been replicated(Shatz, 2008).

While correlations between IQ and fertility may vary in strength, and in case of national IQ measurements there is some room for criticism regarding the general methodology, the reported relationship between IQ and fertility is generally consistently negative (for a review see(Mackintosh and Mackintosh, 2011)).

1.2.3. The K-factor

The fact that intelligence correlates robustly with variables outside the cognitive domain has led to the development of the differential K theory of intelligence, which is basically an extension of Spearman's original concept of the g-factor including its non-cognitive correlates and stating that IQ is in fact only 'one side of the coin' of a much broader construct which is essentially a life history continuum. The differential K theory of intelligence was developed by J. Philippe Rushton and commented on by many of his colleagues and peers, often not without controversy (Suzuki and Aronson, 2005).

Rushton (Rushton, 2004) investigated 234 mammalian species and demonstrated that brain weight, longevity, gestation time, birth weight, litter size (negatively), age at first mating, duration of lactation, body weight and body length of these animals correlate robustly and have heavy loadings on a single factor. This factor was named the K-factor, as it represented the position of a species on the continuum between r and K reproduction strategies (Pianka, 1970), that is, the preference of high reproduction but low survival and specialization versus low reproduction but high survival and specialization rates. Rushton hypothesized that these variables – despite their apparently divergent content – are naturally highly correlated, because they all represent the adaptation to a certain reproductive strategy or 'life history' (Figueredo et al., 2005; Figueredo et al., 2006). Rushton also hypothesized that a similar convergence of the underlying variables of the K-factor will be found by comparing individual humans (within the same society) or a series of different human societies.

A study (Figueredo et al., 2005) found strong positive loadings on the K-factor by variables such as attachment to the biological father and adult romantic attachment and negative loadings by variables such as risk propensity and trait psychopathy. Another

study (Templer, 2008) provided direct factor analytic evidence for the existence of the K-factor by analyzing cross-national data about IQ test performance, birth rate, life expectancy, infant mortality and HIV/AIDS prevalence. A common factor – identified as the K-factor – explained 75% of the variance of these variables. Cross-national differences in IQ test performance correlate strongly with per capita GDP, even if controlled for exposure to education (Meisenberg, 2012), and a 'national K' index was proposed to measure the strongly correlated indicators of intelligence, health, wealth and fertility (Meisenberg and Woodley, 2013). The 'national K' index was most strongly correlated with intelligence (Meisenberg and Woodley, 2013).

Michael Minkov conceptualized the K-factor as a 'hypometropia'-factor, that is, the preference for immediate gratification (high hypometropia) or the preference for future goals (low hypometropia) (Minkov, 2014). Minkov found correlations between this hypometropia index and the prevalence of certain receptor gene polymorphisms – the frequency of lower CAG of the androgen receptor gene AR, the 7-repeat allele of DRD4 dopamin receptor gene and the 5-HTTLPR VNTR short allele, all related to a lack of risk aversion – in a comparison of different human populations (Minkov and Bond, 2015), suggesting that lower K (or higher hypometropia) preferences may be mediated by personality traits and may be in part genetically influenced. A recent neuroimaging study (Smith et al., 2015) for the first time provided solid empirical evidence for the existence of a concept very similar to either Rushton's K-factor or Minkov's hypometropia dimension. This study investigated the canonical correlation patterns of 280 demographic, psychometric and behavioral variables and found a strong single mode of co-variation containing these variables, with 'positive' outcomes (low hypometropia) at one of the extremes and 'negative' outcomes (high hypometropia) at the other. This co-variation correlated with various brain connectivity measures. Importantly, fluid intelligence was one of the variables with the strongest factor loadings on this single co-variation pattern, suggesting its high relevance. Figure 6 (adapted from the original article) illustrates the variables included in the co-variation.

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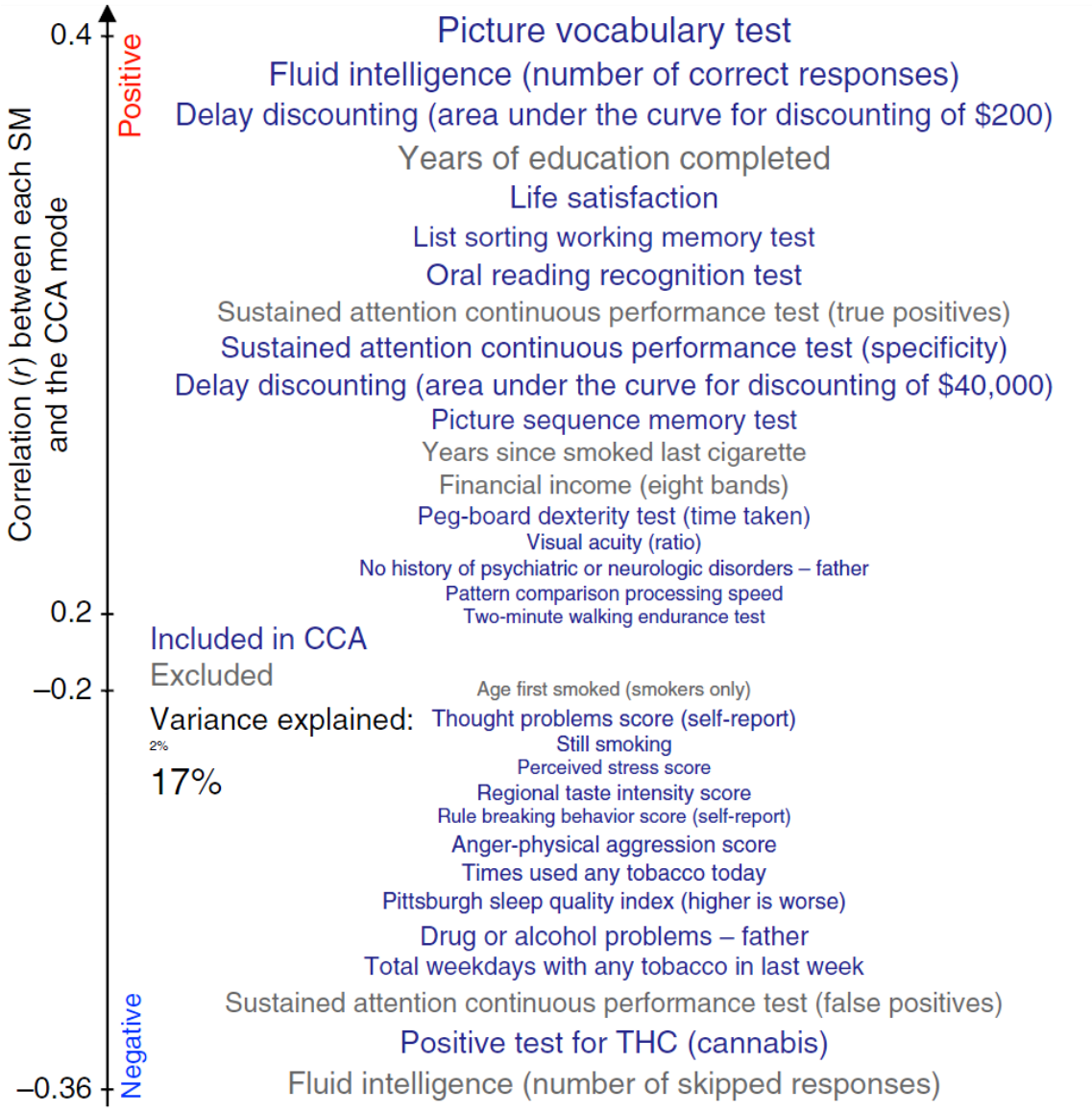

Figure 6. "The set of SMs most strongly associated with the CCA mode of population variability. SMs included in the CCA are colored blue, whereas others (gray) were correlated with the CCA mode post hoc. Vertical position is according to correlation with the CCA mode and font size indicates SM variance explained by the CCA mode." CCA stands for canonical correlation analysis. Figure and caption from (Smith et al., 2015).

The contents of the K-factor are surprisingly similar to the life history variables measured during the follow up of the Stanford Marshmallow Study, a pioneering psychological experiment not originally intended to investigate intelligence (Mischel and Ebbesen, 1970). In this experiment, 3-6 year old young children were placed in an experimental situation where they were able to choose between either eating a delicious piece of candy of their choice, or wait a few minutes where greater reward was

promised (and delivered). This experimental setup was designed to measure the children's ability to delay gratification. In follow-up studies, good delayers had better academic achievement, SAT scores and abilities to cope with stress (Shoda et al., 1990), lower Body Mass Index (Schlam et al., 2013) and lower reaction times in a Go/No-Go task (a measurement of working memory capacity) (Eigsti et al., 2006). Unsurprisingly given the latter results, prefrontal regions were found to be more active in good delayers while the ventral striatum was found to be more active in poor delayers in a forty-year follow-up study (Casey et al., 2011). Given the conceptual similarity between IQ and working memory (Unsworth and Engle, 2005; Colom et al., 2013) and the frontal correlates of both (Gray and Thompson, 2004b; Jung and Haier, 2007; Neubauer and Fink, 2009; Colom et al., 2013) it is unsurprising that the prefrontally mediated ability to delay gratification – a concept very similar to the inverse of Minkov's hypometropia dimension – was found to be unchanged during the lifespan and correlated with better outcomes in terms of health and wealth, much in line with the concept of the K-factor.

Of course when entire human subpopulations – such as cross-national averages – are investigated, it must be considered that cross-national differences cannot be considered 'trait-like' in the sense which is common in case of individuals. Many nations – notably most European nations – have arguably made a transition from an 'r' strategy of high reproduction, mortality and low wealth and specialization to a 'K' strategy of the opposite over the course of a few centuries which is very little time in an ecological sense andcertainly not sufficient to fundamentally change the heritable biological properties of these populations. This change was paralleled by an increase of IQ scores, generally referred to as the Flynn effect(Mackintosh and Mackintosh, 2011). Therefore, even if cross-national differences are found in the K-factor, possibly even with some genetic correlates, it is a reflection of the current level of development and culturally dominant life strategy in a given nation, affected by a plethora of non-biological factors (such as a recent history of warfare, colonization, political turmoil or natural disasters) and it does not by any means show that a given population has reached it maximal possible capacity of adapting either an 'r' or a 'K' strategy due to the biological characteristics of the individuals it is comprised of. The main message of the K-factor is that the change or cross-sectional variability of intelligence, health, wealth and fertility tends to be coupled, possibly because IQ tests reliably measure the trait-like capacity of

the prefrontal networks which are in a very broad and general sense implicated in all the above (as well as working memory). The fact that the effects of intelligence virtually always extend beyond the cognitive domain is evidenced by not only the results shown in the previous subsection, but also by the fact that the coupling of intelligence, health, wealth and fertility can be reliably replicated not only by comparing entire human populations but even by comparing similar variables in various animal species.

This suggests that intelligence has profound effects beyond the cognitive domain; it deserves interest in the field of epidemiology and perhaps even economics, and the frequently very abstract tests which measure IQ in a way seemingly very weakly related to real-life situations is in fact a valid predictor of a vast range of life history outcomes, not at all limited to cognition in the narrow or broad sense. This is perhaps the strongest reason why the biological underpinnings of the apparently abstract and elusive concept of IQ deserve much research. Sleep – as it will be demonstrated in the next subsection – is arguably one of the most abundant source of candidate markers of intelligence, since the physiological processes of the sleeping brain are often characterized by a trait-like nature (Linkowski et al., 1989; Finelli et al., 2001; De Gennaro et al., 2005; Buckelmuller et al., 2006; De Gennaro et al., 2008; Landolt, 2011; Smit et al., 2012) and the investigation of the sleeping brain is free of contamination by the consequences of conscious perception and thinking.

1.3. Sleep, cognition and intelligence

The following subsection summarizes some of the most important scientific knowledge about the relationship between sleep and cognition, with special emphasis on trait cognitive ability (most frequently measured by intelligence tests) and sleep spindling. Other features are described more briefly.

1.3.1. Memory consolidation

It is an old truth that ‘sleeping on’ problems can provide us with new insight the next morning, including better remembrance. Early theories suggested that sleep is important for enhancing memories because it protects them from interference. However, it has

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since been revealed that sleep plays an active role in selecting, strengthening and enhancing memories – for a review, see (Stickgold and Walker, 2005; Csábi and Németh, 2014). Importantly, NREM sleep appears to be the most significant for the consolidation of most memory content, including both implicit and explicit memory, as long as it involves the hippocampus (Csábi and Németh, 2014), while the role of REM sleep seems to be limited to hippocampus-independent learning frequently implicating the amygdala (Genzel et al., 2015).

Based on early clinical studies about pathological sleep spindles in mentally retarded children (Shibagaki et al., 1982), sleep spindles have long been specifically investigated as a candidate mechanism through which sleep has an effect on cognition in wakefulness. The number of sleep spindles was shown to be correlated with memory retention in both verbal (Clemens et al., 2005) and visuospatial (Clemens et al., 2006) domains about a decade ago. While an exhaustive review of the literature on the relationship between sleep spindling and memory consolidation is beyond the scope of this thesis, it must be noted that a correlation between sleep spindling and overnight memory consolidation has been reported in both procedural (Fogel and Smith, 2006; Fogel et al., 2007; Morin et al., 2008) and declarative (Gais and Born, 2004; Genzel et al., 2009) tasks. Treatment with GABA-ergic hypnotic agents increases sleep spindle density, producing physiologically normal spindles which also correlate with overnight memory retention, depending on the type of memory investigated (Mednick et al., 2013; Wamsley et al., 2013).

Sleep spindling was also suggested as a candidate marker of trait ability – that is, a correlate of stable inter-individual differences in memory performance or cognitive ability. This relationship is presented in detail in the following subsection. It has been, however, only rarely investigated whether trait cognitive or memory ability is a confounding factor in studies of overnight memory retention: that is, whether good overnight retainers have good memory or cognitive abilities as a stable trait, reflected by their prominent spindling. One such study (Lustenberger et al., 2012) reported an association between sleep spindle activity and processing speed and initial acquisition rate (learning efficiency before sleep), but not with sleep-related memory consolidation, suggesting that sleep spindling is a marker of trait rather than state ability. Another study (Hoedlmoser et al., 2014) reported similar results with children: sleep spindling

was associated with intelligence and learning ability, but not with overnight memory consolidation. A very recent study, however (Lustenberger et al., 2015a) reported different but significant sleep spindling correlates for trait cognitive ability and overnight memory consolidation.

Taken together, these results suggest that trait cognitive ability may explain a significant amount of the inter-individual variance of overnight memory consolidation scores, and the relationship between trait cognitive ability and sleep spindling is worth serious investigation.

1.3.2. Intelligence

Increased time in stage 2 sleep was linked to higher intelligence in school-age children more than three decades ago (Busby and Pivik, 1983). Abnormalities in sleep spindles, which are predominant features of stage 2 sleep, were linked to mental retardation even earlier (Gibbs and Gibbs, 1962; Bixler and Rhodes, 1968; Shibagaki et al., 1982), and sleep spindling remains one of the principal biological correlates of intelligence. Since sleep spindling promotes long-term plastic changes in the brain (Buzsaki, 1989; Rosanova and Ulrich, 2005; Fogel and Smith, 2011), it is associated with memory consolidation in both procedural (Fogel and Smith, 2006; Fogel et al., 2007; Morin et al., 2008)and declarative (Gais and Born, 2004; Clemens et al., 2005; Genzel et al., 2009) tasks, and much like fluid intelligence, decreases with age (Fogel et al., 2012; Lafortune et al., 2014), it seemed logical that sleep spindling is heavily involved in sleep-related information processing, and it is perhaps a cause (but at least and index) of cognitive ability.

Consequently, several studies found an association between sleep spindling and intelligence – however, these studies are remarkably heterogeneous for both their methodologies and the precise details of their results. (Bodizs et al., 2005) found a positive association between the density of fast (but not slow) spindles and scores on the Raven's Progressive Matrices Test in a sample of five female and 14 male subjects. This effect was strongest on the electrodes Fp2 and F4, while it did not survive a (rather strict) correction for multiple comparisons on other electrodes. A negative association with spindle peak frequency was also found.

(Schabus et al., 2006) found a similar positive correlation between both slow and fast spindle activity and scores on the Raven's Advanced Progressive Matrices Test as well as the Wechsler Memory Scale. This sample consisted of 12 male and 12 female subjects and only one electrode (C3) was analyzed. Fast spindle duration and both slow and fast spindle amplitudes were also found to be positively associated with intelligence.

(Fogel et al., 2007) reported the analysis of three different subject groups consisting of young adult subjects (10 females, 12 females, 29 females and 6 males, respectively) detecting spindles from C3 and C4 for the first twostudies and Cz for the last study and the Multidimensional Aptitude Battery (MAB-II) for intelligence testing. The authors reported a positive relationship between full-scale as well as performance intelligence and the total number of sleep spindles and sigma power in the first two studies. Notably, these authors did not calculate sleep spindle amplitude.

(Lustenberger et al., 2012) found a positive association between sleep spindle activity measured on C4 and intelligence measured by the Zahlenverbindungstest (a number connecting task with a fixed time limit). Fifteen young male subjects participated in this study.

In a child study (Geiger et al., 2011) using the Wechsler Intelligence Scale for Children with a sample of 6 female and 8 male children, a negative association was found between full-scale IQ and sleep spindle peak frequency, while a positive association was found between both full-scale and performance IQ and individually adjusted sigma power, which approximates sleep spindle activity. The electrodes C3 and C4 were used. Notably, verbal IQ was not associated with any measure of sleep spindling.

(Tessier et al., 2015) investigated the sleep spindle correlates of intelligence measured by the Wechsler Intelligence Scale for Children in thirteen typically developing (TD) and thirteen autistic children (all males). In the TD group, spindle duration positively correlated with verbal IQ. In the autistic group, spindle density correlated negatively with both verbal IQ and full-scale IQ.

A previously mentioned study (Hoedlmoser et al., 2014) investigated the relationship between sleep spindling, overnight memory consolidation and intelligence (measured by the Wechsler Intelligence Scale for Children) in 63 healthy children (28 females, 35

males). Sleep spindle activity was positively associated with intelligence scores as well as learning ability in a widely distributed scalp area (but not with overnight memory consolidation).

However, these positive correlations between measures of intelligence and sleep spindling are by no means present in every study of the field. (Clemens et al., 2006) failed to find a correlation between scores on the Raven's Progressive Matrices Test and the total number of spindles recorded from their 15 male subjects over 21 scalp electrodes. In a study of 12 female and 12 male subjects(Tucker and Fishbein, 2009), sigma power on C3 and C4 was not correlated with intelligence measured by the Multidimensional Aptitude Battery-II. Two studies (Peters et al., 2007; Peters et al., 2008) recorded sleep spindling on C3 and C4 and measured intelligence using the Multidimensional Aptitude Batter-II in 12 young female and 12 young male subjects and seven male and seven female subjects in both young and an elderly subgroup, respectively. Neither of these studies found any significant association between sleep spindle parameters and intelligence (Kevin Peters, personal communication).

Two child studies(Chatburn et al., 2013; Gruber et al., 2013) using the Stanford-Binet Intelligence Scale (with 13 female and 14 male children, C3 and C4) and the Wechsler Intelligence Scale for Children (14 female and 15 male children, 8 electrodes), respectively,failed to find an association between full-scale IQ and any sleep spindle parameters. While some aspects of executive functioning were found to be correlated with sleep spindling, this relationship was notably absent for intelligence.

Table 1 summarizes previous findings about the relationship between sleep spindling and intelligence.

Publication	test	age	sex	spindle parameter	electrode	correlation
Bodizs et al., 2005	RPMT: IQ	27-67 years	5 f / 14 m	density slow	Fp1, Fp2, Fpz, F3, F4, Fz, F7, F8, C3, C4, Cz, T3, T4,T5, T6, P3, P4, Pz, O1, O2, Oz	n.s.
Bodizs et al., 2005	RPMT: IQ	27-67 years	5 f / 14 m	density fast	Fp1, Fp2, Fpz, F3, F4, Fz, F7, F8, C3, C4, Cz, T3, T4,T5, T6, P3, P4, Pz, O1, O2, Oz	from r=.25, p=.33 at O2 to r=.79, p=.0001 at Fp2
Clemens et al., 2006	RPMT: IQ	25-47 years, M=35, SD=7.7	15 m	total number	Fp1, Fpz, Fp2, F7, F3, Fz,F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, Oz, O2	n.s.
Schabus et al., 2006	APM: IQ	20-30 years, M=24 SD=2.6	24 f / 24 m	activity slow	C3	r=.40, p<.01
Schabus et al., 2006	APM: IQ	20-30 years, M=24 SD=2.6	24 f / 24 m	activity fast	C3	r=.44, p<.01
Schabus et al., 2006	APM: IQ	20-30 years, M=24 SD=2.6	24 f / 24 m	density slow	C3	r=.06, p=.68
Schabus et al., 2006	APM: IQ	20-30 years, M=24 SD=2.6	24 f / 24 m	density fast	C3	r=–.01, p=.97
Schabus et al., 2006	APM: IQ	20-30 years, M=24 SD=2.6	24 f / 24 m	duration slow	C3	r=.09, p=.54
Schabus et al., 2006	APM: IQ	20-30 years, M=24 SD=2.6	24 f / 24 m	duration fast	C3	r=.34, p=.02
Schabus et al., 2006	APM: IQ	20-30 years, M=24 SD=2.6	24 f / 24 m	amplitude slow	C3	r=.39, p=.01
Schabus et al., 2006	APM: IQ	20-30 years, M=24 SD=2.6	24 f / 24 m	amplitude fast	C3	r=.35, p=.02
Fogel et al., 2007	MAB-II: VIQ	18-29 years	10 f	total number	C3, C4	r=.56, p=.09
Fogel et al., 2007	MAB-II: PIQ	18-29 years	10 f	total number	C3, C4	r=71, p=.02
Fogel et al., 2007	MAB-II: FSIQ	18-29 years	10 f	total number	C3, C4	r=.76, p=.01
Fogel et al., 2007	MAB-II: VIQ	20-25 years	12 f	total number	C3, C4	r=.38, p=.10
Fogel et al., 2007	MAB-II: PIQ	20-25 years	12 f	total number	C3, C4	r=.79, p=.001
Fogel et al., 2007	MAB-II: VIQ	20-25 years	12 f	total number	Cz	r=.01, p=.94
Fogel et al., 2007	MAB-II: PIQ	20-25 years	12 f	total number	Cz	r=.05, p=.79
Fogel et al., 2007	MAB-II: VIQ	18-26 years, M=20, SD=5.3	29 f / 6 m	density	Cz	n.s.
Fogel et al., 2007	MAB-II: PIQ	18-26 years,	29 f / 6 m	density	Cz	n.s.

		M=20, SD=5.3				
Fogel et al., 2007	MAB-II: VIQ	18-26 years, M=20, SD=5.3	29 f / 6 m	duration	Cz	n.s.
Fogel et al., 2007	MAB-II: PIQ	18-26 years, M=20, SD=5.3	29 f / 6 m	duration	Cz	n.s.
Peters et al., 2007	MAB-II: VIQ	M=21, SD=2.4	12 f / 12 m	density	C3, C4	r=–.26, p>.05
Peters et al., 2007	MAB-II: PIQ	M=21, SD=2.4	12 f / 12 m	density	C3, C4	r=.05, p>.05
Peters et al., 2007	MAB-II: FSIQ	M=21, SD=2.4	12 f / 12 m	density	C3, C4	r=–.11, p>.05
Peters et al., 2008	MAB-II: VIQ	17-24 years, M=20, SD=2.3	7 f / 7 m	density	C3, C4	n.s.
Peters et al., 2008	MAB-II: PIQ	17-24 years, M=20, SD=2.3	7 f / 7 m	density	C3, C4	n.s.
Peters et al., 2008	MAB-II: FSIQ	17-24 years, M=20, SD=2.3	7 f / 7 m	density	C3, C4	n.s.
Peters et al., 2008	MAB-II: VIQ	62-79 years, M=70, SD=5.1	7 f / 7 m	density	C3, C4	n.s.
Peters et al., 2008	MAB-II: PIQ	62-79 years, M=70, SD=5.1	7 f / 7 m	density	C3, C4	n.s.
Peters et al., 2008	MAB-II: FSIQ	62-79 years, M=70, SD=5.1	7 f / 7 m	density	C3, C4	n.s.
Tucker & Fishbein, 2009	MAB-II: VIQ	M=21 years	12 f / 12 m	sigma power	C3, C4	n.s.
Tucker & Fishbein, 2009	MAB-II: PIQ	M=21 years	12 f / 12 m	sigma power	C3, C4	n.s.
Tucker & Fishbein, 2009	MAB-II: FSIQ	M=21 years	12 f / 12 m	sigma power	C3, C4	n.s.
Geiger et al., 2011	WISC-IV: VIQ	9-13 years, M=10.5	6 f / 8 m	spindle peak frequency	C3, C4	n.s.
Geiger et al., 2011	WISC-IV: FIQ	9-13 years, M=10.5	6 f / 8 m	spindle peak frequency	C3, C4	n.s.
Geiger et al., 2011	WISC-IV: FSIQ	9-13 years, M=10.5	6 f / 8 m	spindle peak frequency	C3, C4	r=–.56, p<.05
Geiger et al., 2011	WISC-IV: VIQ	9-13 years, M=10.5	6 f / 8 m	sigma power	C3, C4	n.s.
Geiger et al., 2011	WISC-IV: FIQ	9-13 years, M=10.5	6 f / 8 m	sigma power	C3, C4	r=.65, p<.05
Geiger et al., 2011	WISC-IV: FSIQ	9-13 years, M=10.5	6 f / 8 m	sigma power	C3, C4	r=.67, p<.01

Lustenberger et al., 2012	ZVT: IQ	18-20 years, M=19, SD=0.8	15 m	activity	C4	r=.55, p<.05
Chatburn et al., 2013	SBIS: VIQ	4-13 years, M=8, SD=2.1	13 f / 14 m	total number: all, fast, slow	C3, C4	n.s.
Chatburn et al., 2013	SBIS: NVIQ	4-13 years, M=8, SD=2.1	13 f / 14 m	total number: all, fast, slow	C3, C4	n.s.
Chatburn et al., 2013	SBIS: FSIQ	4-13 years, M=8, SD=2.1	13 f / 14 m	total number: all, fast, slow	C3, C4	n.s.
Chatburn et al., 2013	SBIS: VIQ	4-13 years, M=8, SD=2.1	13 f / 14 m	density: all, fast, slow	C3, C4	n.s.
Chatburn et al., 2013	SBIS: NVIQ	4-13 years, M=8, SD=2.1	13 f / 14 m	density: all, fast, slow	C3, C4	n.s.
Chatburn et al., 2013	SBIS: FSIQ	4-13 years, M=8, SD=2.1	13 f / 14 m	density: all, fast, slow	C3, C4	n.s.
Chatburn et al., 2013	SBIS: VIQ	4-13 years, M=8, SD=2.1	13 f / 14 m	duration	C3, C4	n.s.
Chatburn et al., 2013	SBIS: NVIQ	4-13 years, M=8, SD=2.1	13 f / 14 m	duration	C3, C4	n.s.
Chatburn et al., 2013	SBIS: FSIQ	4-13 years, M=8, SD=2.1	13 f / 14 m	duration	C3, C4	n.s.
Chatburn et al., 2013	SBIS: VIQ	4-13 years, M=8, SD=2.1	13 f / 14 m	frequency	C3, C4	n.s.
Chatburn et al., 2013	SBIS: NVIQ	4-13 years, M=8, SD=2.1	13 f / 14 m	frequency	C3, C4	n.s.
Chatburn et al., 2013	SBIS: FSIQ	4-13 years, M=8, SD=2.1	13 f / 14 m	frequency	C3, C4	n.s.
Gruber et al., 2013	WISC-IV: FSIQ	7-11 years, M=9 SD=0.9	14 f /15 m	density	F3, F4, C3, C4, P3, P4, O1, O2	n.s.
Gruber et al., 2013	WISC-IV: FSIQ	7-11 years, M=9 SD=0.9	14 f /15 m	amplitude	F3, F4, C3, C4, P3, P4, O1, O2	n.s.
Gruber et al., 2013	WISC-IV: FSIQ	7-11 years, M=9 SD=0.9	14 f /15 m	duration	F3, F4, C3, C4, P3, P4, O1, O2	n.s.
Gruber et al., 2013	WISC-IV: FSIQ	7-11 years, M=9 SD=0.9	14 f /15 m	frequency	F3, F4, C3, C4, P3, P4, O1, O2	n.s.
Ward et al., 2014	MAB-II: VIQ	18-29 years, M=21, SD=3.0	21 f / 9 m	density	C3	r=.18, p>.05
Ward et al., 2014	MAB-II: PIQ	18-29 years, M=21, SD=3.0	21 f / 9 m	density	C3	r=.14, p>.05
Ward et al., 2014	MAB-II: FSIQ	18-29 years, M=21, SD=3.0	21 f / 9 m	density	C3	r=.22, p>.05
Hoedlmoser et al. 2014	WISC-IV: FSIQ	8-11 years, M=10,	28 f / 35 m	activity (slow)	F3, Fz, F4, C3, C4, P3, Pz,	r=..39, p<0.001

		SD=0.8			P4, O1, O2	
Tessier et al. 2015	WISC-III: FSIQ	6-13 years, M=10, SD=2	13 m (autistic), 13 m (TD)	density, duration, sigma power	Fp1, Fp2, C3, C4	r=-0.55 p=0.05 (density, autistic)
Tessier et al. 2015	WISC-III: VIQ	6-13 years, M=10, SD=2	13 m (autistic), 13 m (TD)	density, duration, sigma power	Fp1, Fp2, C3, C4	r=-.62, p<0.05 (density, autistic) r=0.72, p<0.02 (duration, TD)

Table 1.Previous studies and their results about the relationship between sleep spindling and intelligence. RPMT: Raven Progressive Matrices. APM: Advanced Progressive Matrices. MAB-II: Multidimensional Aptitude Battery-II. SBIS: Stanford-Binet Intelligence Scale. WISC-IV: Wechsler Intelligence Scale for Children IV. WAIS-III: Wechsler Adult Intelligence Scale III. ZVT: Zahlen-Verbindungs-Test. VIQ: Verbal IQ. PIQ: Performance IQ, FSIQ: Full scale IQ. FIQ: fluid IQ. NVIQ: Non-verbal IQ, TD: typically developing. Data from Peters et al., 2007; Peters et al., 2008; and Ward et al., 2014 were added with data from K. Peters, personal communication. Reproduction from (Ujma et al., 2014), with added data.

Overall, many previous studies have investigated the relationship between sleep spindling and intelligence, but both the implemented methods and the results were highly variable. Given the high g-loading of most of the IQ tests used in these studies, it is unlikely that the source of variability was a low concordance between these studies with respect to the psychometric construct they measured. However, most of these studies can be criticized for their sleep spindle detection methods, which either did not separate slow or fast spindles or did it with a generic threshold frequency, did not take into account individual variations in sleep spindle frequency and amplitude, or both of the above. Some of these studies investigated a very small number of subjects (the highest number being 48 in (Schabus et al., 2006)) and none of them specifically investigated potential sex differences in the sleep spindling correlates of IQ, despite much evidence of such differences in other neurobiological correlates of intelligence (Neubauer et al., 2002; Haier et al., 2005; Jausovec and Jausovec, 2005).

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2. Aims

In our studies, we investigated the correlations between sleep spindle parameters, EEG spectral components and intelligence, specifically targeting potential sex differences and employing the IAM method of sleep spindle detection specifically designed to identify slow and fast spindles using individually adjusted amplitude and frequency thresholds.We paid particular attention to avoid the methodological problems seen in previous studies, that is:

1.) We aimed to create a study sample of a greater size than any of the previous studies investigating the relationship between sleep spindling and intelligence.

2.) We detected slow and fast sleep spindles separately, considering individual differences in sleep spindle frequency and amplitude. This was performed using our in-house Individual Adjustment Method of sleep spindle detection.

3.) In line with previous results about the biological correlates of intelligence – which were frequently revealed to be not unequivocal in males and females – wespecifically investigated the possibility of a sexual dimorphism by analyzing not only the study sample as a whole, but also the male and female subsamples separately.

4.) In order to further clarify and to establish the consistency of our findings we repeated the study in three subsamples spanning a significant age range, analyzing i.) a sample of 4-8 year old children, ii.) a sample of adolescents and iii.) a sample of adults. The adult sample also contained individuals of exceptionally high intelligence.

Our ultimate aim was to conduct an investigation of the relationship between sleep spindling and intelligence superior to previous studies both in terms of signal processing methodology and statistical power.

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3. Methods

Our technical and mathematical methods are discussed in this section in the same way they appear in the corresponding articles originally reporting our research (Bódizs et al., 2014; Ujma et al., 2014)and (Ujma et al. submitted), with three exceptions: 1) spectral analysis is described even in case of the studies where it was not originally part of the article (Ujma et al., 2014) and (Ujma et al. submitted) 2) since all three studies implemented the same sleep spindle detection as well as spectral analysis methodology, the description of these methods are removed from the subsections discussing each individual study and instead reported together at the beginning of the Methods section 3) due to overlaps in methodology, multiple comparison correction is described at the beginning of the Methods section instead of individually for the three studies.

The Individual Adjustment Method (IAM) of sleep spindle analysis

The Individual Adjustment Method (IAM) of sleep spindle analysis (Bódizs et al., 2009; Ujma et al., 2015a) has already been mentioned in earlier parts of this thesis, together with its empirical benefits in comparison to other methods. Here, a more detailed description is given according to (Ujma et al., 2015a). According to this method, the following analysis of the EEG signal is performed:

i. Average amplitude spectra. Non-overlapping 4 second artifact-free NREM sleep EEG segments are Hanning-tapered (50%), then zero-padded to 16 second. The average amplitude spectrum of all-night NREM sleep EEG derivations is computed between 9–16 Hz by using an FFT routine (frequency resolution: 0.0625 Hz).

ii. Individually adjusted frequency limits of slow and fast sleep spindles. Determination of the individual slow and fast sleep spindle frequencies is based on second order derivatives of the 9–16 Hz amplitude spectra. In order to avoid small fluctuations in convex and concave segments average amplitude spectra of 0.0625 Hz resolution (i) is downsampled (decimated) by a factor of 4 (0.25 Hz) before calculating the derivation-

specific second-order derivatives in this frequency range. Derivation-specific second order derivatives of the amplitude spectra are then averaged over all EEG derivations resulting in a whole-scalp second order derivative for each subject. Individual-specific frequency limits of sleep spindles are defined as pairs of zero crossing points encompassing a negative peak in the whole-scalp second order derivatives. These zero-crossing points are rounded to the closest bins within the high-resolution (0.0625 Hz) amplitude spectra obtained in step i. Two pairs of individual-specific frequency limits and corresponding ranges are defined (one for slow and one for fast spindles). In cases of uncertainty (lack of zero crossing points indicating slow spindles or partial overlap between slow and fast sleep spindles in some cases), frequencies with predominance of power in averaged frontal (Fp1, Fp2, Fpz, F3, F4, Fz, F7, F8, as available) over averaged centro-parietal (C3, C4, Cz, P3, P4, Pz, as available) amplitude spectra are considered as slow spindle frequencies. In our studies reported here, there was no case of uncertainty related to the individual-specific upper frequency boundary of fast sleep spindling.

iii. Individual-specific spindle middle frequencies. Slow spindle middle frequency of a given subject is quantified as the arithmetic mean of the individual-specific lower and upper limits for slow spindling as obtained above (ii). In case of fast sleep spindling the arithmetic mean of the lower and the upper frequency limits of fast sleep spindles are considered.

iv. Individual- and derivation-specific amplitude criteria for sleep spindles.Spindles are defined as those EEG segments contributing to the peak region of the average amplitude spectrum. Hence we obtain an amplitude criterion corresponding to the line determined by the y-values (μV) pertaining to the individually adjusted pairs of frequency limits (ii) in the average amplitude spectra (i).

iv/a. The number of high resolution (0.0625 Hz) frequency bins (i) falling in the individual-specific slow- and fast sleep spindle frequency ranges (ii) are determined.

iv/b. The amplitude spectral values (i) at the individually adjusted frequency limits for slow and fast sleep spindles (ii) are determined. This is performed in a derivation-specific manner.

iv/c. Number of bins for slow and fast sleep spindling (iv/a) are multiplied with the arithmetic mean of the pairs of derivation-specific amplitude spectral values for slow and fast sleep spindle frequency limits (iv/b), respectively. Outcomes are individual- and derivation specific amplitude criteria for slow and fast sleep spindle detections.

v. Envelopes of sleep spindling. EEG data is band-pass filtered for the slow and fast spindle frequency ranges by using an FFT-based Gaussian filter with 16 sec windows: f(x) = e^− (((x − xm)/(w/2))^2), where x varies between zero and the Nyquist frequency according to the spectral resolution, x_m is the middle frequency of the spindle range (iii), and w is the width of the spindle range (ii) (ii and iii). Filtered signal is rectified and smoothed by a moving average weighted with a Hanning window of 0.1 s length and multiplied with π/2 (the latter is the inverse of the mean of a rectified sine wave).

vi. Detection and characterization of sleep spindles. If envelopes of this band-pass filtered and rectified data (v) exceed the individual and derivation-specific threshold as defined above (iv) for at least 0.5 seconds, a sleep spindle is detected. Sleep spindles detected this way are analyzed and average sleep spindle density (number of spindles per minute), sleep spindle duration (s), as well as median and maximum amplitude (expressed as all-night means of intra-spindle envelopes in μV at the middle of the detected spindles and at the maxima of the spindles, respectively) is calculated for the subject.

The IAM process is illustrated on Figure 7.

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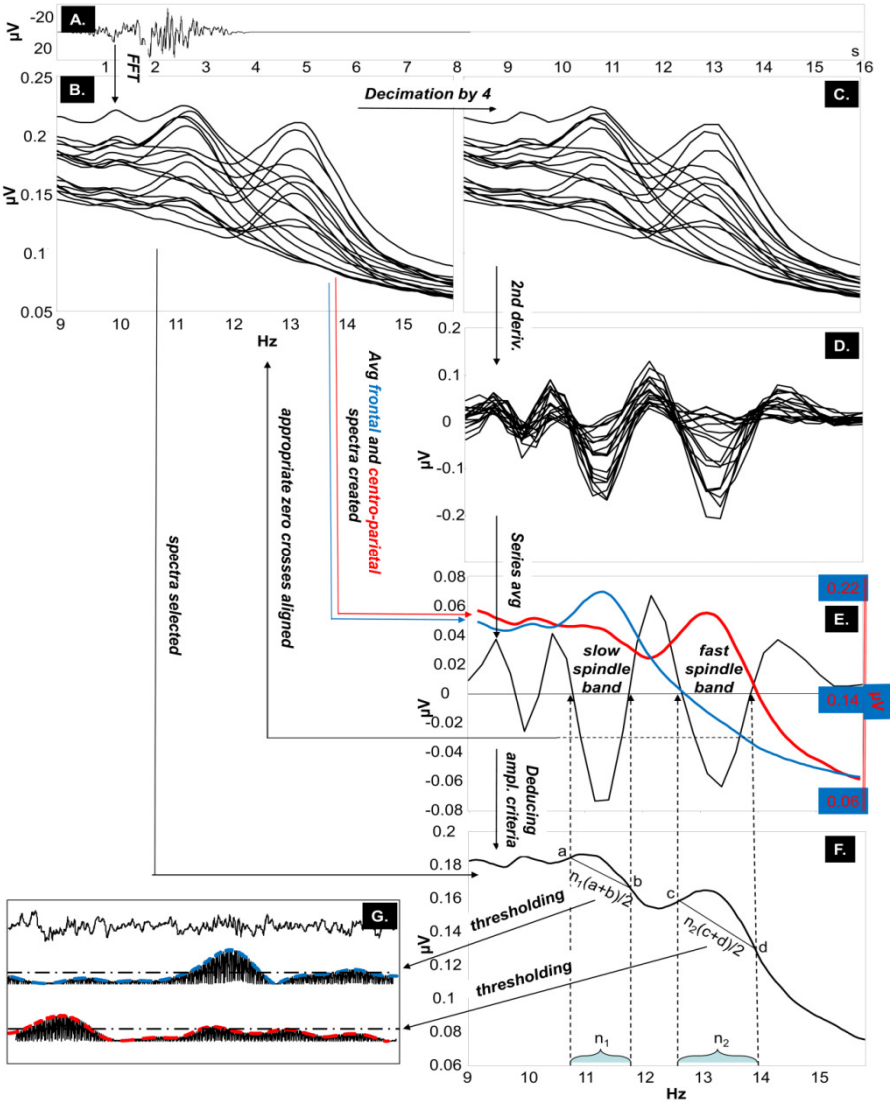

Figure 7. The Individual Adjustment Method (IAM) of sleep spindle analysis. A. Four second EEG epoch Hanning-tapered and zero padded to 16 Hz. B. Fast Fourier Transformation (FFT) is used to calculate 9-16 Hz average amplitude spectra of all night NREM sleep EEG from Hanning-tapered and zero-padded segments. C. Decimated amplitude spectra by a factor of 4. D. Second order derivatives of the decimated amplitude spectra. E. Calculating the whole-scalp second order derivative by series averaging. The series is overplotted with the averaged frontal (generally Fp1, Fp2, Fpz, F3, F4, Fz, F7, F8, as available) and centro-parietal (generally C3, C4, Cz, P3, P4, Pz, as available) amplitude spectra. Appropriate zero-crossing points encompassing individual-specific slow and fast sleep spindle bands are selected according to the frequency scale in B. F. Derivation-specific amplitude criteria is calculated. G. Thresholding of the envelopes of the slow and fast-spindle filtered signal. Reproduced from (Ujma et al., 2015a).

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Spectral analysis

In all studies reported here, we computed the NREM sleep EEG spectrum using the Fast Fourier Transform to compute spectral power. FFT power was computed for all available 4-second epochs (with 2 second overlaps) of artifact-free N2 and SWS EEG signals, and an average spectral power value was calculated by averaging across all 4-second epochs. In line with the relevant guidelines, spectral power was log-transformed before the statistical analyses(Pivik et al., 1993; Jobert et al., 2013)in order to approximate a normal distribution instead of the power law distribution typically seen in raw EEG spectra.

Besides log-transformation, z-scores of the 8–16 Hz spectra were also analyzed. This latter transformation is justified by the findings supporting the striking trait-like reliability(De Gennaro et al., 2005) and the marked sensitivity of this sleep EEG scores expressing discrete frequency points of the individual shapes of the sleep EEG spectra(Bódizs et al., 2012). Z-score spectra are calculated by replacing the power spectral values for each electrode of each individual by the z-scores of the same values (within a specified range, here 8-16 Hz). In all three studies, both log-transformed power (10-base) and z-transformed normalization (x-m/SD) were used in separate statistical models.

Correcting for multiple comparisons

In case of the child and adolescent samples, which had relatively low sample sizes, multiple comparisons correction was performed using a modified version of the Rüger area method (Abt, 1987; Duffy et al., 1990; Bódizs et al., 2014) on correlation data. In this method, instead of determining the significance of individual correlation coefficients, a global null hypothesis is tested on a contiguous area of significant results. This global null hypothesis is kept or rejected for the area as a whole. We defined areas of significance on the scalp where uncorrected p-values on at least two neighboring electrodes were below the conventional significance limit (α=0.05). If the uncorrected

p-values were below α/2 ($p<0.025$) for at least 50% of the correlations within the area of significance, then the global null hypothesis was rejected for the area as a whole.

In order to obtain a better localization of regions with significant correlations between sleep spindling and age or IQ the correlations were represented by significance probability maps (Hassainia et al., 1994).

In case of spectral data, this Rüger area method was used in all three studies. In this case, areas of significance were defined not only in the spatial domain (neighboring electrodes) but also in the frequency domain (neighboring frequency bins). That is, a contiguous area of significance was defined as an area where correlation coefficients were below the conventional significance threshold ($\alpha=0.05$) on at least two neighboring electrodes and in at least two neighboring frequency bins. Likewise, an area of significance was defined from the first frequency bin with a conventionally significant correlation on at least electrode to the last frequency bin with such results. Similarly to sleep spindle parameters, if the uncorrected p-values were below α/2 ($p<0.025$) for at least 50% of the correlations within the area of significance, then the global null hypothesis was rejected for the area as a whole.

In case of the adult sample, the larger sample size allowed a multiple comparison correction method with better spatial resolution. In this case, the Benjamini-Hochberg method of false discovery rate (FDR) correction (Benjamini and Hochberg, 1995) method was applied, which tests the null hypothesis that a statistically significant result is a false discovery using the distribution of p-values in all performed statistical tests. This correction procedure was selected because sleep spindle parameters at different electrodes are expected to correlate positively, rendering a Bonferroni correction overly conservative. The Benjamini-Hochberg procedure, on the other hand, is valid for both independent and positively correlated tests.

3.1. Study 1 – Children

3.1.1. Recruitment, Ethics and Psychometric Testing

We recruited a sample of 33 healthy young children in the greater Budapest area. All the children were healthy; any diagnosis of mental or physical illness caused an

exclusion from the study. Written consent forms were obtained from the parents. Ethical approval of the study was received from the Semmelweis University Ethical Review Board. The children underwent all-night polysomnography recordings in a sleep laboratory (in the presence of their parents) for two consecutive nights. Due to the poor quality of second-night recordings the recording of the first night was used in case of two children (both males, age 4.99 and 4.34 years, respectively). Due to the poor quality of both first and second night recordings a third night was recorded and used for analysis in the case of another four children (3 females, one male, ages 8.22 years, 6.25 years, 7.05 years and 8.5 years, respectively). In case of four additional children the families refused to undergo a third polysomnography recording. Therefore, we analyzed recordings from 29 children (15 females, 14 males, age: 3.84-8.5 years). Because of the presence of high-frequency artifacts in his EEG recordings, one further male subject was rejected from spectral analyses (but not sleep spindle analysis which only uses a narrow frequency band less affected by artifacts).

The age of the children was obtained in months and re-calculated to years including fractions which is how it is reported here. We aimed to reduce the number of nights spent in the sleep laboratory to the minimum necessary, and we used first and third night recordings due to the inter-night stability of the individual EEG spectrum in the typical sleep spindle frequency range even in case of drastic manipulations (De Gennaro et al., 2005).

All children completed a psychological and neuropsychological battery,among them the Raven's Colored Progressive Matrices, a nonverbal test of IQ (Raven et al., 1962). The CPM raw score was used to assess the children's cognitive ability.

3.2.2. Polysomnography Recording and Scoring

On both nights, subjects were fitted with 19 EEG electrodes (Fp1, Fp2, F3, F4, Fz, F7, F8, C3, C4, Cz, P3, P4, Pz, T3, T4, T5, T6, O1, O2) according to the 10–20 electrode placement system(Jaspers, 1958) as well as with two EOG electrodes (bipolar channel) monitoring vertical and horizontal eye-movements; EMG electrodes (bipolar channels) for the chin muscles, two ECG electrodes according to standard lead I. Gold coated Ag/AgCl EEG cup electrodes were fixed with EC2 Grass Electrode Cream (Grass

Technologies, USA) and referred to the mathematically- linked mastoids. Impedances were kept below 10 kΩ. In 27 children, signals were collected using the 32 channel EEG/polysystem (Brain-Quick BQ 132S, Micromed, Italy), prefiltered (0.33–1500 Hz, 40 dB/decade anti-aliasing hardware input filter), amplified and digitized with 4096 Hz/channel sampling rate (synchronous) with 12 bit resolution. A further 40 dB/decade anti-aliasing digital filter was applied by digital signal processing which low-pass filtered the data at 450 Hz. Finally, the digitized and filtered EEG was undersampled at 1024 Hz. Two further children were recorded in their homes by using the newly available SD-LTM 32 Express ambulatory home polysomnography device and the System Plus Evolution Software (Micromed, Italy) with the following technical characteristics: 0.15-250 Hz hardware input filtering (40 dB/decade), 4096 Hz/channel synchronous sampling rate, 22 bit resolution, downsampling (decimation) to 1024 Hz after 463.3 Hz anti-aliasing filtering performed by firmware. Because of the small amplitude attenuation due to the hardware filter characteristics of the EEG devices in the spindle frequency range data from the two recording systems were pooled without correcting for device-specific amplitude differences (Ujma et al., 2014).

All polysomnography recordings were scored according to standard criteria (Iber et al., 2007) based on 20 second epochs, artifacts were manually rejected based on 4 second epochs using in-house software, FerciosEEG (© 2009-2014. Ferenc Gombos).

3.2.3. Spectral Analysis, Sleep Spindle Detection and Statistics

Artifact-free N2 and SWS EEG epochs were fed to the Individual Adjustment Method (IAM) sleep spindle detection algorithm (Bódizs et al., 2009; Ujma et al., 2015a). Frontal electrodes for IAM input were Fp1, Fp2, F3, F4, Fz, F7 and F8, while centro-parietal electrodes were C3, C4, Cz, P3, P4 and Pz. The IAM method calculated individual averages for slow and fast spindle frequency (Hz), density (no./minute), duration (second) and amplitude (μV, based on the envelope of the EEG signal filtered to the individual frequencies). Raw power spectral values (10-base log-transformed) and spectrum z-scores were calculated as described at the beginning of the Methods section. Spectral power was computed and used in statistical analyses in 0.25 Hz bins. Due to electrode failures, 18 electrodes from 12 subjects were excluded from spectral analysis and treated as missing data. These electrode failures occurred 3 times on Cz, F7 and F8, 2 times on O1, T3 and Pz, and once on Fp2, O2 and T5, respectively. Since these

electrode failures produced either low or high frequency artifacts not affecting the spindle range, exclusion of the same electrodes from sleep spindle analysis was not deemed necessary.

We investigated the correlates between CPM scores, age and individual sleep spindle parameters using Pearson's point-moment correlations with a modified version of the Rüger area method (Abt, 1987; Duffy et al., 1990; Bódizs et al., 2014) in order to adjust for multiple comparisons.

In order to assess the correlations between sleep spindling and cognitive performance both from a developmental/maturational and trait perspective (Geiger et al., 2010), we computed the correlations between spindle parameters and CPM scores both with and without correcting for age, similarly to our previous study in an adolescent (postpubertal) sample (Bódizs et al., 2014).

3.2. Study 2 – Adolescents

3.1.1. Recruitment, Ethics and Psychometric Testing

Subjects (N = 24, 12 males) were adolescents recruited by a convenience sampling procedure.

Subjects were interviewed on their health status by the authors of the study. Exclusion criteria for the participants were self-reported sleep problems or psychiatric, neurological or other medical disorder. Subjects were requested to not to drink alcohol containing beverages, to not to take drugs other than caffeine and to not to take naps during the study. Habitual doses of caffeine were allowed.

The research protocol was approved by the Ethical Committee of the Pázmány Péter Catholic University Budapest. Adult participants or the parents of the underage participants signed informed consent for the participation in the study according to the Declaration of Helsinki.

Intelligence was tested by using the Raven Progressive Matrices Test (RPMT), which is based on items assessing the abilities in the field of non-verbal reasoning(Raven, 2000; Raven et al., 2004). Scores of the RPMT were shown to be among the most reliable

measures of the general factor of mental abilities(Gray and Thompson, 2004a). Raw RPMT scores were transformed to IQ by using the Hungarian standards (Raven et al., 2004).

3.3.2. Polysomnography Recording and Scoring

Subjects' sleep was recorded at their homes by using ambulatory home polysomnography. Sleep recordings on two consecutive weekend nights were performed according to the subjects' sleeping habits. We used a portable SD LTM 32BS Headbox together with a BRAIN QUICK System PLUS software (Micromed, Italy) for polysomnographic data recording. We recorded EEG according to the 10–20 system (Jasper, 1958) at 21 recording sites (Fp1, Fp2, Fpz, F3, F4, F7, F8, Fz, C3, C4, Cz, P3, P4, Pz, T3, T4, T5, T6, O1, O2, Oz) referred to the mathematically linked mastoids. Bipolar EOG, ECG and submental as well as tibial EMG were also recorded. EEG and polygraphic data were high-pass filtered at .15 Hz and low-pass filtered at 250 Hz (both 40 dB/decade). Data were collected with an analogue to digital conversion rate of 4096 Hz/channel (synchronous, 22 bit). A further 40 dB/decade anti-aliasing digital filter was applied by digital signal processing (firmware) which low pass filtered the data at 463.3 Hz before the decimation by a factor of 4, resulting in a sampling rate of 1024 Hz.

Sleep recordings of the second nights were visually scored according to standard criteria (Rechtschaffen and Kales, 1968) in 20 second epochs. The following definitions were used for sleep architecture evaluation: time in bed (as the time from lights out to final awakening), sleep time (defined as the amount of sleep from sleep onset to final awakening), wake time after sleep onset (WASO, excluding wakefulness after the final awakening), sleep efficiency (calculated as the percent of sleep time without WASO divided by the time in bed), sleep latency (defined as the period between lights off and the first appearance of S2 sleep), non-rapid eye movement (NREM), Stage 1 (S1), S2, SWS (defined as the amount of time spent in Stages 3 and 4), rapid eye movement sleep (REM), REM latency (defined as the period between sleep onset and the first epoch scored as REM), number of sleep cycles (number of REM periods separated from each other by more than 15 min), average REM period duration (duration of REM sleep divided by the number of REM periods) and average sleep cycle duration in minutes

(sleep time from the sleep onset to the end of the last REM period divided by the number of sleep cycles).

The 4 second epochs containing artefactual sleep EEG (movement, sweating or technical artifacts) were manually removed before further automatic sleep EEG analyses. One male subject was excluded from the below listed quantitative EEG analyses because of technical artifacts interfering with deliberate and reliable signal processing approaches.

3.3.3. Spectral Analysis, Sleep Spindle Detection and Statistics

The Individual Adjustment Method (IAM) of sleep spindle analysis (Bódizs et al., 2009) was used to unravel the potential peculiarities of NREM sleep (stages 2-4) EEG spindling. Frontal derivations were Fp1, Fp2, Fpz, F3, F4, Fz, F7, and F8; while centro-parietal derivations wereC3, C4, Cz, P3, P4 and Pz.FFT-based measurement (10-base logarithmized raw spectra and z-transformed spectra) of binwise spectral power in the 8–16 Hz range of all-night average NREM sleep (stages 2-4) was also performed based on 0.25 Hz bins. Our aim was to compare the results based on the more sophisticated IAM of sleep spindle analysis with the relatively simple spectral analysis. While IAM is sensitive to sleep spindle features at the individual frequencies, spectral power mapping is able to provide evidence for the importance of sleep spindle activity occurring at specific frequencies.

We investigated the correlates between RPMT scores, age and individual sleep spindle parameters using Pearson's point-moment correlations with a modified version of the Rüger area method (Abt, 1987; Bódizs, et al., 2014; Duffy, et al., 1990) in order to adjust for multiple comparisons.

3.3. Study 3 – Adults

3.3.1. Recruitment, Ethics and Psychometric Testing

A total of 160 subjects (72 females, 88 males) participated in this study, in a cooperation of the Max Planck Institute for Psychiatry, Munich, and the Psychophysiology and Chronobiology Research Group of Semmelweis University,

Budapest. The sleep spindle database was created using previously existing polysomnography recordings with available IQ scores, but it has never been used in publications addressing the relationship between sleep spindles and intelligence, either in its entirety or in part. Subjects were recruited for different research projects by advertisements and personal contacts in Hungary and Germany. To include also a considerable number of subjects in the high to very-high intelligence range, subjects were also recruited among the members of the high-IQ society Mensa.

The research protocols were approved by the Ethical Committee of the Semmelweis University, Budapest or the Medical Faculty of the Ludwig Maximilians University, Munich in accordance with the Declaration of Helsinki. All subjects signed informed consent for the participation in the studies. According to semi-structured interview with experienced psychiatrists or psychologists, all subjects were healthy, had no history of neurologic or psychiatric disease and were free of any current drug effects excluding contraceptives. However, small doses of caffeine (max. 2 cups of coffee before noon) were allowed. Alcohol consumption was not allowed. 6 male and 2 female subjects were light to moderate smokers (self-reported), while the rest of the subjects were non-smokers.

Based on their availability, all subjects completed one or two standardized nonverbal intelligence tests. The tests used in the study were the Culture Fair Test (CFT, (Weiss and Weiss, 2006)) and Raven Advanced Progressive Matrices (Raven APM, (Raven et al., 2004)). Both the CFT and Raven APM are nonverbal intelligence tests where subjects are required to complete abstract patterns by finding their organizing rules. Performance in these tests was shown to correlate strongly and to be a particularly good measurement of the general factor of intelligence (Cattell, 1973; Duncan et al., 2000; Prokosch et al., 2005). A total of 113 subjects completed the CFT and 89 subjects completed the Raven APM test. 42 subjects completed both tests.

Sleep spindle parameters were expected to change as a factor of age, and IQ scores derived from intelligence tests are age-corrected, while raw scores of different intelligence tests are on different scales. Therefore, a composite raw intelligence test score was calculated, expressed as a Raven equivalent score. Raven equivalent scores for Raven APM tests were equal to the actual raw test score. For CFT raw scores,

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Raven equivalent scores were equal to the Raven APM score corresponding to the IQ percentile derived from CFT performance and the age of the subject – in other words, the Raven APM score which would have yielded the same population percentile score as the actually completed CFT test. If both Raven APM and CFT scores were available for a subject, the two Raven equivalent scores were averaged. Raven APM was chosen as a basis of standardization because of the availability of detailed norms. For this study, norms from the 1993 Des Moines (Iowa) standardization (Raven et al., 2004) of APM were used.

3.3.2. Polysomnography Recording and Scoring

Sleep was recorded for two consecutive nights by standard polysomnography, including EEG according to the 10-20 system (Jaspers, 1958) (common recording sites across the studies and laboratories were: Fp1, Fp2, F3, F4, Fz, F7, F8, C3, C4, Cz, P3, P4, T3, T4, T5, T6, O1, and O2), electro-oculography (EOG), bipolar submental electromyography (EMG), as well as electrocardiography (ECG). EEG electrodes were re-referenced to the mathematically-linked mastoids. Impedances for the EEG electrodes were kept below 8 kΩ. Signals were collected, pre-filtered, amplified and digitized at different sampling rates using different recording apparatus in the different subsamples (see Table 2 for details).

DOI:10.14753/SE.2016.1895

	N	EEG recording sites (10-20 system)	Polygraphic channels	Electrodes used	Effective sampling rate/sampling rate (Hz)	Precision	Hardware prefiltering (Hz)	Amplitude attenuation, 10-15 Hz (mean [std. dev.])	Recording apparatus	Recording software
Budapest – I.	31	Fp1, Fp2, F3, F4, Fz, F7, F8, C3, C4, Cz, P3, P4, T3, T4, T5, T6, O1, O2	left and right EOG, bipolar submental EMG, ECG, thoracic and abdominal respiration	Au coated Ag/AgCl fixed with EC2 Grass electrode cream	249/249	12 bit	0.5-70	0.9705 [0.0036]	Flat Style SLEEP La Mont Headbox, HBX32-SLP preamplifier (La Mont Medical Inc. USA)	DataLab (Medcare, Iceland)
Budapest – II.	16	Fp1, Fp2, F3, F4, Fz, F7, F8, C3, C4, Cz, P3, P4, Pz, T3, T4, T5, T6, O1, O2	bipolar EOG, bipolar submental EMG, ECG	Au coated Ag/AgCl fixed with EC2 Grass electrode cream	4096/1024	12 bit	0.33-1500 (<450 Hz antialiasing digital filtering before undersampling)	0.9356 [0.0021]	Brain-Quick BQ 132S (Micromed, Italy)	System 98 (Micromed, Italy)
Munich – I.	93	Fp1, Fp2, Fpz, AF1, AF2, F3, F4, Fz, F7, F8, C3, C4, Cz, P3, P4, Pz, T3, T4, T5, T6, O1, O2	bipolar EOG, bipolar submental EMG, ECG	Ag/Ag-Cl, with EC2 Grass Electrode Cream for EEG and Nihon Kohden ELEFIX for EMG	250/250	8 bit	0.53-70	0.9693 [0.0016]	Comlab 32 DigitalSleep Lab	Brainlab V 3.3
Munich – II.	20	Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2	bipolar EOG, bipolar submental EMG, ECG	Ag/Ag-Cl, with EC2 Grass Electrode Cream for EEG and Nihon Kohden ELEFIX for EMG	250/250	8 bit	0.53-70	0.9693 [0.0016]	Comlab 32 DigitalSleep Lab	Brainlab V 3.3

Table 2. Details of the recording precedures in different subsamples

Sleep EEG recordings for the second nights spent in the laboratory were manually scored on a 20 second basis by applying standard criteria (Iber et al., 2007). Epochs with artifacts were removed on a 4 second basis by visual inspection of all recorded channels (including polygraphy).

3.3.3. Spectral Analysis, Sleep Spindle Detection and Statistics

In order to correct for the different analog EEG filter characteristics of our machines, we connected an analog waveform generator to the C3 and C4 electrode inputs (with original recording reference, re-referenced for A1-A2 common references for further analysis) of all EEG devices and applied 40 and 355 μV amplitude sinusoid signals of various amplitudes (0.05 Hz, every 0.1 Hz between 0.1-2 Hz, every 1 Hz between 2-20 Hz, every 10 Hz between 10 Hz-100 Hz).

We determined the amplitude reduction rate of each recording system by calculating the proportion between digital (measured) and analog (generated) amplitudes of sinusoid signals at typical sleep spindle frequencies (10, 11, 12, 13, 14 and 15 Hz) for both inducing (40 and 355 μV amplitude) signals. Machine-specific amplitude reduction rates were given as the mean amplitude rate between digital and analog values at the

two amplitudes and six measured frequencies (see Table 2 for the reduction rates). Sleep spindle amplitudes were corrected by dividing their calculated values by the amplitude reduction rate of the recording system.

The individual adjustment method (IAM) of sleep spindle analysis was applied for N2 and SWS sleep. Frontal derivations for the IAM were Fp1, Fp2, F3, F4, Fz, F7, and F8; while centro-parietal derivations were C3, C4, Cz, P3 and P4. FFT-based measurements of raw (10-base logarithmized and z-score) power spectral density were also computed. Spectral power was computed and used in statistical analysis in 0.25 Hz bins. Due to electrode failures, data from a total of 27 electrodes from 21 subjects was excluded and was treated as missing data in all subsequent analyses. Electrode failures occurred on Fp1 in 10 cases; Fp2 in 3 cases; F4, F8, F7 and Fpz in 2 cases; F3, T3, T5, C3, O2 and T6 in 1 cases, respectively.

Given the individual- and derivation-specific adjustment inherent to the procedure, sleep spindle densities and durations are amplitude-insensitive measures (see an empirical demonstration in (Bodizs et al., 2005). Thus, there was no need for the compensation of the different recording systems in these values. Group comparisons (male vs. female) were performed by independent samples t-tests. Partial Pearson correlation coefficients were calculated to test the relationship between sleep spindle parameters and Raven equivalent scores, controlling for the effects of age. This was deemed necessary due to the potential effects of age on both sleep spindle parameters (De Gennaro and Ferrara, 2003; Fogel and Smith, 2011) and intelligence test performance (Tucker-Drob, 2009). In order to control for multiple comparisons across electrodes, we performed the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) controlling for the false discovery rate for each sleep spindle parameter.

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4. Results

Results are reported as they were originally published (Bódizs et al., 2014; Ujma et al., 2014)and (Ujma et al., submitted) with the exception that spectral analysis results are also reported in both studies where they were originally not (Ujma et al., 2014)and (Ujma et al., submitted).

4.1. Study 1 – Children

4.1.1. Basic biological and psychometric data

Mean age was 6.17 years (SD 1.5 years, range 3.8-8.5 years). Mean CPM score was 25.69 (SD 6.09, range 13-35). Male and female children did not differ in their age ($Mean_{male}$= 5.95; $Mean_{female}$=6.4; t=0.8; p>0.4) or CPM score ($Mean_{female}$= 24.47; $Mean_{male}$=27; t=1.12; p>0.25).

Unsurprisingly, CPM scores correlated very strongly and positively with age (r=0.76, p<0.001) without notable sex differences.

4.1.2. Sleep macrostructure and sleep spindles

Table 3 shows sleep macrostructure variables in the child sample.

	Mean	Minimum	Maximum	SD
Sleep duration (min)	538.9310	463.0000	633.0000	45.48438
Sleep efficiency (%)	95.1910	81.8902	99.7312	3.99250
WASO (min)	3.4483	0.0000	25.0000	5.66126
Sleep latency (min)	23.1839	2.0000	61.3333	17.53966
NonREM duration (min)	366.6897	289.6667	465.6667	39.44626
Relative NREM duration (%)	68.1265	53.9231	80.2294	5.66865
N1 duration (min)	2.1609	0.0000	6.3333	1.65381
Relative N1 duration (%)	0.4135	0.0000	1.3149	0.33943
N2 duration (min)	187.1034	91.0000	283.6667	43.47633
Relative N2 duration (%)	34.8415	16.1443	52.2678	8.09940
SWS duration (min)	177.4253	54.0000	269.3333	43.76950
Relative SWS duration (%)	32.8715	11.6631	53.7787	7.86736
REM duration (min)	172.2414	97.6667	291.6667	37.76177
Relative REM duration (%)	31.8735	19.7706	46.0769	5.66865

Table 3. Sleep macrostructure in the child sample.

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After correcting for multiple comparisons (correction for false discovery rate), longer sleep duration was significantly correlated with higher intelligence in the entire sample ($r=0.56$, $p<0.01$). This association was seen in both male and female children but only reached statistical significance in the combined sample. Longer NREM duration in female children and shorter sleep latency and shorter wake duration in male children is significantly associated with intelligence, but these correlations are not significant after correcting for multiple comparisons.

Table 4 shows sleep spindle descriptive data in the child sample. Sex differences were not significant in case of any sleep spindle parameter.

			Mean	SD	Min.	Max.				Mean	SD	Min.	Max.
Fp1	Slow	*Density*	7.11	0.73	5.92	8.77	Cz	Slow	*Density*	7.22	1.02	5.31	9.45
		Duration	1.82	0.33	1.10	2.43			*Duration*	1.74	0.37	0.98	2.32
		Amplitude	4.20	2.14	1.78	10.47			*Amplitude*	4.45	1.72	2.53	8.98
	Fast	*Density*	6.83	0.99	5.39	9.14		Fast	*Density*	7.74	0.84	6.08	8.97
		Duration	1.30	0.22	0.87	1.92			*Duration*	1.41	0.19	1.07	1.91
		Amplitude	4.71	1.69	2.54	8.53			*Amplitude*	7.77	1.95	4.38	12.11
Fp2	Slow	*Density*	7.09	0.78	5.75	8.95	C4	Slow	*Density*	7.30	0.93	5.46	9.38
		Duration	1.81	0.33	1.09	2.34			*Duration*	1.72	0.36	0.96	2.29
		Amplitude	4.16	2.05	1.77	9.44			*Amplitude*	3.50	1.49	1.82	7.54
	Fast	*Density*	6.87	0.94	5.49	9.23		Fast	*Density*	7.58	0.83	6.36	9.53
		Duration	1.27	0.18	0.94	1.83			*Duration*	1.37	0.19	1.08	1.90
		Amplitude	4.84	2.32	2.52	13.56			*Amplitude*	5.85	2.18	2.95	13.15
F7	Slow	*Density*	7.20	0.98	4.33	9.15	T4	Slow	*Density*	7.47	1.00	5.51	9.66
		Duration	1.80	0.30	1.28	2.36			*Duration*	1.69	0.37	0.95	2.30
		Amplitude	2.92	1.41	1.30	6.93			*Amplitude*	2.01	0.88	1.08	4.32
	Fast	*Density*	6.77	1.21	4.28	9.60		Fast	*Density*	7.42	1.18	5.50	10.15
		Duration	1.25	0.27	0.87	2.29			*Duration*	1.20	0.18	0.91	1.80
		Amplitude	3.62	2.15	1.44	12.94			*Amplitude*	2.96	2.30	1.23	13.44
F3	Slow	*Density*	7.11	0.71	5.89	8.74	T5	Slow	*Density*	7.48	1.14	4.43	9.61
		Duration	1.80	0.32	1.07	2.37			*Duration*	1.67	0.38	0.92	2.31
		Amplitude	5.14	2.38	2.47	10.30			*Amplitude*	2.07	1.56	0.95	9.26
	Fast	*Density*	7.17	0.83	6.04	9.00		Fast	*Density*	7.52	1.30	4.52	10.35
		Duration	1.33	0.19	0.97	1.89			*Duration*	1.23	0.20	0.79	1.80
		Amplitude	6.66	2.02	3.09	11.52			*Amplitude*	3.23	3.51	1.37	20.32
Fz	Slow	*Density*	7.12	0.76	5.83	8.84	P3	Slow	*Density*	7.29	1.06	4.55	9.37
		Duration	1.80	0.33	1.08	2.38			*Duration*	1.69	0.38	0.93	2.27
		Amplitude	5.87	2.73	2.56	11.83			*Amplitude*	2.67	1.00	1.59	5.27
	Fast	*Density*	7.38	0.77	6.13	9.13		Fast	*Density*	7.42	0.92	5.90	9.30
		Duration	1.34	0.19	1.04	1.88			*Duration*	1.38	0.20	1.04	1.97
		Amplitude	7.42	2.38	3.54	13.72			*Amplitude*	4.43	1.24	2.25	7.41
F4	Slow	*Density*	7.15	0.78	5.82	9.08	Pz	Slow	*Density*	7.04	1.31	2.83	9.07
		Duration	1.79	0.33	1.05	2.33			*Duration*	1.73	0.46	0.90	3.15
		Amplitude	5.13	2.60	2.17	10.82			*Amplitude*	3.34	1.44	0.67	6.64
	Fast	*Density*	7.24	0.81	6.20	9.25		Fast	*Density*	7.45	0.94	5.28	8.86
		Duration	1.34	0.17	1.05	1.86			*Duration*	1.48	0.22	0.96	2.05
		Amplitude	6.94	2.53	3.29	12.72			*Amplitude*	6.08	2.32	1.55	14.29
F8	Slow	*Density*	7.28	0.83	5.98	9.48	P4	Slow	*Density*	7.35	1.01	4.99	9.37
		Duration	1.76	0.33	1.02	2.27			*Duration*	1.67	0.38	0.94	2.27
		Amplitude	2.91	1.32	1.39	6.61			*Amplitude*	2.75	1.15	1.55	5.92
	Fast	*Density*	6.96	1.02	5.07	9.37		Fast	*Density*	7.38	1.08	3.89	9.23
		Duration	1.22	0.17	0.91	1.78			*Duration*	1.35	0.23	0.78	1.94
		Amplitude	3.70	2.21	1.57	12.98			*Amplitude*	4.50	1.61	1.94	9.79
T3	Slow	*Density*	7.38	1.23	3.73	9.59	T6	Slow	*Density*	7.57	1.09	4.81	9.63
		Duration	1.74	0.34	1.10	2.30			*Duration*	1.66	0.40	0.89	2.33
		Amplitude	2.14	1.17	1.03	6.34			*Amplitude*	1.96	1.15	0.89	6.34

	Fast	*Density*	7.22	1.36	4.19	10.34
		Duration	1.22	0.27	0.87	2.29
		Amplitude	2.95	2.09	1.16	12.01
C3	Slow	*Density*	7.29	0.91	5.62	9.09
		Duration	1.73	0.35	0.99	2.29
		Amplitude	4.24	4.36	1.89	25.77
	Fast	*Density*	7.44	1.01	4.90	9.42
		Duration	1.37	0.21	0.84	1.91
		Amplitude	7.13	9.35	2.86	55.17
		Slow spindle low frequency	10.36	0.47	9.59	11.43
		Slow spindle high frequency	11.04	0.50	10.13	12.13
		Slow spindle middle frequency	10.70	0.48	9.86	11.73
		Fast spindle low frequency	11.58	0.36	10.87	12.21
		Fast spindle high frequency	12.58	0.40	11.66	13.24
		Fast spindle middle frequency	12.08	0.37	11.26	12.70

	Fast	*Density*	7.63	1.21	5.78	10.24
		Duration	1.22	0.19	0.88	1.81
		Amplitude	2.99	2.52	1.29	14.57
O1	Slow	*Density*	7.36	1.26	4.36	9.85
		Duration	1.72	0.53	0.87	3.70
		Amplitude	3.06	3.55	1.12	19.85
	Fast	*Density*	7.65	1.97	4.28	15.74
		Duration	1.24	0.21	0.76	1.78
		Amplitude	4.48	5.58	1.46	29.76
O2	Slow	*Density*	7.50	1.19	4.39	9.81
		Duration	1.67	0.40	0.85	2.31
		Amplitude	2.43	1.61	1.05	9.60
	Fast	*Density*	7.56	1.24	4.86	9.75
		Duration	1.23	0.20	0.90	1.74
		Amplitude	3.61	3.59	1.43	21.25

Table 4. Sleep spindle descriptive statistics in children. Density is given in spindle/minute, duration in seconds and amplitude in μV.

No statistically significant differences (using independent-sample t-tests) were seen between the sleep spindle parameters of male and female children.

4.1.3. Correlations between EEG data and intelligence

There was no significant correlation between age and sleep spindle parameters when the entire sample was considered. Fast spindle density on Fz and O1 correlated positively and significantly with age, but these correlations did not constitute an area of significance.

A more in-depth analysis revealed that these correlations originated purely from the male subsample. In male subjects, an acceleration of slow spindle frequency ($r=0.54$, $p<0.05$), an increase in fast spindle density on F3, Fz, C4 and Cz and an increase in slow spindle density on T5, O1 and O2 was seen. These correlations ($0.5<r<0.65$), however, did not form an area of significance. In females, only a tendency for lower slow spindle density with increasing age was seen. This was only statistically significant on Fp2 and Cz and did not form an area of significance (Figure8).

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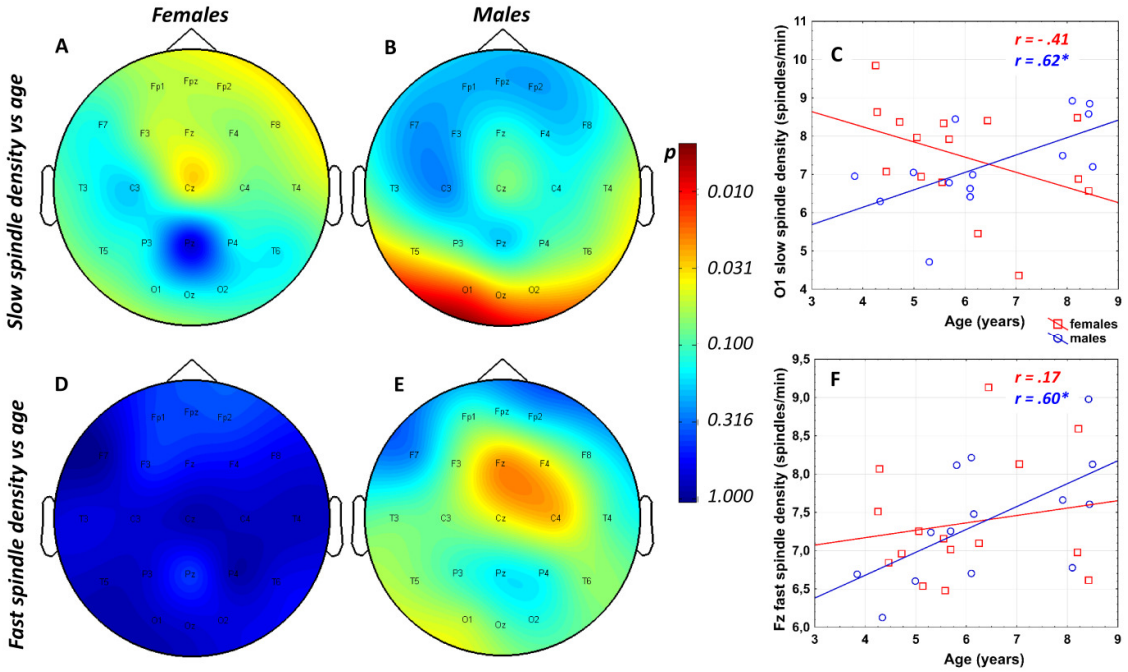

*Figure 8. The correlation between sleep spindle density and age in children. A. Significance probability map for the region-specific correlations depicting the age-related changes in sleep EEG slow spindle density in female children (effects are non-significant after correction for multiple comparisons). B. Significance probability map for the region-specific correlations depicting the age-related changes in sleep EEG slow spindle density in male children (effects are non-significant after correction for multiple comparisons). C. Scatterplot representing the correlation between left occipital (O1) slow spindle density and age in female and male children. D. Significance probability map for the region-specific correlations depicting the age-related changes in sleep EEG fast spindle density in female children (effects are non-significant after correction for multiple comparisons). E. Significance probability map for the region-specific correlations depicting the age-related changes in sleep EEG fast spindle density in male children (effects are non-significant after correction for multiple comparisons). F. Scatterplot representing the correlation between frontal midline (Fz) fast spindle density and age in female and male children. (P-values plotted on inverted logarithmic scale, * $p < .05$. Scatterplots represent the electrode where the effect was strongest. Electrodes Fpz and Oz are only shown for better localization)*

A similar sexual dimorphism was seen in the age-uncorrected correlates of CPM scores and sleep spindle parameters. In females no significant correlations were seen, except for one between slow spindle amplitude on T4 and CPM scores (r=0.527, p<0.05) which was insufficient to form an area of significance. In males, a positive

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correlation between CPM scores and fast spindle density on Fp1, F3, Fz, F4 and C4 was seen, forming an area of significance (Figure9).

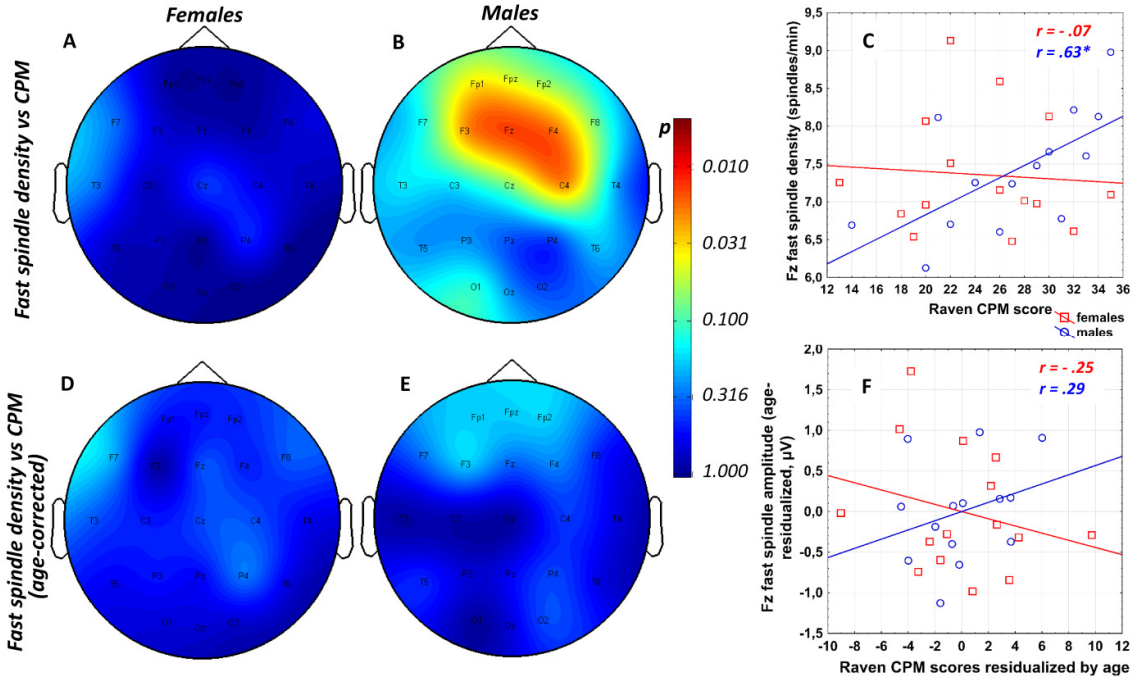

*Figure 9. Age-corrected and age-uncorrected correlation between fast sleep spindle density and Raven CPM scores in children. A. Significance probability map depicting the age-uncorrected associations between fast spindle densities and Raven CPM scores in female children. B. Significance probability map depicting the age-uncorrected associations between fast spindle densities and Raven CPM scores in male children. C. Scatterplot representing the age-uncorrected correlation between frontal midline (Fz) fast sleep EEG spindle density and Raven CPM scores in female and male children. D. Significance probability map depicting the age-corrected associations between fast spindle densities and Raven CPM scores in female children. E. Significance probability map for depicting the age-corrected associations between fast spindle densities and Raven CPM scores in male children. F. Scatterplot representing the age-corrected correlation between frontal midline (Fz) fast sleep EEG spindle density and Raven CPM scores in female and male children. The scatterplot illustrates residuals after regression for the effects of age, in order to reliably illustrate partial correlations. (P-values plotted on inverted logarithmic scale, * $p < .05$. Scatterplots represent the electrode where the effect was the strongest. Electrodes Fpz and Oz are only shown for better localization.)*

This pattern of correlation changed after correcting for the effects of age. In males, only a tendency for a negative correlation with fast spindle duration was seen with no

area of significance. In females, however, positive correlations with slow and fast spindle amplitude emerged (Table 5 and Table 6). While the correlations with fast spindles remained a tendency, the correlations with slow spindle amplitude formed a large area of significance along a sagittal line over both hemispheres (not including the midline) with a right temporal maximum (Figure 10).

	Slow spindles						Fast spindles					
	Density		Duration		Amplitude		Density		Duration		Amplitude	
	r	p	r	p	r	p	r	p	r	p	r	p
Fp1	-0.287	0.320	-0.281	0.330	0.539*	0.047	-0.178	0.542	0.177	0.544	0.384	0.175
Fp2	-0.151	0.606	-0.317	0.270	0.496	0.072	-0.210	0.471	0.237	0.416	0.322	0.261
F7	-0.277	0.337	-0.203	0.486	0.576*	0.031	-0.337	0.238	0.177	0.546	0.548	0.042
F3	-0.133	0.651	-0.325	0.258	0.603*	0.022	-0.035	0.905	0.163	0.577	0.418	0.137
Fz	-0.298	0.301	-0.338	0.238	0.332	0.246	-0.258	0.374	0.223	0.443	0.173	0.554
F4	-0.181	0.537	-0.305	0.289	0.505	0.065	-0.203	0.487	0.238	0.412	0.387	0.172
F8	-0.234	0.421	-0.250	0.389	0.635*	0.015	-0.268	0.355	0.213	0.466	0.367	0.197
T3	-0.291	0.312	-0.235	0.419	0.509	0.063	-0.258	0.374	0.148	0.613	0.672	0.008
C3	-0.289	0.316	-0.345	0.227	0.611*	0.020	-0.196	0.501	0.237	0.415	0.480	0.083
Cz	-0.059	0.841	-0.367	0.197	0.480	0.082	-0.250	0.388	0.246	0.396	0.314	0.275
C4	-0.248	0.394	-0.332	0.247	0.658*	0.011	-0.254	0.381	0.356	0.211	0.560	0.037
T4	-0.237	0.414	-0.312	0.278	0.701*	0.005	-0.151	0.608	0.123	0.675	0.548	0.043
T5	-0.269	0.353	-0.373	0.189	0.478	0.084	-0.157	0.591	0.145	0.622	0.316	0.271
P3	-0.282	0.328	-0.375	0.187	0.539*	0.047	-0.191	0.513	0.176	0.547	0.492	0.074
Pz	-0.125	0.670	-0.290	0.315	0.389	0.169	-0.174	0.552	0.312	0.278	0.192	0.510
P4	-0.323	0.261	-0.362	0.204	0.607*	0.021	-0.296	0.303	0.337	0.239	0.595	0.025
T6	-0.238	0.412	-0.381	0.179	0.477	0.085	-0.132	0.653	0.119	0.686	0.376	0.186
O1	-0.317	0.270	-0.377	0.184	0.547*	0.043	-0.123	0.674	0.263	0.365	0.519	0.057
O2	-0.238	0.412	-0.402	0.154	0.543*	0.045	-0.108	0.714	0.192	0.510	0.514	0.060

Table 5. Age-corrected correlations between sleep spindle parameters and CPM scores in female subjects. Electrodes belonging to an area of significance are indicated with an asterisk.

	Slow spindles						Fast spindles					
	Density		Duration		Amplitude		Density		Duration		Amplitude	
	r	p	r	p	r	p	r	p	r	p	r	p
Fp1	-0.324	0.281	0.316	0.293	-0.019	0.951	0.386	0.193	-0.363	0.223	0.339	0.257
Fp2	-0.363	0.223	0.339	0.257	0.113	0.713	0.395	0.182	-0.485	0.093	0.429	0.143
F7	-0.295	0.327	0.283	0.349	-0.018	0.954	0.315	0.294	-0.514	0.072	0.331	0.269
F3	-0.274	0.365	0.305	0.312	-0.062	0.840	0.389	0.190	-0.566	0.044	0.341	0.255
Fz	-0.345	0.249	0.319	0.288	-0.200	0.512	0.291	0.335	-0.567	0.044	0.210	0.491
F4	-0.285	0.345	0.324	0.280	0.040	0.897	0.326	0.276	-0.528	0.063	0.472	0.103
F8	-0.364	0.221	0.322	0.283	0.218	0.474	0.216	0.479	-0.379	0.201	0.450	0.123
T3	-0.170	0.578	0.212	0.486	0.153	0.618	-0.035	0.910	-0.471	0.104	0.346	0.247
C3	-0.268	0.377	0.311	0.301	0.323	0.282	-0.056	0.856	-0.574	0.040	0.345	0.248
Cz	-0.236	0.439	0.296	0.326	-0.076	0.806	0.040	0.897	-0.499	0.083	0.283	0.348
C4	-0.314	0.297	0.353	0.237	0.127	0.679	0.245	0.420	-0.514	0.072	0.430	0.143
T4	-0.168	0.584	0.263	0.386	0.285	0.346	-0.129	0.674	-0.513	0.073	0.355	0.234
T5	-0.128	0.677	0.237	0.436	0.362	0.224	-0.219	0.472	-0.662	0.014	0.365	0.220
P3	-0.093	0.763	0.249	0.412	0.039	0.898	-0.117	0.703	-0.553	0.050	0.228	0.454
Pz	-0.062	0.841	0.290	0.337	-0.219	0.473	-0.173	0.573	-0.515	0.072	-0.122	0.690
P4	-0.211	0.489	0.265	0.381	0.314	0.296	-0.256	0.399	-0.542	0.056	0.355	0.235
T6	-0.033	0.916	0.262	0.388	0.333	0.266	-0.146	0.633	-0.582	0.037	0.358	0.229
O1	-0.443	0.130	0.329	0.273	0.469	0.106	-0.027	0.931	-0.393	0.184	0.521	0.068
O2	-0.325	0.278	0.280	0.354	0.359	0.229	-0.263	0.386	-0.635	0.020	0.365	0.221

Table 6. Age-corrected correlations between sleep spindle parameters and CPM scores in male subjects.

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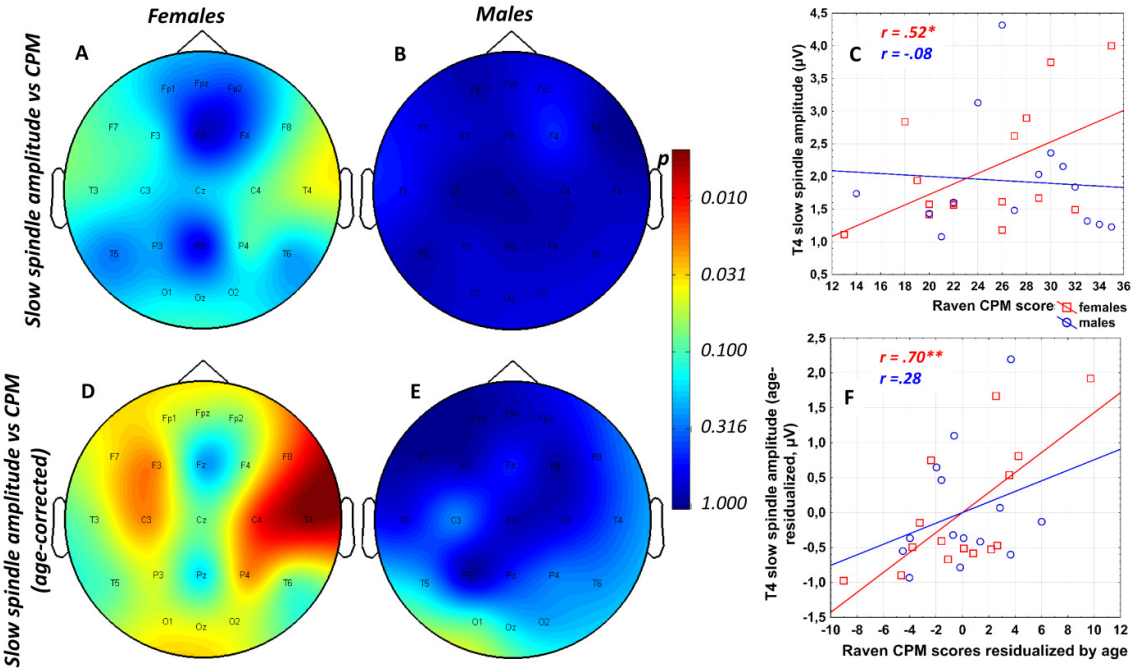

*Figure 10. Age-corrected and age-uncorrected correlations between slow sleep spindle amplitude and Raven CPM scores. A. Significance probability map for the region-specific correlations depicting the age-uncorrected associations between slow sleep spindle amplitudes and Raven CPM scores in female children. B. Significance probability map for the region-specific correlations depicting the age-uncorrected associations between slow sleep spindle amplitudes and Raven CPM scores in male children. C. Scatterplot representing the age-uncorrected correlation between right temporal (T4) slow sleep EEG spindle amplitude and Raven CPM scores in female and male children. D. Significance probability map for the region-specific correlations depicting the age-corrected associations between slow sleep spindle amplitudes and Raven CPM scores in female children. E. Significance probability map for the region-specific correlations depicting the age-corrected associations between slow sleep spindle amplitudes and Raven CPM scores in male children. F. Scatterplot representing the age-corrected correlation between right temporal (T4) slow sleep EEG spindle amplitude and Raven CPM scores in female and male children. The scatterplot illustrates residuals after regression for the effects of age, in order to reliably illustrate partial correlations. (P-values plotted on inverted logarithmic scale, * $p < .05$. Scatterplots represent the electrode where the effect was the strongest. Electrodes Fpz and Oz are only shown for better localization)*

A comparison of the strongest correlation coefficients illustrated on Figures 9 and 10 using Fisher's r to z method revealed that they do not reach significance (one-tailed

p=0.08 in case of age-corrected slow spindle amplitude on T4 and p=0.053 in case of age-uncorrected fast spindle density on Fz). Of course, the small sample size (N=14 for males and N=15 for females) must be taken into account when interpreting these results.

A spectral analysis using 10-base log-transformed spectra revealed a positive correlation between Raven scores and spectral power over the entire 8-16 Hz range in female children, which was significant both with and without controlling for the effects of age ($p<0.05/2$ in 80.2% of cases and $p<0.05/3$ in 68.7% of cases with age control, $p<0.05/2$ in 56.7% of cases and $p<0.05/3$ in 39.1% of cases without age control, respectively). In male children, no Rüger-significant association was seen between log-transformed spectral power in the 8-16 Hz range and intelligence with or without controlling for the effects of age.

No significant effects were seen in case of z-score spectra either in male or female children, regardless of the presence or absence of a statistical control for the effects of age.

Figure 11 illustrates the relationship between intelligence and log-transformed power spectral density in female and male subjects in the comparison most compatible with the other two studies, that is, after controlling for the effects of age.

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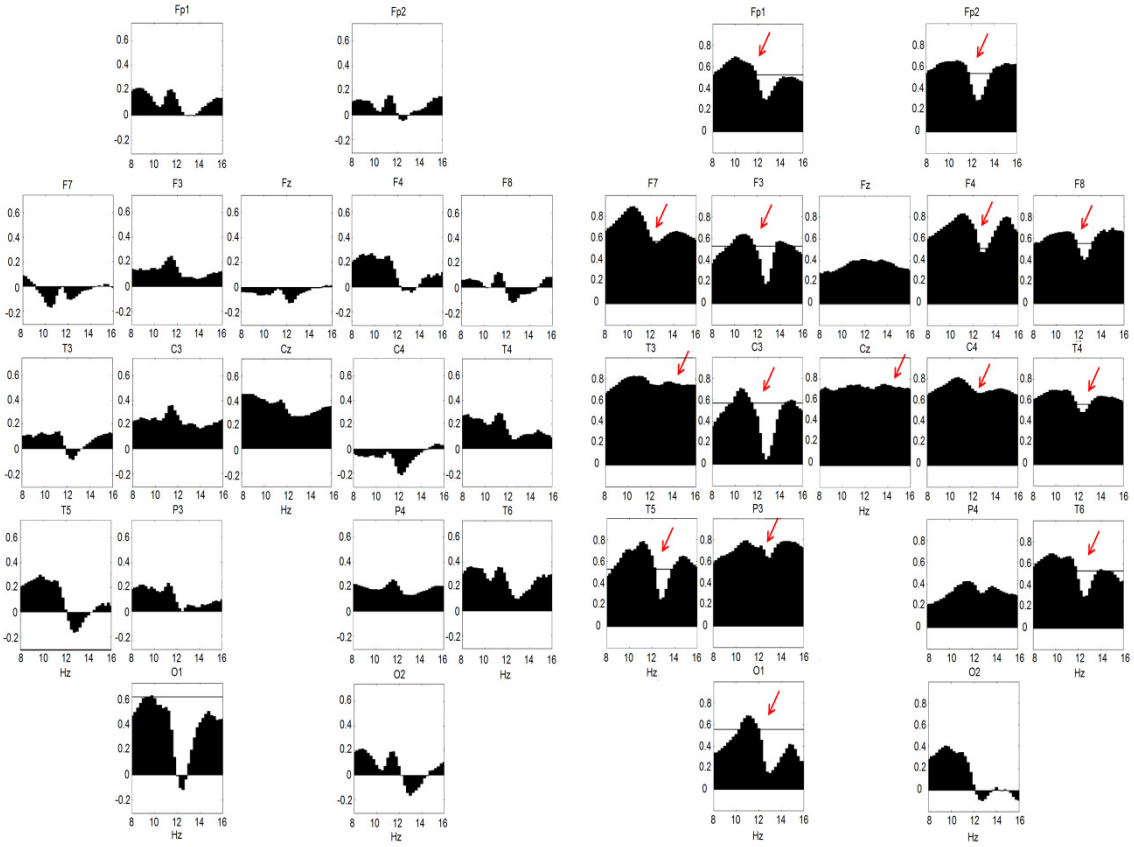

Figure 11. Correlation coefficients (axis y) at various frequencies from 8 Hz to 16 Hz (axis x) on all electrodes (subpanels) in male (left panel) and female (right panel) children. Horizontal lines parallel to axis x indicate the critical correlation coefficients in case of electrodes where at least one uncorrected correlation coefficient was significant. Red arrows indicate areas of correlations which are significant after correcting for multiple comparisons using the Rüger area method.

4.2. Study 2 – Adolescents

4.2.1. Basic biological and psychometric data

Age range was 15–22 years, while mean age was 18 years (SD: 2.3 years). Subjects were evenly distributed over the age range as an equal number (3 males and 3 males) of subjects were present over four evenly distributed age subgroups (groups of 15–16, 17–18, 19–20 and 21–22 years old subjects). Mean height of the subjects was 173.04 cm (range: 160–198, SD: 10.57). Subjects' weight averaged 63.83 kg (range: 47–92, SD:

11.92), while their body mass index (BMI) was between the normal limits (mean: 21.19, range: 17.68–27.01, SD: 2.6).

RPMT-derived IQ-scores of the sample resulted in a group average of 104.12 (range: 91–126, SD: 10.82). Neither age (r = .30; p = .15), nor weight (r = .13; p = .51), height (r = .14; p = .50) nor BMI (r = .06; p = .77) correlated significantly with IQ. Males and females did not differ in their general mental abilities (t = 0.31; p = .75) and a possible difference in age was eliminated by the deliberately symmetrical recruitment of male and female subjects from the same age 1-year ranges.

4.2.2. Sleep macrostructure and sleep spindles

Table 7 shows sleep macrostructure variables in the adolescent sample. Intelligence was significantly correlated with relative N2 duration in females (r=0.69, p=0.13), but not in males (r=-0.25, p=0.434). This correlation, however, did not survive correcting for multiple comparisons.

	Mean	Min	Max	SD
Total sleep time (min)	494.33	368.33	617.00	54.60
Sleep efficiency (%)	94.84	85.25	99.09	3.36
WASO (min)	19.50	1.00	81.66	19.02
Sleep latency (min)	10.72	2.00	38.00	10.09
NREM duration (min)	365.86	302.00	447.00	38.33
Relative NREM duration (%)	74.16	66.28	81.99	4.00
N1 duration (min)	10.68	3.00	33.66	6.36
Relative S1 duration (%)	2.16	0.62	6.28	1.23
N2 duration (min)	294.34	208.33	386.00	49.70
Relative S2 duration (%)	59.59	43.61	75.83	7.93
SWS duration (min)	60.83	3.00	162.33	37.15
Relative SWS duration (%)	12.40	0.56	33.98	7.70
REM duration (min)	128.47	66.33	170.00	27.35
Relative REM duration (%)	25.83	18.00	33.71	4.00

Table 7. Sleep macrostructure in adolescent subjects.

Table 8 shows descriptive data of the sleep spindle parameters of the adolescent sample.

	Slow spindles				Fast spindles			
	Mean	Min.	Max.	SD	Mean	Min.	Max.	SD

Density (spindle/min)	Fp2	7.13	5.34	9.22	1.16	Fp2	5.87	1.15	7.69	1.34
	F8	7.10	4.77	9.33	1.21	F8	6.05	3.81	7.76	0.88
	T4	6.98	3.97	9.45	1.47	T4	6.57	4.96	8.14	0.78
	T6	6.91	3.68	9.44	1.59	T6	6.88	5.54	8.14	0.77
	O2	6.86	3.27	9.51	1.66	O2	6.98	4.96	8.32	0.86
	Fp1	7.12	4.98	9.51	1.27	Fp1	6.25	3.99	7.73	0.94
	F7	6.89	0.62	9.47	1.93	F7	6.20	2.56	7.76	1.22
	T3	7.01	4.00	9.50	1.54	T3	6.83	5.07	8.24	0.90
	T5	6.91	3.65	9.48	1.63	T5	7.06	5.47	8.25	0.86
	O1	6.85	3.28	9.42	1.72	O1	7.03	4.92	8.29	1.00
	F4	7.13	5.20	9.11	1.12	F4	6.88	4.75	8.34	0.80
	C4	6.97	4.32	9.38	1.35	C4	7.45	5.95	8.73	0.75
	P4	6.82	3.68	9.35	1.57	P4	7.67	6.25	8.92	0.76
	F3	7.12	4.97	9.22	1.17	F3	7.03	5.02	8.30	0.91
	C3	6.97	4.07	9.36	1.41	C3	7.68	6.34	9.07	0.77
	P3	6.85	3.81	9.53	1.60	P3	7.81	6.56	9.25	0.81
	Fpz	7.09	4.95	9.16	1.20	Fpz	5.95	3.04	7.83	1.01
	Fz	7.09	5.14	9.08	1.09	Fz	7.13	5.12	8.71	0.89
	Cz	6.94	4.29	9.21	1.29	Cz	8.00	6.63	9.35	0.67
	Pz	6.72	3.62	9.21	1.53	Pz	8.18	6.76	9.89	0.77
	Oz	6.76	3.22	9.47	1.67	Oz	7.20	4.27	8.54	1.00
Duration (sec)	Fp2	1.41	0.89	2.70	0.43	Fp2	1.05	0.80	2.78	0.39
	F8	1.38	0.87	2.61	0.43	F8	0.96	0.79	1.14	0.08
	T4	1.33	0.82	2.49	0.42	T4	0.99	0.84	1.17	0.09
	T6	1.30	0.81	2.47	0.42	T6	1.03	0.84	1.23	0.10
	O2	1.28	0.81	2.54	0.42	O2	1.04	0.82	1.24	0.11
	Fp1	1.39	0.88	2.60	0.41	Fp1	0.98	0.80	1.16	0.08
	F7	1.82	0.86	12.95	2.44	F7	1.05	0.80	2.77	0.39
	T3	1.32	0.84	2.57	0.42	T3	1.00	0.84	1.23	0.10
	T5	1.30	0.83	2.56	0.43	T5	1.03	0.86	1.27	0.10
	O1	1.28	0.82	2.57	0.44	O1	1.06	0.85	1.29	0.11
	F4	1.41	0.88	2.69	0.43	F4	1.04	0.88	1.24	0.10
	C4	1.34	0.83	2.54	0.42	C4	1.11	0.91	1.30	0.11
	P4	1.31	0.83	2.58	0.43	P4	1.14	0.91	1.35	0.12
	F3	1.41	0.87	2.68	0.42	F3	1.05	0.88	1.23	0.09
	C3	1.34	0.84	2.66	0.43	C3	1.12	0.93	1.36	0.10
	P3	1.30	0.84	2.61	0.43	P3	1.15	0.95	1.42	0.11
	Fpz	1.40	0.88	2.69	0.44	Fpz	0.96	0.78	1.14	0.09
	Fz	1.41	0.87	2.78	0.44	Fz	1.07	0.88	1.41	0.12
	Cz	1.34	0.83	2.62	0.43	Cz	1.16	0.99	1.35	0.10
	Pz	1.31	0.82	2.59	0.43	Pz	1.21	0.99	1.50	0.12
	Oz	1.28	0.79	2.55	0.42	Oz	1.08	0.82	1.30	0.12
Amplitude (µV)	Fp2	4.65	1.66	10.92	2.21	Fp2	5.15	3.44	7.91	1.05
	F8	4.05	1.39	8.22	1.71	F8	4.86	3.39	6.97	0.88
	T4	3.49	1.26	6.83	1.37	T4	4.93	3.38	7.30	0.90
	T6	3.37	1.22	6.07	1.27	T6	5.24	3.64	7.88	1.10
	O2	3.21	1.14	5.34	1.23	O2	5.03	3.37	7.34	1.14
	Fp1	4.55	1.44	10.20	2.22	Fp1	4.92	3.48	6.95	0.87
	F7	5.04	1.43	19.71	3.68	F7	6.63	3.38	44.59	8.32
	T3	3.56	1.26	7.10	1.50	T3	4.95	3.27	7.18	0.89
	T5	3.39	1.19	6.33	1.30	T5	5.24	3.55	7.39	1.00
	O1	3.23	1.14	5.34	1.15	O1	5.23	3.32	6.68	1.15
	F4	5.41	1.79	11.14	2.46	F4	7.07	4.62	10.52	1.57
	C4	4.23	1.49	8.92	1.84	C4	7.05	4.80	10.44	1.49
	P4	3.72	1.40	7.22	1.50	P4	6.94	4.34	10.39	1.52
	F3	5.50	1.68	12.42	2.68	F3	6.87	4.43	9.16	1.42
	C3	4.28	1.51	9.15	1.88	C3	7.22	4.49	10.47	1.43
	P3	3.81	1.41	7.41	1.58	P3	7.19	4.31	9.62	1.49
	Fpz	4.07	1.62	8.76	1.86	Fpz	4.51	3.09	6.07	0.83
	Fz	5.41	1.87	12.41	2.67	Fz	7.40	4.27	11.29	1.98
	Cz	4.40	1.56	8.99	1.84	Cz	8.53	5.18	13.06	2.02
	Pz	3.61	1.42	6.44	1.41	Pz	8.04	5.08	12.33	1.83
	Oz	2.86	1.04	4.95	1.12	Oz	4.80	2.88	6.66	1.23

Table 8. Sleep spindle parameters in adolescent subjects.

Female subjects had significantly longer fast spindle durations on Fpz ($Mean_{male}$=0.92, $Mean_{female}$=0.99, t=-2.25, p=0.03), and higher fast spindle amplitudes on Cz ($Mean_{male}$=7.66, $Mean_{female}$=9.33, t=-2.12, p=0.04), Pz ($Mean_{male}$=7.22, $Mean_{female}$=8.78, t=-2.22, p=0.04), Oz ($Mean_{male}$=4.1, $Mean_{female}$=5.44, t=-3.07, p=0.005), P3 ($Mean_{male}$=6.5, $Mean_{female}$=7.81, t=-2.29, p=0.03), F4 ($Mean_{male}$=6.38, $Mean_{female}$=7.68, t=-2.15, p=0.04) and O1 ($Mean_{male}$=4.69, $Mean_{female}$=5.72, t=-2.35, p=0.02).

4.2.3. Correlations between EEG data and intelligence

IQ was shown to be significantly and positively related to average fast spindle density (r=.43; p = .04) and amplitude (r=.41; p=.049). While females were characterized by significant fast spindle density vs. IQ, as well as fast spindle amplitude vs. IQ correlations [r=.80 (p=.002) and r=.67 (p =.012), respectively, males were not [r=.00 (p=.99) for both measures]. Differences between the correlation coefficients depicting the linear relationship between fast spindle density vs. IQ of females and males was significant (p=.017, one-sided). However, the female-male difference in fast spindle amplitude vs. IQ correlation proved to be a tendency only (p=.055, one-sided). One-sided statistics were used because of our explicit hypothesis on female predominance in the spindle vs. IQ correlations.

The region-specific analysis of the fast spindle density vs. IQ correlation of females revealed significant correlations in 21 out of 21 derivations, 19 of which were significant at the level of .025 (Figure 12). Thus, findings fulfill the criteria for rejecting the global null hypothesis. Maximal significances were revealed over the frontal midline region (r=.90; p=.0001 at derivation Fz).

Likewise, the region-specific analysis of the fast spindle amplitude vs. IQ correlation of females revealed significant correlations in 12 out of 21 derivations (Fp1, Fpz, F3, F7, Fz, C3, Cz, P3, P4, Pz, T3, T6), 8 of which were significant at the level of .025 (Figure 13). Again, based on these findings the global null hypothesis can be rejected. Maximal significances were revealed over the left central region (r=.82; p=.001 at derivation C3).

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In order to test whether individual levels of fast sleep spindling age-independently predict general mental ability in adolescent females, partial correlations were calculated and entered in the procedure of descriptive data analysis and significance probability mapping (Figure 14). We found 13 significant correlations (out of 21) between FS density and IQ with the effects of age corrected for. The Rüger's area consisted of a wide region including frontopolar-prefrontal, central, parietal and posterior temporal locations (Fp1, Fpz, F3, F4, Fz, C3, C4, Cz, T5, T6, P3, P4, Pz) with p values less than .025 at 11 derivations. Thus, the area includes significant fast spindle density vs. IQ partial correlation (with the effects of age held constant) in adolescent females. Maximal correlation emerged at the frontal midline derivation Fz (r=.90; p=.0002).

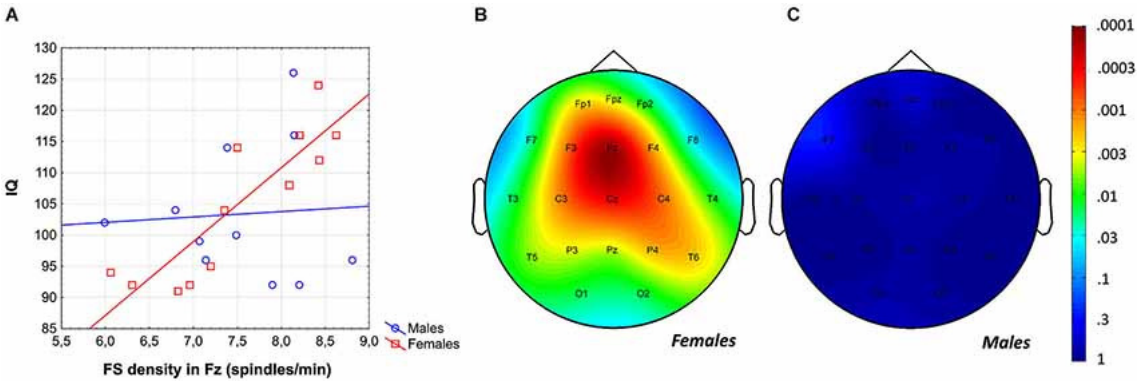

Figure 12. Gender-specific sleep EEG fast spindle (FS) density vs. IQ relationship in adolescents. (A) Scatterplot representing the frontal midline FS density vs. IQ relationship. (B) Significance probability map of the FS density vs. IQ correlations in females. (C) Significance probability map of the FS density vs. IQ correlations in males. P-values are plotted on inverted logarithmic scale.

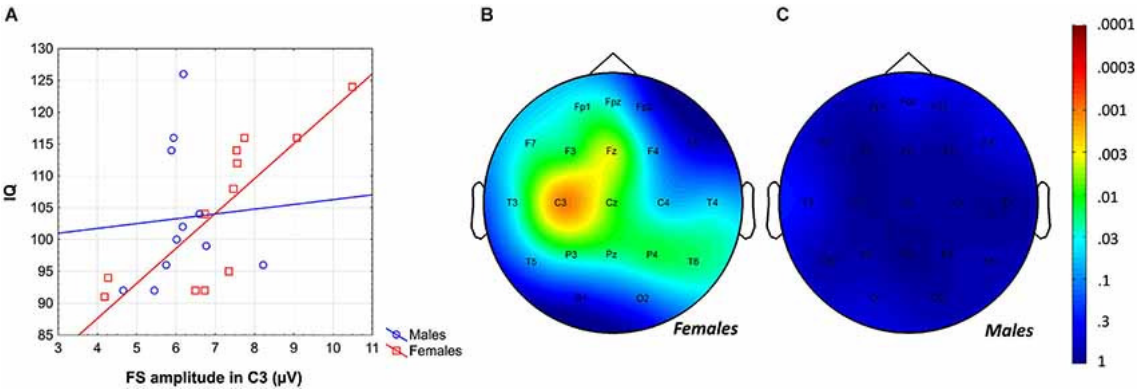

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Figure 13. Gender-specific sleep EEG fast spindle (FS) amplitude vs. IQ relationship in adolescents. (A) Scatterplot representing the frontal midline FS amplitude vs. IQ relationship. (B) Significance probability map of the FS amplitude vs. IQ correlations in females. (C) Significance probability map of the FS amplitude vs. IQ correlations in males. P-values are plotted on inverted logarithmic scale.

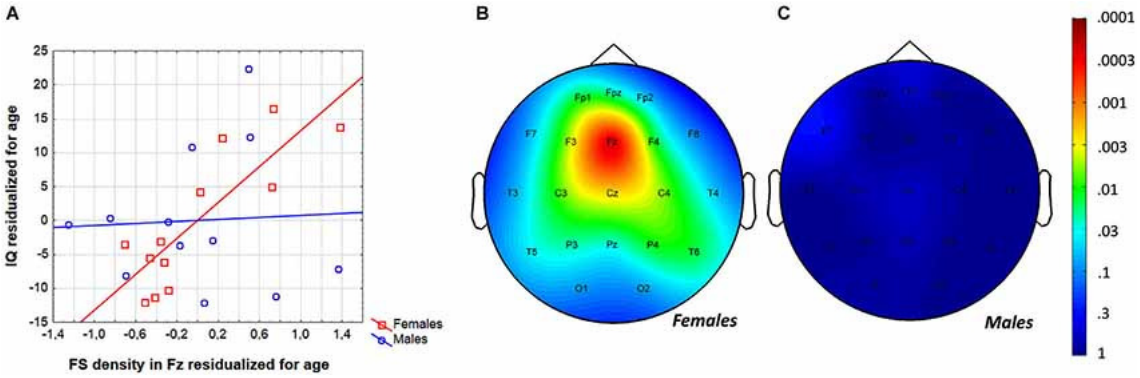

Figure 14. Age-independence of the sleep EEG fast spindle (FS) density vs. IQ relationship in females. (A) Scatterplot representing the partial correlations between FS density and IQ (both were residualized for age). (B) Significance probability map of the FS density vs. IQ partial correlations (effects of age partialled out) in females. (C) Significance probability map of the FS density vs. IQ partial correlations (effects of age partialled out) in males. P-values are plotted on inverted logarithmic scale.

The same analyses were run with fast spindle amplitudes. Eight out of 21 partial correlations were significant in adolescent females, depicting a scattered parasagittal area (F7, Fz, C3, Cz, T6, P3, P4, Pz) with four p values being less than .025. Thus, the null hypothesis cannot be unambiguously rejected for this Rüger's area.

In males, a significant correlation of fast spindle frequency with IQ was revealed (r = .60; p = .04; Figure 15). Correcting for the effects of age even slightly increased the strength of this relationship (r = .65; p = .04). However, no other correlation between sleep spindle measures and IQ in males proved to be significant.

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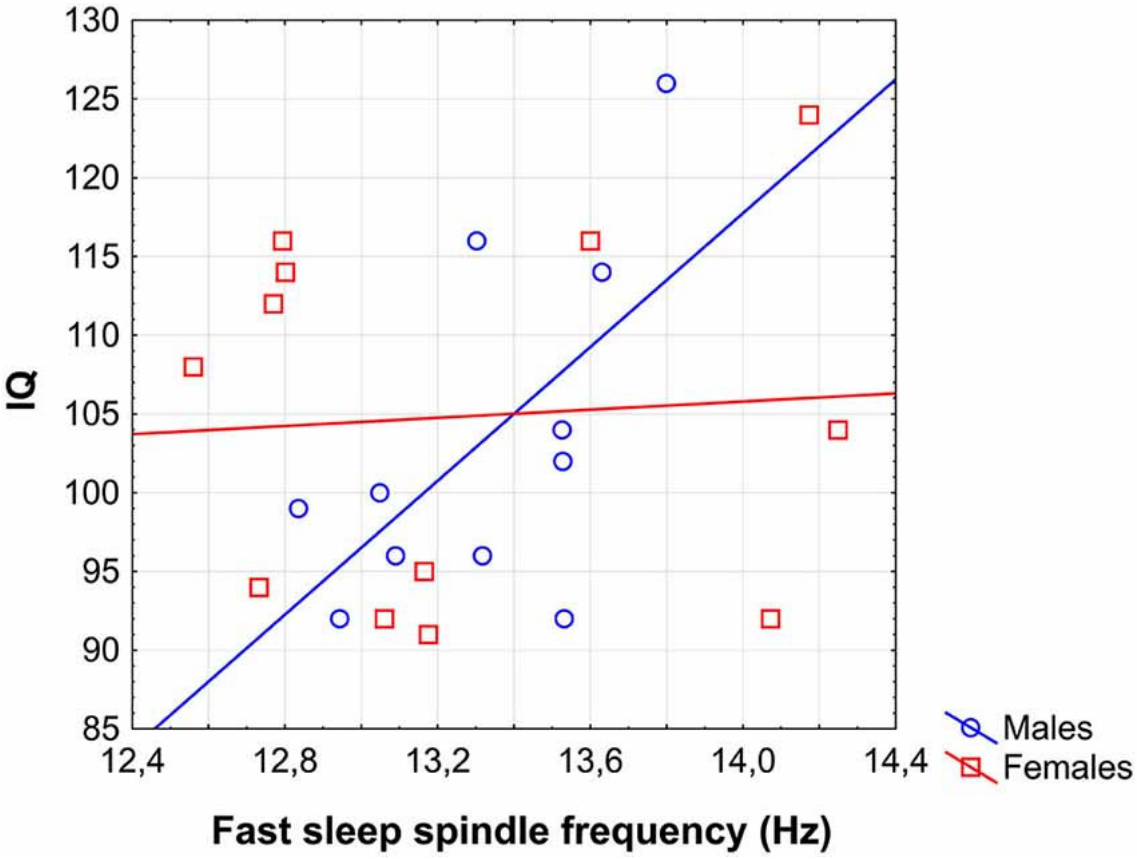

Figure 15. Scatterplot representing the correlation between sleep EEG FS frequency and IQ in males.

In females, neither log-transformed EEG powers nor z-scores revealed significant associations with IQ after the Rüger area correction, with or without control for the effects of age.

In males, however, a positive association between log-transformed EEG power on F3, C3 and C4 between 13.75 and 15 Hz (r_{max} = .70; p = .014 on F3 at 14 Hz) is significant after Rüger correction, while there is a tendency (with significant correlations not surviving Rüger correction) for a negative correlation between IQ and log-transformed power between 12.75 and 13 Hz on T5 and Pz (Figure 16). Using EEG power z-scores, a significant negative correlation between IQ and power is present between 12 and 13.25 Hz on C3, C4, P3, P4, Pz, T3, T4, T5, T6, O1 and O2 (r_{max} = -.78; p = .001 on T5 at 12.75 Hz; Figure 16). Similar results were obtained if age-controlled correlations were used. In this case, no Rüger-significant effects are evident in females, while there

is a significant negative correlation between IQ and power z-scores between 12 and 13.5 Hz (on C3, P3, P4, Pz, T3, T4, T5, T6, O1, O2, and Oz) in males. The positive correlation between IQ and log power is present between 13.75 and 15 Hz (on F3, C3, and C4) in males, but does not reach significance after correcting with the Rüger area method.

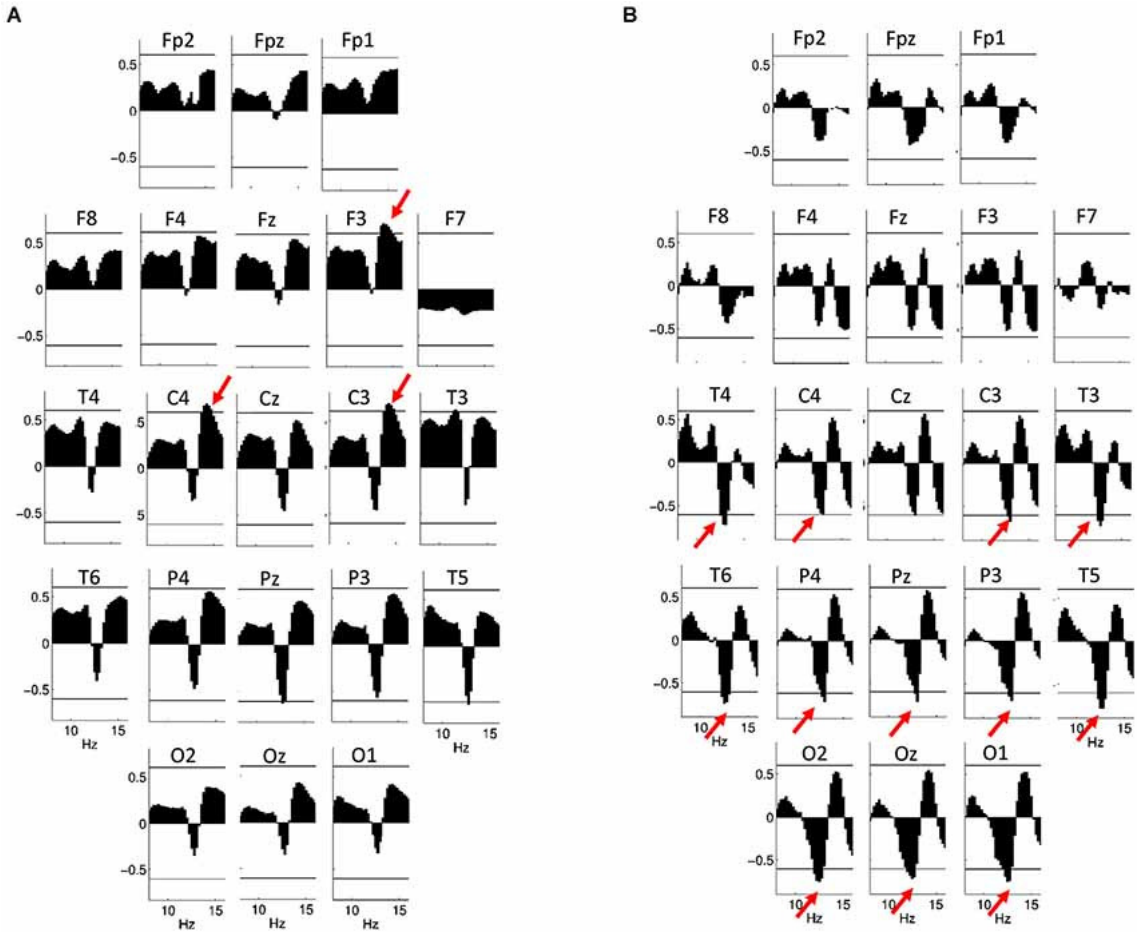

Figure 16. Correlations between NREM sleep EEG spectral power of 8–16 Hz frequency and IQ in males. Graphs are indicating region-specific correlations as revealed at different scalp locations. Horizontal lines denote critical values for $p < 0.05$. ***(A)*** *Binwise spectral data were log-transformed (10-base) before implementing correlation analyses. Positive correlations of NREM sleep EEG 13.75–15 Hz spectral power at derivations F3, C3 and C4 with IQ (red arrows) are significant after controlling for multiple testing according to the procedure of descriptive data analysis.****(B)*** *Binwise spectral data were z-transformed before implementing correlation analyses. Negative correlations of NREM sleep EEG 12–13.25 Hz spectral power at derivations C3, C4, P3, P4, Pz, T3, T4, T5, T6, O1, O2 and Oz with IQ (red arrows) are*

significant after controlling for multiple testing according to the procedure of descriptive data analysis

4.3. Study 3 – Adults

4.3.1. Basic biological and psychometric data

Mean age of subjects was 29.7 years (standard deviation 10.7 years, range: 17-69 years). Mean Raven equivalent score was 26.8 (standard deviation: 6.2, range: 10.5-36). There was no difference between age ($F=1.16$, $p>0.9$) or Raven equivalent scores ($F=1.36$, $p>0.1$) of males (mean age: 29.5 years, SD: 10.4; mean Raven: 27.5, SD: 5.7) and females (mean age: 29.3 years, SD: 11.2; mean Raven: 26.0, SD: 6.7).

4.3.2. Sleep macrostructure and sleep spindles

Table 9 shows sleep macrostructure variables in the adult sample. Sleep macrostructure was not significantly correlated with intelligence with or without age correction and with or without the separate analysis of males and females.

	Mean	Minimum	Maximum	SD
Sleep duration (min)	441.3520	271.3333	607.6667	46.61235
Sleep efficiency (%)	88.5966	55.4874	98.6241	7.39900
WASO (min)	30.4438	0.3333	134.6667	28.16106
Sleep latency (min)	29.7250	1.0000	121.0000	20.64266
NonREM duration (min)	332.0331	207.3333	459.3333	32.72640

Relative NonREM duration (%)	75.4232	63.6364	86.5604	4.49874
N1 duration (min)	16.3499	1.6667	86.3333	12.36285
Relative N1 duration (%)	3.8066	0.3618	19.0722	2.99318
N2 duration (min)	236.1408	121.3333	379.6667	37.89928
Relative N2 duration (%)	53.5469	35.4766	70.4316	7.00109
SWS duration (min)	79.5424	2.0000	172.0000	28.69109
Relative SWS duration (%)	18.0697	0.4615	37.7469	6.44168
REM duration (min)	109.3188	48.0000	189.0000	26.65566
Relative REM duration (%)	24.5768	13.4396	36.3636	4.49874

Table 9. Sleep macrostructure in the adult sample. These data include one female subject who was excluded from analyses involving intelligence due to her missing IQ test score. Movement artifacts are not included in relative sleep and wake durations.

Table 10 shows descriptive data of sleep spindle parameters in the adult sample, as adopted from (Ujma et al., 2015a). Mean peak frequency was 11.43 Hz (standard deviation .76 Hz, range 9.59-13.28 Hz) for slow spindles and 13.72 Hz (standard deviation .59 Hz, range 12.5-15.38 Hz) for fast spindles.

		Mean	SD			Mean	SD
C3				**Fz**			
Slow spindles	*Density*	6.830	1.428	Slow spindles	*Density*	6.876	1.245
	Duration	1.413	0.467		*Duration*	1.435	0.462
	Amplitude	3.548	1.848		*Amplitude*	4.902	2.507
Fast spindles	*Density*	7.176	0.921	Fast spindles	*Density*	6.571	1.007
	Duration	1.074	0.141		*Duration*	1.435	0.462
	Amplitude	5.471	1.533		*Amplitude*	5.588	1.732
C4				**O1**			
Slow spindles	*Density*	6.878	1.430	Slow spindles	*Density*	6.737	1.947
	Duration	1.411	0.462		*Duration*	1.365	0.476
	Amplitude	3.638	1.831		*Amplitude*	2.460	1.406

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Fast spindles	*Density*	6.878	1.430	Fast spindles	*Density*	7.062	1.104
	Duration	1.411	0.462		*Duration*	1.073	0.146
	Amplitude	5.542	1.536		*Amplitude*	4.062	1.395
Cz				**O2**			
Slow spindles	*Density*	6.692	1.526	Slow spindles	*Density*	6.728	1.944
	Duration	1.381	0.465		*Duration*	1.366	0.479
	Amplitude	4.211	2.094		*Amplitude*	2.479	1.377
Fast spindles	*Density*	6.692	1.526	Fast spindles	*Density*	7.051	1.109
	Duration	1.381	0.465		*Duration*	1.066	0.142
	Amplitude	7.324	2.076		*Amplitude*	3.975	1.319
F3				**P3**			
Slow spindles	*Density*	6.920	1.193	Slow spindles	*Density*	6.743	1.741
	Duration	1.459	0.459		*Duration*	1.376	0.471
	Amplitude	4.518	2.341		*Amplitude*	3.050	1.687
Fast spindles	*Density*	6.323	0.982	Fast spindles	*Density*	7.506	0.932
	Duration	1.014	0.117		*Duration*	1.110	0.149
	Amplitude	4.846	1.525		*Amplitude*	5.773	1.670
F4				**P4**			
Slow spindles	*Density*	6.966	1.182	Slow spindles	*Density*	6.761	1.754
	Duration	1.456	0.456		*Duration*	1.371	0.473
	Amplitude	4.585	2.316		*Amplitude*	2.992	1.616
Fast spindles	*Density*	6.357	0.996	Fast spindles	*Density*	7.468	0.961
	Duration	1.456	0.456		*Duration*	1.104	0.150
	Amplitude	4.945	1.541		*Amplitude*	5.532	1.646
F7				**T3**			
Slow spindles	*Density*	6.953	1.318	Slow spindles	*Density*	6.927	1.521
	Duration	1.420	0.455		*Duration*	1.388	0.470
	Amplitude	3.253	1.617		*Amplitude*	2.312	1.201
Fast spindles	*Density*	5.561	1.101	Fast spindles	*Density*	6.210	1.142
	Duration	0.964	0.102		*Duration*	0.993	0.113
	Amplitude	2.998	0.875		*Amplitude*	2.529	0.702
F8				**T4**			
Slow spindles	*Density*	6.979	1.334	Slow spindles	*Density*	6.929	1.546
	Duration	1.418	0.456		*Duration*	1.379	0.466
	Amplitude	3.303	1.626		*Amplitude*	2.348	1.198
Fast spindles	*Density*	5.534	1.099	Fast spindles	*Density*	6.031	1.228
	Duration	0.960	0.101		*Duration*	0.985	0.117
	Amplitude	3.039	0.885		*Amplitude*	2.601	0.785
Fp1				**T5**			
Slow spindles	*Density*	7.043	1.228	Slow spindles	*Density*	6.753	1.808
	Duration	1.448	0.455		*Duration*	1.354	0.480
	Amplitude	3.755	1.943		*Amplitude*	2.276	1.293
Fast spindles	*Density*	5.500	1.061	Fast spindles	*Density*	6.849	1.058
	Duration	0.969	0.099		*Duration*	1.045	0.139
	Amplitude	3.325	1.010		*Amplitude*	3.279	1.074
Fp2				**T6**			
Slow spindles	*Density*	7.064	1.238	Slow spindles	*Density*	6.785	1.852
	Duration	1.445	0.454		*Duration*	1.348	0.475
	Amplitude	3.783	1.927		*Amplitude*	2.241	1.213
Fast spindles	*Density*	5.569	1.070	Fast spindles	*Density*	6.750	1.074
	Duration	0.965	0.098		*Duration*	1.033	0.132
	Amplitude	3.345	1.031		*Amplitude*	3.108	0.876

Table 10. Descriptive data of sleep spindle parameters in the adult sample (Ujma et al., 2015a). Density is given in spindle/minute, duration in seconds and amplitude in μV. These data include one female subject who was excluded from analyses involving intelligence due to her missing IQ test score.

Sex differences were found in various sleep spindle parameters. Women had significantly higher fast spindle amplitudes in derivations F3 ($Mean_{male}$=4.61, $Mean_{female}$=5.13, t=-2.18, p=0.03), F4 ($Mean_{male}$=4.66, $Mean_{female}$=5.3, t=-2.66, p=0.008), Fz ($Mean_{male}$=5.29, $Mean_{female}$=5.99, t=-2.39, p=0.02), C3 ($Mean_{male}$=5.20, $Mean_{female}$=5.82, t=-2.55, p=0.01), C4 ($Mean_{male}$=5.24, $Mean_{female}$=4.92, t=-2.83,

p=0.005), Cz ($Mean_{male}$= 6.81, $Mean_{female}$=8.02, t=-3.55, p=0.0005), P3 ($Mean_{male}$=5.43, $Mean_{female}$=6.2, t=-2.99, p=0.003), P4 ($Mean_{male}$=5.22, $Mean_{female}$=5.91, t=-2.66, p=0.009), T6 ($Mean_{male}$=2.97, $Mean_{female}$=3.28, t=-2.07, p=0.04), O1 ($Mean_{male}$=3.81, $Mean_{female}$=4.36, t=-2.51, p=0.01), and O2 ($Mean_{male}$=3.77, $Mean_{female}$=4.22, t=-2.14, p=0.03), and higher peak frequencies (Hz) both in case of slow ($Mean_{male}$=11.28, $Mean_{female}$=11.61, t=-2.82, p=0.005) and fast ($Mean_{male}$=13.55, $Mean_{female}$=13.92, t=-4.13, p=0.00006) spindles. Men had significantly higher fast spindle densities (No./min) on derivations P3 ($Mean_{male}$=7.64, $Mean_{female}$=7.34, t=2.00, p=0.04), P4 ($Mean_{male}$=7.60, $Mean_{female}$=7.30, t=2.00, p=0.04), O1 ($Mean_{male}$=7.24, $Mean_{female}$=6.84, t=2.35, p=0.02) and O2 ($Mean_{male}$=7.29, $Mean_{female}$=6.76, t=3.08, p=0.002), and significantly higher fast spindle durations on O2 ($Mean_{male}$=1.09, $Mean_{female}$=1.03, t=2.57, p=0.01).

4.3.3. Correlations between EEG data and intelligence

Strong sex differences were found in correlations between sleep spindle parameters and Raven equivalent scores. In females, age-corrected partial correlations were significant between Raven equivalent scores and fast spindle amplitude (central, frontal and parietal derivations, r_{max}=0.412 on Cz) and slow spindle duration (all derivations with the exception of C3, r_{max}=0.379 on T3). In males, age-corrected partial correlations revealed a negative association between Raven equivalent scores and fast spindle density (posterior derivations, r_{max}=-0.337 on O1). After correction for multiple testing, partial correlation coefficients were significant between Raven equivalent scores and fast spindle amplitude (electrodes Cz, C3, C4, Fz) and slow spindle duration (electrodes F7, F8, T3, T4, T5, T6, Cz, Fz) in females, as well as fast spindle density (electrodes O1, O2, P3, P4, T5) in males. Age-uncorrected correlations were not considered in this study since the robust effects of age on sleep spindling in the wide age range we analyzed made age-corrected correlations more viable.

Table 11 gives an overview of the partial correlations found in females. Table 12 gives an overview of the partial correlations found in males. Table 13 gives an overview of partial correlations in all subjects. Figure 17 illustrates the most prominent partial correlations between Raven equivalent scores, fast spindle amplitude, slow spindle duration and fast spindle density in both sexes.

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			Slow Spindles								Fast Spindles							
			Density		Duration		Median Amplitude		Maximum Amplitude		Density		Duration		Median Amplitude		Maximum Amplitude	
	N	*df*	*R*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Fp1	72	69	0,273	0,036	0,271	0,038	-0,075	0,570	-0,081	0,540	0,114	0,391	0,056	0,672	0,285	0,029	0,292	0,025
Fp2	72	69	0,291	0,026	0,262	0,045	-0,086	0,516	-0,094	0,480	0,140	0,290	0,089	0,505	0,265	0,042	0,267	0,041
Fz	60	57	0,286	0,028	0,338*	0,009	-0,187	0,156	-0,188	0,155	0,089	0,503	0,050	0,709	0,334	0,010	0,335*	0,010
F3	72	69	0,265	0,042	0,260	0,047	-0,076	0,568	-0,083	0,533	0,107	0,421	0,101	0,447	0,274	0,036	0,277	0,034
F4	72	69	0,261	0,046	0,262	0,045	-0,102	0,441	-0,108	0,417	0,127	0,336	0,120	0,364	0,277	0,034	0,281	0,031
F7	60	57	0,328	0,011	0,368*	0,004	-0,162	0,220	-0,166	0,208	-0,012	0,930	-0,019	0,889	0,183	0,167	0,185	0,160
F8	60	57	0,328	0,011	0,374*	0,004	-0,165	0,213	-0,167	0,207	0,059	0,656	0,015	0,910	0,234	0,075	0,231	0,078
C3	72	69	0,247	0,060	0,254	0,052	-0,110	0,408	-0,117	0,379	0,082	0,537	0,133	0,316	0,365	0,004	0,367*	0,004
C4	72	69	0,259	0,047	0,259	0,048	-0,131	0,324	-0,135	0,308	0,134	0,310	0,130	0,327	0,371	0,004	0,371*	0,004
Cz	60	57	0,295	0,023	0,356*	0,006	-0,194	0,142	-0,194	0,142	0,083	0,533	0,092	0,488	0,412	0,001	0,410*	0,001
P3	72	69	0,231	0,078	0,268	0,040	-0,148	0,264	-0,150	0,256	0,036	0,788	0,135	0,308	0,281	0,031	0,283	0,030
P4	72	69	0,241	0,066	0,270	0,039	-0,136	0,305	-0,140	0,290	0,084	0,528	0,126	0,340	0,282	0,030	0,284	0,029
T3	60	57	0,314	0,015	0,379*	0,003	-0,172	0,193	-0,176	0,183	0,027	0,837	0,019	0,887	0,210	0,110	0,203	0,123
T4	60	57	0,306	0,018	0,374*	0,004	-0,214	0,104	-0,214	0,104	-0,017	0,898	-0,010	0,940	0,030	0,819	0,027	0,842
T5	60	57	0,288	0,027	0,372*	0,004	-0,226	0,085	-0,223	0,089	-0,019	0,886	0,070	0,598	0,152	0,251	0,154	0,245
T6	60	57	0,312	0,016	0,363*	0,005	-0,282	0,030	-0,278	0,033	0,033	0,806	0,045	0,737	0,059	0,656	0,064	0,629
O1	72	69	0,258	0,049	0,263	0,045	-0,173	0,191	-0,173	0,189	0,027	0,841	0,116	0,380	0,158	0,233	0,160	0,225
O2	72	69	0,273	0,036	0,261	0,046	-0,190	0,149	-0,194	0,141	0,089	0,503	0,122	0,359	0,129	0,330	0,133	0,316

Table 11. Partial Pearson correlation coefficients (corrected for Age) between sleep spindle parameters and Raven APM scores in female subjects. In the first two columns, the number of available subjects and the corresponding degrees of freedom are given for each electrode. Correlations which remain significant after multiple comparisons correction are marked with an asterisk.

			Slow Spindles								Fast Spindles							
			Density		Duration		Median Amplitude		Maximum Amplitude		Density		Duration		Median Amplitude		Maximum Amplitude	
	N	*df*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Fp1	88	85	-0,016	0,890	-0,100	0,379	-0,102	0,370	-0,101	0,374	-0,182	0,106	-0,123	0,278	-0,173	0,126	-0,177	0,117
Fp2	88	85	0,005	0,963	-0,102	0,366	-0,087	0,442	-0,077	0,500	-0,168	0,135	-0,090	0,429	-0,172	0,128	-0,165	0,145
Fz	81	78	0,045	0,690	-0,080	0,481	-0,038	0,741	-0,030	0,791	-0,241	0,032	-0,086	0,450	-0,110	0,330	-0,109	0,337
F3	88	85	0,043	0,707	-0,083	0,466	-0,065	0,565	-0,057	0,617	-0,241	0,031	-0,107	0,345	-0,124	0,274	-0,125	0,271
F4	88	85	0,012	0,917	-0,095	0,401	-0,078	0,493	-0,068	0,552	-0,211	0,060	-0,041	0,719	-0,136	0,228	-0,134	0,236
F7	81	78	0,045	0,694	-0,094	0,405	-0,036	0,754	-0,030	0,792	-0,172	0,128	-0,073	0,520	-0,093	0,413	-0,087	0,445
F8	81	78	0,027	0,815	-0,108	0,341	-0,078	0,492	-0,071	0,530	-0,167	0,139	-0,027	0,816	-0,145	0,199	-0,134	0,237
C3	88	85	0,096	0,395	-0,099	0,384	-0,073	0,518	-0,065	0,568	-0,238	0,033	-0,127	0,262	-0,114	0,316	-0,110	0,331
C4	88	85	0,064	0,573	-0,109	0,335	-0,093	0,411	-0,083	0,462	-0,219	0,051	-0,084	0,460	-0,128	0,259	-0,124	0,273
Cz	81	78	0,094	0,407	-0,106	0,350	-0,055	0,629	-0,050	0,661	-0,234	0,037	-0,090	0,426	-0,081	0,476	-0,079	0,489
P3	88	85	0,098	0,388	-0,135	0,232	-0,111	0,325	-0,102	0,367	-0,309*	0,005	-0,121	0,286	-0,189	0,093	-0,184	0,103
P4	88	85	0,122	0,282	-0,118	0,296	-0,059	0,602	-0,051	0,656	-0,312*	0,005	-0,128	0,260	-0,138	0,222	-0,134	0,236
T3	81	78	0,085	0,456	-0,124	0,272	-0,117	0,301	-0,117	0,302	-0,165	0,144	-0,066	0,563	-0,190	0,092	-0,182	0,107
T4	81	78	0,062	0,584	-0,121	0,285	-0,134	0,235	-0,125	0,271	-0,162	0,150	-0,055	0,626	-0,197	0,080	-0,163	0,148
T5	81	78	0,097	0,391	-0,132	0,244	-0,069	0,542	-0,065	0,565	-0,287*	0,010	-0,108	0,340	-0,063	0,577	-0,059	0,604
T6	81	78	0,074	0,512	-0,134	0,235	-0,121	0,286	-0,113	0,317	-0,266	0,017	-0,089	0,432	-0,144	0,204	-0,140	0,214
O1	88	85	0,083	0,462	-0,140	0,216	-0,081	0,477	-0,071	0,531	-0,337*	0,002	-0,140	0,216	-0,128	0,256	-0,125	0,268
O2	88	85	0,104	0,357	-0,126	0,265	-0,066	0,559	-0,054	0,634	-0,315*	0,004	-0,128	0,259	-0,143	0,207	-0,139	0,219

Table 12. Partial Pearson correlation coefficients (corrected for Age) between sleep spindle parameters and Raven APM scores in male subjects. In the first two columns, the number of available subjects and the corresponding degrees of freedom are given for each electrode. Correlations which remain significant after multiple comparisons correction are marked with an asterisk.

			Slow Spindles								Fast Spindles							
			Density		Duration		Mediian Amplitude		Maximum Amplitude		Density		Duration		Median Amplitude		Maximum Amplitude	
	N	*df*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Fp1	160	157	0,127	0,135	0,073	0,393	-0,083	0,327	-0,085	0,321	-0,039	0,650	-0,025	0,769	0,038	0,659	0,035	0,685
Fp2	160	157	0,144	0,089	0,066	0,441	-0,082	0,338	-0,079	0,354	-0,025	0,769	0,007	0,935	0,021	0,806	0,023	0,791
Fz	141	138	0,156	0,066	0,076	0,371	-0,075	0,381	-0,074	0,388	-0,071	0,406	0,007	0,937	0,052	0,544	0,053	0,535

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F3	160	157	0,136	0,109	0,070	0,409	-0,096	0,257	-0,094	0,270	-0,049	0,567	0,050	0,561	0,038	0,652	0,040	0,636
F4	160	157	0,183	0,031	0,112	0,188	-0,107	0,207	-0,106	0,214	-0,100	0,242	-0,035	0,681	0,021	0,804	0,024	0,776
F7	141	138	0,168	0,047	0,106	0,211	-0,129	0,129	-0,126	0,137	-0,077	0,365	-0,001	0,995	0,011	0,902	0,015	0,861
F8	141	138	0,167	0,049	0,111	0,193	-0,127	0,135	-0,123	0,147	-0,084	0,327	-0,011	0,895	0,068	0,424	0,069	0,415
C3	160	157	0,173	0,041	0,064	0,452	-0,103	0,225	-0,102	0,229	-0,071	0,406	0,011	0,902	0,082	0,339	0,083	0,328
C4	160	157	0,160	0,059	0,060	0,481	-0,121	0,156	-0,118	0,165	-0,042	0,626	0,034	0,690	0,076	0,372	0,078	0,359
Cz	141	138	0,198	0,019	0,103	0,224	-0,143	0,093	-0,140	0,099	-0,078	0,360	0,005	0,954	0,094	0,269	0,095	0,264
P3	160	157	0,168	0,047	0,052	0,542	-0,141	0,098	-0,137	0,108	-0,111	0,190	0,021	0,804	0,010	0,907	0,015	0,864
P4	160	157	0,182	0,032	0,058	0,493	-0,111	0,191	-0,109	0,199	-0,093	0,277	0,014	0,868	0,034	0,687	0,037	0,661
T3	141	138	0,200	0,018	0,098	0,252	-0,154	0,070	-0,155	0,068	-0,064	0,453	-0,017	0,842	-0,035	0,678	-0,035	0,686
T4	141	138	0,179	0,035	0,096	0,261	-0,179	0,034	-0,174	0,040	-0,104	0,222	-0,030	0,725	-0,104	0,221	-0,090	0,292
T5	141	138	0,198	0,019	0,089	0,295	-0,171	0,044	-0,167	0,049	-0,127	0,134	-0,006	0,943	-0,003	0,974	-0,001	0,996
T6	141	138	0,192	0,023	0,083	0,329	-0,224	0,008	-0,219	0,009	-0,107	0,206	-0,011	0,902	-0,087	0,307	-0,083	0,328
O1	160	157	0,170	0,044	0,044	0,603	-0,145	0,087	-0,140	0,099	-0,122	0,152	0,004	0,964	-0,022	0,797	-0,020	0,814
O2	160	157	0,184	0,030	0,051	0,551	-0,147	0,083	-0,142	0,095	-0,062	0,468	0,017	0,839	-0,036	0,671	-0,033	0,697

Table 13. Partial Pearson correlation coefficients (corrected for Age) between sleep spindle parameters and Raven APM scores in all subjects. In the first two columns, the number of available subjects and the corresponding degrees of freedom are given for each electrode. No correlations are significant after multiple comparisons correction.

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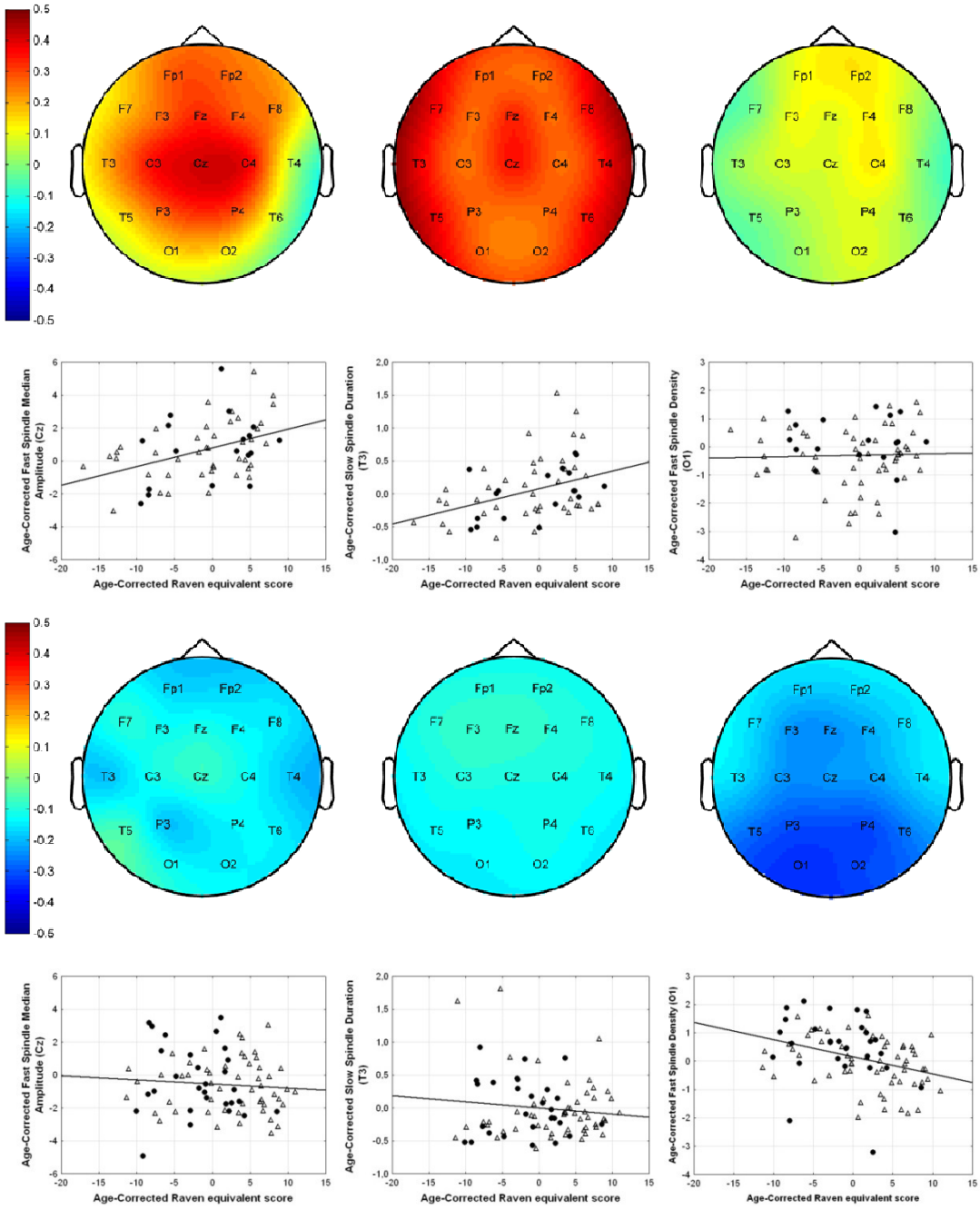

Figure17.Scalp maps and partial regression plots for females (upper half) and males (lower half), for Cz fast spindle median amplitude (left panels), T3 slow spindle duration (middle panels), and O1 fast spindle density (right panels). Scalp maps illustrate the topographical distribution of the strength of partial correlations between Raven equivalent scores and sleep spindle parameters. On the partial regression plots, X axes represent the residuals after regressing Raven APM scores against Age. Y axes represent the residuals after regressing

spindle parameters against Age. Thus, these scatterplots demonstrate the relationship between Raven APM scores and spindle parameters after pruning both variables for the effects of Age. Standard Pearson correlation between the shown residuals equals the age-corrected partial correlations between Raven APM scores and spindle parameters. Dots represent data points from the Budapest sample while triangles represent data points from the Munich sample. Reproduced from (Ujma et al., 2014).

Sex differences in the correlations between Raven equivalent scores and sleep spindle parameters were confirmed by statistical comparison of the maximal significant correlations illustrated in Figure 17. Using Fisher's r to z transformation method, correlation coefficients found in males and females were significantly different for fast spindle amplitude on Cz ($z=3.2$, $p=0.001$), slow spindle duration on T3 ($z=3.23$, $p=0.001$) and fast spindle density on O1 ($z=2.23$, $p=0.02$).

Sleep spindle peak frequencies were not correlated with Raven equivalent scores in either sex and in either slow or fast spindles (age-corrected partial correlation with slow spindle peak frequency is .17 [p=.160] in females, -.06 [p=.539] in males; correlation with fast spindle peak frequency is -.04 [p=.744] in females, .095 [p=.379] in males).

Similar results were seen if individual intelligence test raw scores (CFT or Raven) were used instead of the combined score. Correlations were also not exclusively driven by either subgroup (Budapest or Munich) used in the study (see scatterplots on Figure 17 for details). Inclusion or exclusion of the 8 smoking subjects did not change the results of the study.

The sexually dimorphic nature of the correlation between NREM sleep measures and IQ were confirmed by spectral analysis as well. Log-transformed (10 base) power spectral density correlated significantly with intelligence in a Rüger area encompassing the entire analyzed range (8-16 Hz) and involving electrodes Fp1, Fp2, Fz, F4, C3, C4, Cz, P3, P4, T4, O1 and O2. $p<0.05/2$ was true for 52% of all tests within this range and $p<0.05/3$ was true for 39% of tests. While due to the rules of Rüger areas such a wide area had to be considered, effects extending continuously into the alpha range were only seen on P3, P4 and C4, and the maximal effect had a clear peak around 13 Hz, that is, in the fast spindle (sigma) frequency range (Figure 18). No significant effects were seen, however, with z-transformed spectra in females and in males in general. Figure 18 also

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shows the correlations between raw (10-base logarithmized) spectral power and intelligence scores in males.

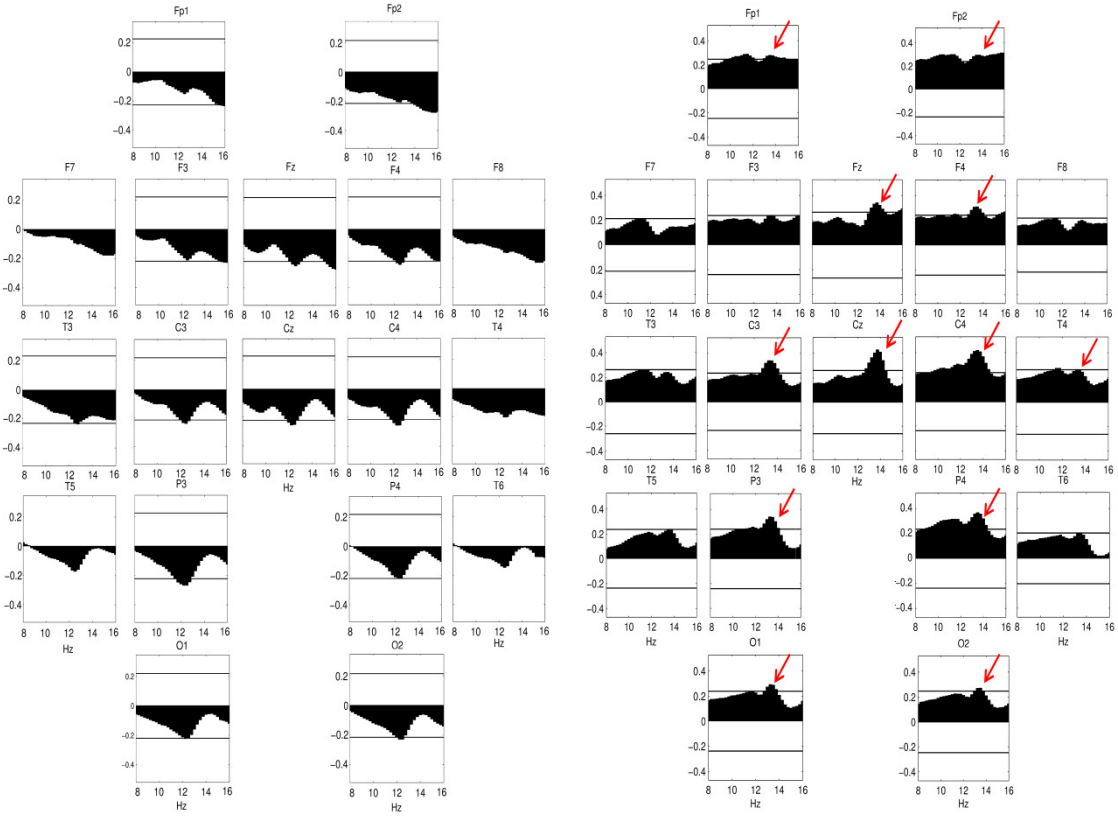

Figure 18. Correlation coefficients (axis y) at various frequencies from 8 Hz to 16 Hz (axis x) on all electrodes (subpanels) in male (left panel) and female (right panel) subjects. Horizontal lines parallel to axis x indicate the critical correlation coefficients in case of electrodes where at least one uncorrected correlation coefficient was significant. Red arrows indicate areas of correlations which are significant after correcting for multiple comparisons using the Rüger area method.

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5. Discussion

In the three studies which are presented in this doctoral thesis, we investigated the relationship between trait intelligence (measured by nonverbal IQ tests with a high g-loading) and sleep spindling and NREM sleep EEG spectral power in over two hundred healthy subjects ranging from less than four to nearly seventy years old, including a particularly broad range of IQ scores in the adult sample (85-160), making it the largest and most extensive study of the relationship between sleep spindling and intelligence to date. Besides recruiting a large number of subjects, we also intended to improve the methodological quality of our studies by implementing the IAM algorithm of sleep spindle detection and analysis, which – unlike some previous studies with similar aims – separated slow and fast spindles and detected both using adaptive, individually determined amplitude and frequency criteria. Using this methodology, we were able to confirm that

1. sleep spindling (particularly sleep spindle amplitude) is indeed a biological marker of trait intelligence throughout the lifespan, and
2. the relationship between sleep spindling and intelligence exhibits substantial sexual dimorphism, with a positive relationship usually observed only in case of females.

Our results were relatively homogeneous within the three age groups and confirmed similar trends in 4-8 year old children, adolescents and adults from a wide age range. Table 14 summarizes our results for all three age ranges.

		Children		**Adolescents**		**Adults**	
		Male	***Female***	***Male***	***Female***	***Male***	***Female***
Slow spindles	**Density**						
	Duration						*positive, temporal*
	Amplitude		*positive after age correction, lateral*				
	Frequency						
Fast spindles	**Density**	*positive, but not after age correction, frontal*			*positive*	*negative, occipital*	
	Duration						
	Amplitude				*positive, tendency only after age-correction, central*		*positive, central*

	Frequency			*positive*			
	Alpha power		*positive, lateral, with or without age correction*				*positive, frontal*
	Sigma power		*positive, lateral, with or without age correction*	*low frequency negative, high frequency positive*			*positive, central*

Table 14. A summary of significant correlations between intelligence and sleep spindling/EEG power measures

In sum, we found evidence for a positive relationship between sleep spindle amplitude and intelligence in females. This relationship was strongly present in case of fast spindles in the adult and adolescent sample (albeit in the latter case became a mere tendency after correcting for the effects of age) and slow spindles in the child sample (where it became especially evident after age correction). Logarithmized NREM sleep EEG power – an approximate measure of sleep spindling – was also positively correlated with intelligence in young female children and adult females (albeit not in adolescents), with the positive correlation extending into the alpha frequency range. While there was a correlation between NREM sleep EEG power in the sigma range in case of adolescent males, this correlation was negative for the lower frequency ranges and positive in the higher ones, thus it probably rather reflected the higher dominant fast spindle frequency of more intelligent subjects (which was revealed to be an independent significant effect) than a simple unidirectional relationship with between EEG power and IQ. Though sleep spindle density was the earliest reported correlate of IQ (Bodizs et al., 2005), we found relatively little evidence for such a relationship. Fast spindle density correlated positively with IQ only in adolescent females, and in fact in adult males a negative correlation was found (albeit in a very restricted occipital area). The positive relationship between fast spindle density and intelligence in young male children was revealed to be entirely due to the effects of age. The positive relationship between slow spindle duration and intelligence in adult females was not replicated in the other two studies. Notably, most significant effects were found in case of fast spindles.

What is the meaning of sleep spindle parameters? Sleep spindle density reflects the number of spindle events, which can be affected by previous wakefulness, such as the effects of learning (Morin et al., 2008; Peters et al., 2008; Barakat et al., 2011). Sleep

spindle duration may reflect the length of the slow oscillation up-states spindles are coupled to (Steriade, 2003; Clemens et al., 2007; Heib et al., 2013) which may actually be in itself a correlate of IQ (Bodizs et al., 2005) although this was not investigated in these studies. The intra-individual stability – in contrast to significant inter-individual variability – of NREM sleep, which is what ultimately justifies the investigation of possible trait markers in NREM sleep EEG, was generally demonstrated using spectral power (De Gennaro et al., 2005; De Gennaro et al., 2008) This can be affected by either more frequent, longer or larger oscillations and the precise practical contribution of these measures is currently unknown. However, measures of density and duration are arguable more malleable (in response to wakeful events or homeostatic pressure) than amplitude, which ultimately relies on the underlying cortical structures and subcortical (thalamocortical) connections (Piantoni et al., 2013; Saletin et al., 2013). Therefore, it is unsurprising that we found sleep spindle amplitude and log sigma spectral power – themost 'trait-like' parameters – tobe the most frequently replicated markers of intelligence. Intelligence correlated positively with sleep spindle amplitude in all three and with log sigma spectral power in two out of three age groups. Notably, however, these effects were found exclusively in female subjects.

While many studies investigated the relationship between sleep spindling and intelligence, with somewhat diverging results (see Table 1. for review) it is notable not none of them searched for possible sexual dimorphisms. This is surprising because many other studies from other neuroscience domains, such as structural or chemical imaging (Gur et al., 1999; Haier et al., 2005; Jung et al., 2005), functional imaging (Haier and Benbow, 1995; Schmithorst and Holland, 2006) and wakeful EEG monitoring (Neubauer et al., 2002; Jausovec and Jausovec, 2005; Neubauer et al., 2005) revealed quite profound sex differences in the biological and physiological correlates of intelligence. While there is one exception (Dunst et al., 2014), most studies reported stronger white matter correlates of IQ in female subjects. This is in line with the reliance of sleep spindle oscillations on the structural integrity of thalamocortical white matter tracts (Piantoni et al., 2013) constituting the networks in which spindles are generated. Therefore, based on our results and some others, a hypothesis may be proposed that a triangular relationship exists between the integrity of thalamocortical white matter connections, intelligence and sleep spindle amplitude in case of female subjects. It is

notable that white matter connections are generally more robust in females than males (Gong et al., 2009; Ingalhalikar et al., 2014; Satterthwaite et al., 2014), suggesting the neural underpinnings are not only sexually dimorphic, but that in females they rely on cerebral characteristics which are more 'feminine' by default.

Our results, however, are not completely unanimous. In adults and adolescents, more intelligent females had higher central fast spindle amplitudes, but female children had higher *slow* spindle amplitudes in lateral derivations. In adolescent females, the positive relationship between fast spindle amplitude and intelligence was at least in part due to the effects of age. How certain can we be of the presence of such an effect in females and its absence in males? Two further results seem to confirm this idea. First, a re-analysis of the currently second-largest sleep spindle/intelligence database (Schabus et al., 2006) to investigate sex differences revealed stronger associations between sleep spindle amplitude and intelligence in case females (Manuel Schabus, personal communication). Second, a new study from our laboratory(Ujma et al., 2015b) in over 80 male subjects monitored during an afternoon nap no association between sleep spindle amplitude and intelligence (although, unlike in case of the night sleep subjects, there was a low positive correlation with spindle density). Overall, the majority of results seem to confirm the positive relationship between some measure of sleep spindle amplitude and intelligence in females, but not males. It is also worth mentioning that the only previous paper using exclusively female samples in two out of the three studies it reported (Fogel et al., 2007) found a robust correlation with sigma power, though it did not calculate spindle amplitude.

IQ correlates with fast spindle amplitude in adolescent and adult females, but slow spindle amplitude in female children. While the amplitude of both spindle types is presumably affected by connectivity in similar ways despite different generating systems (Shinomiya et al., 1999; Schabus et al., 2007), this dichotomy deserves some reflection. Most studies explicitly investigating the different cognitive correlates of slow and fast spindling confirmed that the association between sleep spindling and memory or intelligence is different in case of slow and fast spindles (Tamaki et al., 2009; Lustenberger et al., 2015b; Nader and Smith, 2015). The distribution and frequency of slow and fast spindles is strongly affected by ageing during childhood (Shinomiya et al.,

1999), with an acceleration of spindles in older children. In fact, one study (Hoedlmoser et al., 2014) did not analyze fast spindles in children at all, because they failed to find a spectral peak in the traditional fast spindle frequency range (13-15 Hz). We did find typical dual spectral peaks in 4-8 year old children and used them as slow and fast spindle frequency ranges according to standard IAM methodology, but these were indeed much slower, with fast spindles were generally below the 13 Hz frequency limit and slow spindles as slow as 10 Hz. Thus, slow and fast spindles may contribute to cognition in different ways during different stages of life, and accelerated adult-like spindles may have different functional characteristics than spindles in early childhood. It is notable that slow spindle amplitude correlated with IQ in temporal derivations, possibly reflecting local – specifically language-related – processes, in line with evidence about the local nature of spindles and their role in local processes (Tamaki et al., 2009; Nir et al., 2011). The different contribution of slow and fast spindles to cognition throughout the lifespan certainly deserves further investigation.

There is much less consistency in the results about other sleep spindle parameters, however, which only occasionally correlate with intelligence with little success in replication. Our results do not provide decisive results about whether or not spindle density or duration correlates with intelligence. It is possible that these parameters are affected by other factors – such as wakeful, even involuntary, learning – which may serve as a proxy for IQ depending on the experimental design and the composition of the subject pool, leading to a correlation with IQ only occasionally.

The effects of ageing on sleep spindling and its potential confounding effects deserve further comment. Our results were in generally in line with previous studies (Landolt et al., 1996; Shinomiya et al., 1999; Fogel et al., 2012; Martin et al., 2013) reporting an increase in sleep spindling during childhood and adolescence and a decrease during adulthood (albeit earlier data from younger subjects is sparse), in line with the proposed rule of sleep spindles in fluid cognitive ability which also increases during maturation but decreases with ageing. This is reflected by the fact that standard IQ scores are calculated from raw scores following an inverted U-shaped curve (Raven et al., 2004), that is, average performance is highest in young adolescents and lower average performance is seen in both younger children and older adults. We found robust

correlations between age and sleep spindle parameters as well as IQ test performance, which was strongly in line with these previous results. Due to the potential confounding effects of age, controlling for the effects of age was considered the most reliable analysis of the direct relationship between sleep spindling and IQ. Despite this fact, the correlations between sleep spindling and IQ were similar with or without age correction, providing further support that our results are not due to the confounding effects of age. It is very important, however, that this is not the case for all sleep spindle parameters. Fast spindle density was positively correlated with both age and IQ in both child and the adolescent subsamples, revealing the role of spindling as a potential developmental marker (Shinomiya et al., 1999). After correcting for the effects of age, the positive correlation between fast spindle density and IQ completely disappeared in children and became weaker in adolescents, suggesting that at least some of the common variance in IQ and sleep spindling is due to the effects of age, and supporting the view that sleep spindle parameters are not only sensitive to trait-like cognitive ability (such as IQ), but they can also be interpreted as developmental markers.

Some comments must be made on the statistical reliability of our results, mainly concerning corrections multiple comparisons. Statistical methods involving multiple EEG channels require specific correction approaches due to the highly correlated nature of neighboring channels, which is why it is empirically wrong to treat analyses involving them as statistically independent, which is assumed by methods such as the Bonferroni correction. In our studies, we used two different approaches: a significance map approach using Rüger areas (Abt, 1987; Duffy et al., 1990) and a more standard method (false detection rate, FDR) which does not require a topographical relationship between statistical tests (Benjamini and Hochberg, 1995). The Rüger area method requires that a significant portion of conventionally significant results be stronger than a certain limit (50% stronger than p=0.05/2 or 33% stronger than p=0.05/3, respectively) and rejects or keeps the null hypothesis for an entire statistical area according to these parameters. In contrast, the FDR method provides a corrected p-value for each statistical test based on the distribution of p-values across the entire sample. As a consequence, the ‘critical’ effect size necessary for FDR-corrected significance can only be assumed based on the other (even non-significant) p-values. If most p-values are close to 1, a lower p-value will be necessary to reject the null hypothesis after FDR correction, but if

all p-values are conventionally significant, all of them remain significant after FDR correction even if they do not exceed the significance threshold by much. To put the differences of the Rüger area, FDR and Bonferroni methods in perspective, in the spindle parameter where our strongest results were measured (Ujma et al., 2014), that is, fast spindle amplitude in adult females, the critical correlation (assuming N=72) coefficient was 0.292 or 0.283 for the Rüger area method (p=0.05/2 or p=0.05/3, which must be met on at least 50% or 33% of neighboring significant electrodes), 0.315 for the FDR method (as with the given distribution of p-values p=0.007 was the critical p-value for FDR significant effect sizes) and 0.35 for the Bonferroni method (assuming a critical p of 0.05/18=0.0027, given the 18 electrodes in the analyses). Absolute p-values heavily depend on sample size, which may make it difficult to produce significant FDR-, or let alone Bonferroni-corrected significant results in relatively small samples. For this reason, we chose the Rüger area method in the child and adolescent study where the sample size was relatively low, losing some spatial resolution due to the fact that the Rüger area method only tests the null hypothesis over a large area of significance, but for the adult study with a larger sample we deemed the FDR method to be more adequate for its better spatial resolution. Clearly, there is not one true method of multiple comparisons correction and it is possible to argue against the concept of multiple comparisons correction in general (Rothman, 1990). A very important feature supporting our results, however, is that they were reproducible across samples, as evidenced by the independent analyses of child, adolescent and adult samples.

A significant problem with any study investigating correlates of intelligence is the concept of intelligence itself. It has been argued that intelligence is a statistical artifact (Schlinger, 2012), a proxy for working memory and executive functions (Geary, 2005) or a very specific combination of these (Conway et al., 2003; Unsworth and Engle, 2005). The concept of intelligence certainly overlaps with executive and memory functions(Colom et al., 2006; Colom, 2007) and it is cannot be elegantly distilled to a single brain area or neurologically testable function (Jung and Haier, 2007; Colom et al., 2010). However, the concept of intelligence is not a neurological but rather a phenomenological reality, which is evidenced by the fact that intelligence is reliably related to a vast variety of social, health, wealth and fertility life outcomes beyond the realm of cognition (Rushton, 2004; Figueredo et al., 2005; Templer, 2008). Therefore, it

is perhaps best to view intelligence from a cognitive neuroscience point of view as a stable combination of skills and abilities, relying on a distributed and probably quite redundant set of brain networks (Colom et al., 2006; Jung and Haier, 2007) specifically relevant for life outcomes, rather than a singular ability. This perspective would suggest that while intelligence relies on perhaps more than a single brain network (Haier et al., 2009), its entirety is regardless relevant for an individual's cognitive, health, wealth and fertility history.

This approach also provides a meaningful conceptual framework for the results presented in the present thesis. Our studies confirmed that the amplitude of NREM sleep spindle oscillations is a relatively stable correlates of intelligence across the lifespan, possibly reflecting more efficient thalamocortical white matter connections. However, this association is only present in females, providing support for earlier studies reporting a sexual dimorphism in the biological correlates of intelligence, and confirming that intelligence may rely on more than a single specific neural network or function. The most important field of further study would be to analyze the relationship between sleep spindling and intelligence in subjects with structural imaging data. The hypothesis that higher spindle amplitudes in more intelligent subjects reflect more efficient thalamocortical connections could be confirmed if morphometric and DTI structural imaging data was available.

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Summary

Intelligence, as measured by standard psychometric tests, has been linked to a wide variety of life history outcomes, including better performance in various cognitive domains, better educational success, lower lifetime prevalence of psychiatric disease and leading causes of death including heart disease and cancer, lower criminality and a longer lifespan. These correlates make the biological mechanisms of intelligence an important target for scientific research.

Biological correlates of intelligence include brain size, the volume and functional measures of widespread cerebral areas, as well as electroencephalographic measures. Many previous studies reported a correlation between intelligence and sleep spindles, NREM sleep oscillations generated by thalamocortical and reticular thalamic circuits and also linked to sleep-related memory consolidation. Biological correlates of intelligence were frequently found to be sexually dimorphic, but this was never investigated for sleep spindles previously.

In our research, we investigated the association between sleep EEG measures and nonverbal intelligence (measured by variants of Raven's Progressive Matrices) in over two hundred subjects, divided into three age groups (4-8 year old children, 15-22 year old adolescents and 17-69 year old adults). We detected sleep spindles with the IAM method, taking into account inter-individual variations in sleep spindle amplitude and frequency and separating slow and fast spindles.

We found evidence about an association between intelligence and sleep spindling in all three age groups, most prominently in case of sleep spindle amplitude. We also found this association to be highly and consistently sexually dimorphic: sleep spindle amplitude was positively associated with intelligence in female children, adolescents and adults, but never in males.

Our study, the largest so far investigating sleep EEG correlates of intelligence, confirmed the association between sleep spindling and intelligence, but also provided evidence that this relationship is highly sexually dimorphic.

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Összefoglalás

A pszichometriai tesztekkel mérhető intelligencia összefügg a kogníció számos területén megfigyelhető jobb teljesítménnyel, jobb tanulmányi előmenetellel, pszichiátriai betegségek és vezető halálokok (például szív- és daganatos betegségek) alacsonyabb élettartam-prevalenciájával, a bűnözővé válás alacsonyabb valószínűségével és hosszabb várható élettartammal. Ezek az összefüggések az intelligencia biológiai háttérmechanizmusait a tudományos kutatások fontos célpontjává teszik.

Az intelligencia biológiai korrelátumai magukban foglalják az agyméretet, változatos agyterületek térfogatát és funckionális sajátosságait, illetve elektroenkefalográfiás méréseket. Számos korábbi kutatás számolt be összefüggésekről az intelligencia és az alvási orsózás között. Az alvási orsók NREM alvásban thalamocorticalis és reticularis thalamicus hálózatokban generált oszcillációk és az alvás során történő emlékezeti konszolidációval is összefüggenek. Az intelligencia biológiai korrelátumai gyakran nemi dimorfizmust mutattak, de az alvási orsók esetében ezt korábban soha nem vizsgálták.

Kutatásunkban több mint kétszáz, három korcsoportba (4-8 éves gyemekek, 15-22 éves serdülők, 17-69 éves felnőttek) osztott vizsgálati személyen vizsgáltuk az alvási EEG sajátossai és a Raven Progresszív Mátrixok változatai által mért nonverbális intelligencia összefüggéseit. Az alvási orsókat az IAM módszer segítségével detektáltuk, figyelembe véve az alvási orsók amplitúdójában és frekvenciájában megfigyelhető egyéni különbségeket és különválasztva a lassú és gyors orsókat.

Mindhárom csoportban bizonyítékát találtuk az intelligencia és az alvási orsózás közötti összefüggésnek, legtöbbször az alvási orsók amplitúdója esetében. Ez az összefüggés erős nemi dimorfizmust mutatott: az alvási orsók amplitúdója pozitívan függött össze az intelligenciával a gyermekkorú és serdülők lányok és felnőtt nők esetében, de a fiúk és férfiak esetében nem.

Kutatásunkaz eddigi legnagyobb vizsgálata az alvási EEG-paraméterek és az intelligencia közötti összefüggésnek. Eredményeink megerősítették az alvási orsózás és az intelligencia között korábban leírt összefüggést, de bizonyítékot szolgáltattak annak erős nemi dimorfizmusára is.

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Publications

Relevant to the thesis

1. Péter P. Ujma, Boris Konrad, Lisa Genzel, Annabell Bleifuss, Péter Simor, Adrián Pótári, János Körmendi, Ferenc Gombos, Axel Steiger, Róbert Bódizs, Martin Dresler (2014). Sleep spindles and intelligence: Evidence for a sexual dimorphism. The Journal of Neuroscience, 34(49):16358-68.
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Other publications

1. Péter Simor, Klára Horváth, Péter P. Ujma, Róbert Bódizs (2013). Increased alpha power indicates wake-like EEG oscillations during different sleep stages in nightmare disorder. Biological Psychology 94:592-600.
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