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## The sleep EEG spectrum is a sexually dimorphic marker of general intelligence

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The shape of the EEG spectrum in sleep relies on genetic and anatomical factors and forms an individual “EEG fingerprint”. Spectral components of EEG were shown to be connected to mental ability both in sleep and wakefulness. EEG sleep spindle correlates of intelligence, however, exhibit a sexual dimorphism, with a more pronounced association to intelligence in females than males. In a sample of 151 healthy individuals, we investigated how intelligence is related to spectral components of full-night sleep EEG, while controlling for the effects of age. A positive linear association between intelligence and REM anterior beta power was found in females but not males. Transient, spindle-like “REM beta tufts” are described in the EEG of healthy subjects, which may reflect the functioning of a recently described cingular-prefrontal emotion and motor regulation network. REM sleep frontal high delta power was a negative correlate of intelligence. NREM alpha and sigma spectral power correlations with intelligence did not unequivocally remain significant after multiple comparisons correction, but exhibited a similar sexual dimorphism. These results suggest that the neural oscillatory correlates of intelligence in sleep are sexually dimorphic, and they are not restricted to either sleep spindles or NREM sleep.

Intelligence, as expressed by the results of standardized IQ tests such as Raven Advanced Progressive Matrices (RAPM) or the Culture Fair Test (CFT), is a statistically and temporally stable trait with a great degree of heritability<sup>1–3</sup>. Such characteristics would imply a strong, well-defined biological basis, however, the precise mechanisms through which IQ is implemented in the nervous system remain elusive<sup>4–6</sup>, and the search for potential biological markers is still ongoing.

In recent years, an increasing body of research suggests EEG sleep spindles as a biological marker of intelligence<sup>7–14</sup>, however the methodology of these studies is quite heterogeneous and their results not always consistent<sup>15</sup>. Our previous research<sup>15–17</sup> confirmed that sleep spindles – particularly sleep spindle amplitude – are indeed positively correlated with IQ, although in a sexually dimorphic manner: in children, adolescents as well as adults, sleep spindle parameters are preferentially associated with IQ in females.

Some evidence suggests that sleep spindles are not the only potentially relevant electrophysiological biomarkers of IQ. First, a relationship between intelligence and wake EEG features such as alpha power, event-related alpha desynchronization and coherence has been described<sup>18–22</sup>. Second, one study<sup>7</sup> investigated the correlates of IQ not with individually detected sleep spindle events, but with NREM sleep EEG spectral power, and indeed found an association between IQ and spectral power well outside the conventional sleep spindle frequency range, specifically with theta, alpha and beta power. Uniquely, this study also analyzed REM sleep EEG power, and found similar associations with IQ.

Sleep spindles were conceptualized as potential correlates of IQ because of the existence of the sleep EEG spectral fingerprint<sup>14,23,24</sup>, that is, the inter-individual variability, intra-individual stability and genetic determination of the shape of the NREM sleep EEG spectrogram. The reliability of the sleep EEG spectrogram, approximated

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by within-subject inter-night correlations, is very high, typically around 0.9 (Tan *et al.*, 2000; Tan *et al.*, 2001; Van Dongen *et al.*, 2005). It must be pointed out, however, that these reliability estimates were usually obtained using the sleep EEG recordings of healthy, young subjects: therefore, a potential effect of age, sex, minor illnesses or other confounders on the reliability of the sleep EEG spectrogram is not known. Originally, the high reliability of the sleep EEG spectrogram was demonstrated well outside the sigma range in NREM<sup>25–29</sup>. Notably, the descriptive parameters<sup>30,31</sup> as well as EEG characteristics<sup>32,33</sup> of REM sleep are similarly stable and heritable. Therefore, the scarcity of data on the relationship between IQ and sleep EEG features other than sleep spindles is somewhat surprising.

We hypothesized that REM and NREM spectral features of the sleep encephalogram also outside the sigma range are good candidate markers of IQ due to their individual stability and genetic determination. To test this hypothesis, we computed EEG spectral power from a large sample of subjects ( $N = 151$ ) and investigated the association of a broad range of REM and NREM EEG spectral features with measurements of intelligence in order to find other potential IQ markers in the sleep EEG fingerprint. Given the sexually dimorphic association between sleep spindles and IQ<sup>15–17</sup>, we expected a similar sexual dimorphism also for the relationship between EEG spectral power and IQ.

## Materials and Methods

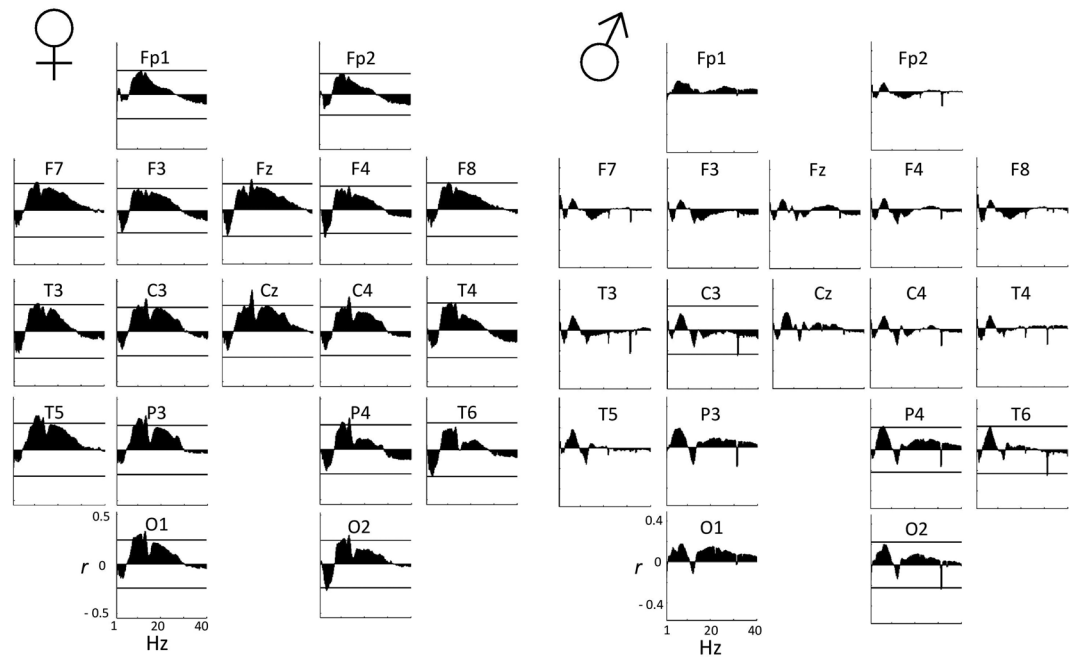
Polysomnography data from 151 subjects (68 females, 83 males, mean age 29.3 years, age range 17–69 years) was analyzed in this study. Another 9 subjects were excluded due to heavily artifact-contaminated data. Data was combined from multiple databases (Max Planck Institute of Psychiatry, Munich, Germany; Institute of Behavioural Sciences of Semmelweis University, Budapest, Hungary) for this retrospective multicenter study<sup>15,34</sup>. The research protocols were approved by the Ethical Committee of the Semmelweis University, Budapest, or the Ludwig Maximilian University, Munich; and research was carried out in accordance with the Declaration of Helsinki. All subjects signed informed consent for the participation in the studies. According to a 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. Consumption of small habitual doses of caffeine (max. 2 cups of coffee before noon), but no alcohol was allowed before the recordings. 6 male and 2 female subjects were light to moderate smokers (self-reported), while the rest of the subjects were non-smokers.

Sleep was recorded for two consecutive nights by standard polysomnography, including EEG according to the 10–20 system (recordings sites: Fp1, Fp2, F3, F4, Fz, F7, F8, C3, C4, Cz, P3, P4, T3, T4, T5, T6, O1, and O2, re-referenced to mathematically linked mastoids), electro-oculography (EOG), bipolar submental electromyography (EMG), and electrocardiography (ECG). Impedances for the EEG electrodes were kept below 8 k $\Omega$ . Supplementary Table 1 shows further recording details including the precise distribution of subjects by study center. Due to electrode failure, data from a total of 26 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 T5 in 2 cases; F3, T3, C3, O2 and T6 in 1 case, respectively.

Visual stage scoring on a 20 second basis by according to standard criteria<sup>35</sup> and visual artifact rejection on a 4 second basis was performed on sleep EEG recordings from the second laboratory nights. Artifact-free NREM2 and SWS epochs were analyzed to obtain NREM spectral data, and artifact-free REM epochs were analyzed to obtain REM spectral data. Spectral analysis was performed by the mixed-radix FFT method using 4 s Hanning-tapered windows with a 2 s overlap and averaging power spectral densities from all 4 s windows. Power spectral densities were calculated for 0.25 Hz bins from 0 Hz to the Nyquist frequency (sampling rate/2). In all analyses, relative log-transformed power spectral density from 1 Hz to 40 Hz was used. This was calculated by dividing the amplitude reduction corrected power of each frequency bin of each electrode of the corrected spectra in the 1–40 Hz range by the sum of power in all frequency bins in this range, and then replacing each value by its 10-base logarithm.

EEG recording devices have different analog filter characteristics which results in different machines yielding different spectral power densities for the same recording, but it is possible to control for such discrepancies<sup>36</sup>. 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  $\mu$ V 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). The amplitude reduction rate of each recording system at each frequency was determined by calculating the proportion between digital (measured) and analog (generated) amplitudes of sinusoid signals at the corresponding frequency. Amplitude reduction rates calculated from 40 and 355  $\mu$ V signals were averaged for each frequency, and amplitude reduction rates for intermediate frequencies were calculated by spline interpolation using frequency responses at neighboring frequencies. Power spectral density values of all frequencies were corrected by dividing the original value by the squared amplitude reduction rate of the appropriate recording device at the corresponding frequency.

All subjects completed one or two standardized nonverbal intelligence tests, the Culture Fair Test (CFT) or Raven Advanced Progressive Matrices (Raven APM), similar tests of abstract pattern completion which yield strongly correlating results and which are particularly good measures of the general factor of intelligence<sup>37–39</sup>. A total of 110 subjects completed the CFT and 81 subjects completed the Raven APM test. 41 subjects completed both tests. A composite raw intelligence test score was calculated, expressed as a Raven equivalent score (RES). RES for Raven APM tests were equal to the actual raw test score. RES of CFT raw scores were equal to the Raven APM score corresponding to the IQ percentile derived from CFT performance and the age of the subject. In case of Raven APM and CFT scores both being available, RES were averaged. The 1993 Des Moines (Iowa) standardization of APM was used.



**Figure 1.** Spectro-correlograms of the age-corrected relationship between relative REM EEG power spectral density (by 0.25 Hz bins) and RES by electrode. Axis X represents frequency between 1 Hz and 40 Hz, while axis Y shows the partial Pearson correlation coefficient between RES and relative EEG power in the given bin, corrected for the effects of age. A horizontal line indicates the critical partial correlation coefficient ( $p = 0.05$ ) if at least one significant correlation is present on the given electrode.

Pearson's partial correlation coefficients (correcting for age) were calculated to determine the relationship between power spectral density in each frequency bin of each electrode and RES. Since data from neighboring electrodes and frequency bins are expected to be strongly correlated, rendering a Bonferroni correction overly conservative, multiple comparison correction was performed using the R uger area method<sup>17,40–42</sup>. In this method, areas of significance are determined along both the spatial and the frequency domain. A R uger area of potential significance extends from the first frequency bin in which a statistical test is significant on any electrode to the last frequency bin in which a statistical test is significant on any electrode. Areas of potential significance in which the effect was present only on a single electrode or in less than 4 frequency bins ( $< 1$  Hz) were not considered in order to eliminate the confounding effects of narrow-frequency artifacts or outlier values. If  $p < 0.05/2$  ( $p < 0.025$ ) for at least 50% of significant results, or if  $p < 0.05/3$  ( $p < 0.016$ ) for at least 33% of significant results within this area, then the area is considered statistically significant.

## Results

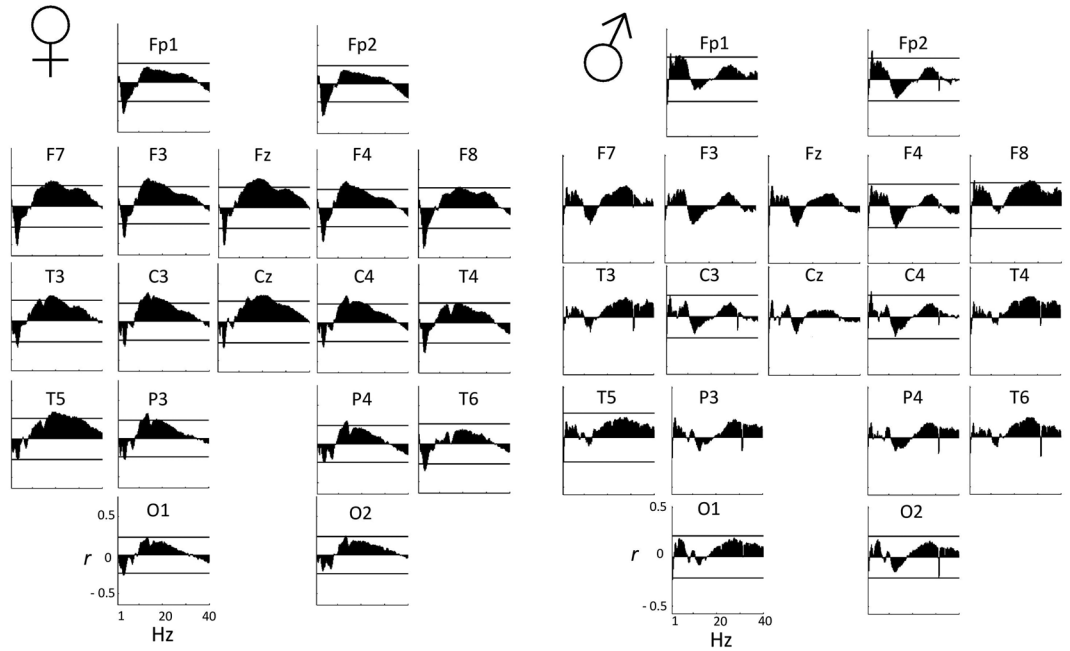
In REM sleep in females, a significant negative partial correlation with delta/theta power and a significant positive partial correlation with beta power was apparent. Both delta/theta (2.25–5.25 Hz,  $p < 0.05/2$  79.3%,  $p < 0.05/67.4\%$ , maximum association at 3.5 Hz on F7) and beta (10.25–26.75 Hz,  $p < 0.05/2$  63%,  $p < 0.05/3$  38.3%, maximum association at 18.75 Hz on Fz) formed significant R uger areas (see Fig. 1).

In NREM sleep in females, age-corrected partial Pearson correlation coefficients between RES and NREM alpha and sigma power were positive and significant. The associations consisted of two effects overlapping in both the spatial and the frequency domain (Fig. 2) with a posterior, left-lateralized alpha (maximum independent association 11.75 Hz on T5) and a midline sigma effect (maximum association at 13.75 Hz on Cz). However, the overall R uger area fell slightly short of significance (8–15 Hz,  $p < 0.05/2$  44.44%,  $p < 0.05/31.11\%$ ).

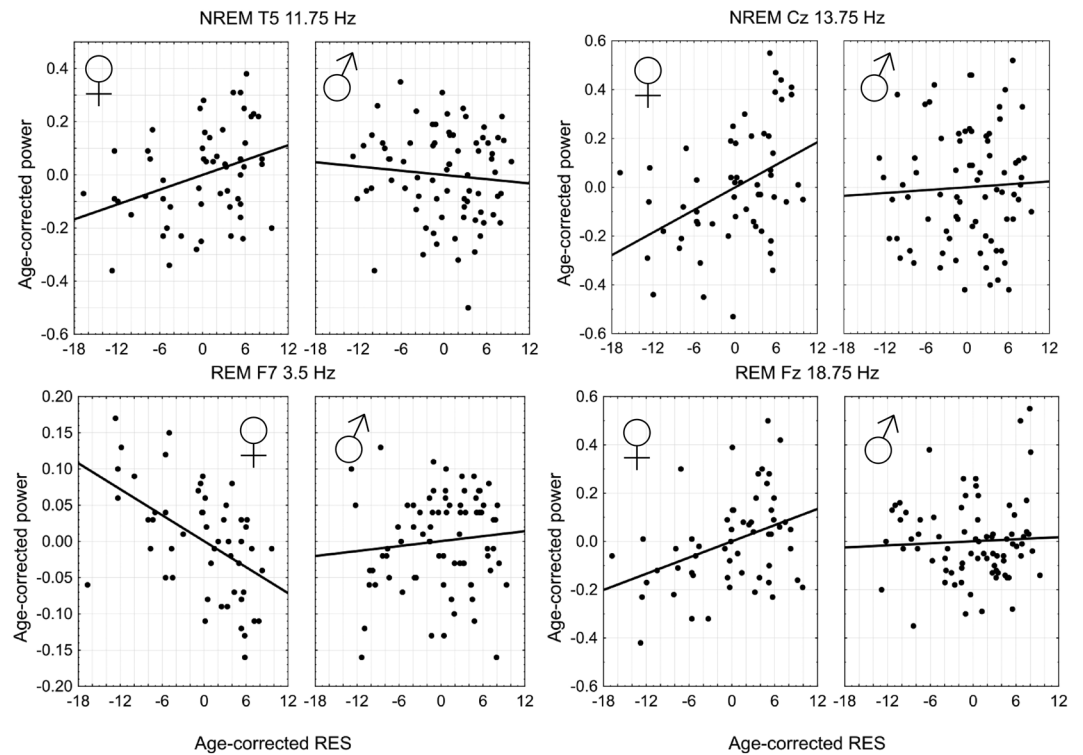
In males, no R uger significant correlations emerged either in REM or NREM sleep. Figure 3 illustrates the maximal partial correlations between relative spectral power and RES in both sexes, while Fig. 4 illustrates the topographical distribution of these associations.

In order to provide evidence for different effect sizes in male and female subjects, we compared the correlation coefficients of each area of potential significance at the derivation and frequency where the association was maximal using Fisher's  $r$ -to- $z$  method. We also considered associations within the NREM R uger area which fell short of significance because of the strong absolute effect sizes and an interest in the discovery of sexually dimorphic effects. These comparisons were significant in three cases (NREM 13.75 Hz on Cz:  $z = 2.22$ ,  $p = 0.0264$ ; NREM 11.75 Hz on T5:  $z = 2.43$ ,  $p = 0.0151$ ; REM 3.5 Hz on F7:  $z = -3.67$ ,  $p = 0.0001$ ), but remained a trend in the fourth (REM 18.75 Hz on Fz:  $z = 1.92$ ,  $p = 0.0549$ ).

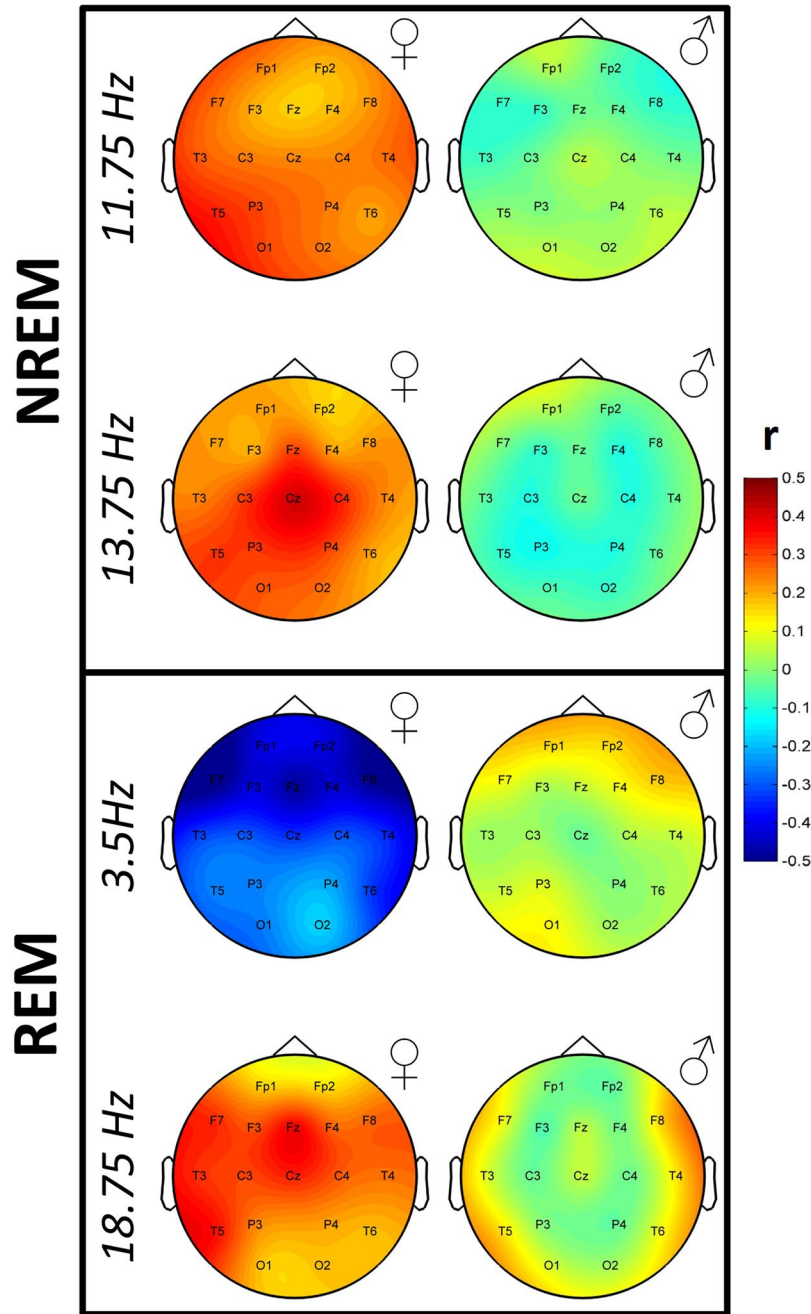
In order to test the robustness of our corrected results, we implemented an alternative, permutation-based method of multiple comparisons correction<sup>43</sup>, using the script made available at <https://www.mathworks.com/matlabcentral/fileexchange/34920-mult-comp-perm-corr>. We obtained age-corrected values of both RES and



**Figure 2.** Spectro-correlograms of the age-corrected relationship between relative NREM EEG power spectral density (by 0.25 Hz bins) and RES by electrode. Axis X represents frequency between 1 Hz and 40 Hz, while axis Y shows the partial Pearson correlation coefficient between RES and relative EEG power in the given bin, corrected for the effects of age. A horizontal line indicates the critical partial correlation coefficient ( $p = 0.05$ ) if at least one significant correlation is present on the given electrode.



**Figure 3.** Scatterplots illustrating the age-corrected relationship between RES and relative EEG power for each of the four maximal associations within R uger areas of potential significance, at the frequency and derivation where the absolute value of the partial correlation coefficient was maximal, separated by sex. Data points indicate the unstandardized residuals of RES (axis X) and relative power (axis Y) after regressing for the effects of age, as the Pearson correlation of these values is equal to the age-corrected partial correlation coefficient of the original values.

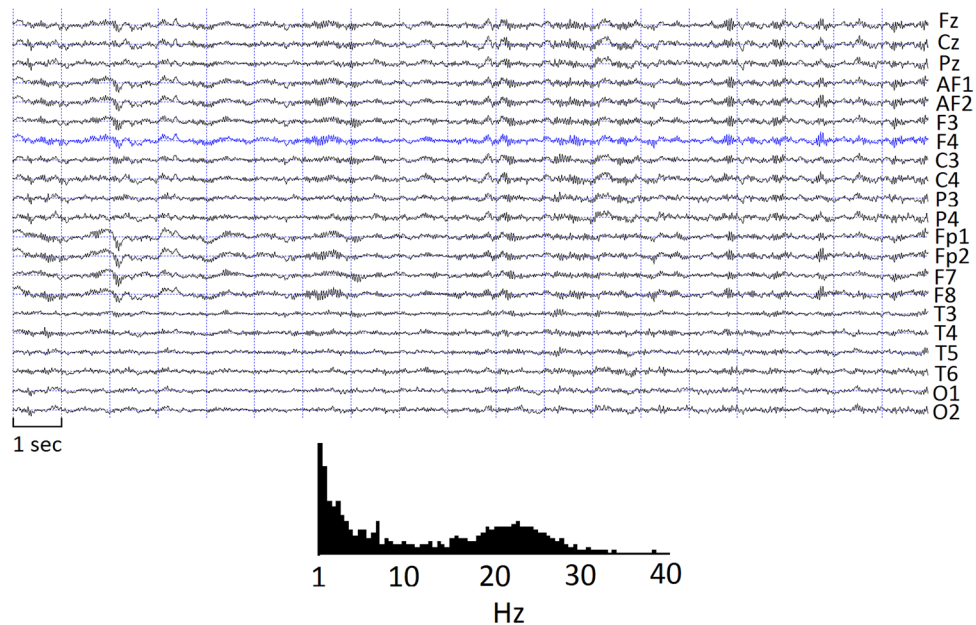


**Figure 4.** The topographical distribution of association strength at the frequencies of maximal association illustrated on Fig. 3 in females (left column) and males (right column).

spectral power by linearly regressing these values against age and calculating the residuals, and performed 5000 permutations across subjects and electrodes for each frequency bin in order to obtain the p-values corrected for family-wise error. As in our original analysis, we performed this correction separately for NREM and REM sleep data, as well as for males and females.

Since this method is sensitive to missing data, we only used spectral data from 12 channels: the 10 electrodes common across all subjects (F3, F4, C3, C4, P3, P4, O1 and O2) and Fz and Cz, which were imputed for subjects without these electrodes as the average spectral value of F3–F4 and C3–C4, respectively. Any other missing channels in other subjects were imputed using the average spectral values at neighboring channels in a similar manner. Electrodes in the temporal arc (F7, F8, T3, T4, T3 and T6) were not used due to the difficulty of interpolating data for these electrodes in the absence of neighboring channels in all but one direction.

This alternative method yielded similar results to the original analysis. In females the correlation between IQ scores and NREM spectral power were significant between 10.25–12 Hz (P3, O1) and 13.25–14 Hz (C3, C4, Cz, P3, O1, O2), while the correlation between IQ scores and REM spectral power was significant between 3.25–4.75 Hz (Fp1, Fp2, F3, F4, Fz, C3, C4) and 12.25–19.5 Hz (F3, F4, Fz, C3, C4, Cz, P3, P4). (Significant frequency



**Figure 5.** Top: Sample EEG in REM sleep, showing transient bouts of beta activity (“REM beta tufts”). Bottom: spectral composition of the highlighted signal (frequency in Hz, spectral power in arbitrary units).

ranges are reported here as the contiguous series of frequency bins in which the corrected association is significant for at least one channel. Channels are mentioned as long as they have at least one significant corrected association within a given frequency range. As in the Ruger area method, we ignored significant frequency ranges with a significant effect of only one electrode. There was one such frequency range in the REM sleep of males where a negative association with 2.75 and 3 Hz spectral power on Fp1 was significant).

This method, unlike the Ruger area approach, reported the female NREM alpha-sigma association as significant, and all our maximal correlations represented on Fig. 3 (11.75 Hz and 13.75 Hz for NREM, 3.5 Hz and 18.75 Hz for REM, all in females only) fell within the range of significant corrected associations with this new method. Supplementary Figure S1 reports adjusted p-values in detail.

## Discussion

Our results demonstrate that spectral characteristics of sleep EEG are indeed related to measures of intelligence, and these associations are not limited to the sigma range: We found significant associations between RES and both low (2.25–5.25 Hz) and high (10.25–26.75 Hz) frequency activity in REM sleep, the former of which exhibited statistically significant sexual dimorphism. NREM alpha and sigma associations with RES were significantly stronger in females than males, but only reached statistical significance using one of the two methods of multiple comparisons correction. Due to the generally high intra-individual reliability of sleep EEG spectral features<sup>29</sup>, it is unlikely that these effects are the result of sex differences in sleep EEG spectrum reliability – that is, lower reliability in males, resulting in the failure of detecting the same association present in females – but in the absence of both previous studies concerning this question and EEG data from multiple nights in our own dataset this remains a theoretical possibility.

**REM sleep.** We wish to use REM beta activity – according to our results, a positive correlate of general intelligence – as an example of a functionally important, but severely under-researched oscillation. Beta EEG activity is an inherent part of the electrical activity patterns of cortical structures in REM sleep<sup>44–46</sup>. The relationship between REM beta activity and cognitive performance has been previously shown in patient populations<sup>47–49</sup>. However, beta activity in REM sleep often does not appear as background activity (comparable to wakefulness), but rather in transient bouts not unlike sleep spindles (see Fig. 5). Such “REM beta tufts” are often readily visible in the EEG and they are obvious contributors to the REM beta spectral power which was shown here to correlate with general intelligence.

Similar beta oscillations have recently been described to be visible over the anterior cingulate and the dorso-lateral prefrontal cortex in a small clinical sample with cortically implanted electrodes<sup>50</sup>. The authors speculate that these cortical areas are active during REM sleep and contribute to cognitive functions such as motor memory consolidation and emotion regulation. While our data are not suited to directly test this hypothesis, the reported frontal topography, frequency range and visual appearance of these oscillations is very similar to what we found in the scalp EEG recordings of healthy subjects, and their association with general intelligence highlights their functional importance for cognition.

**NREM sleep.** Only one previous study exists about the NREM spectral power correlates of IQ outside the sigma range<sup>7</sup>. While the authors do not attempt to explain this relationship in detail and express doubts about the generalizability of this finding to adult populations, we found a similar relationship in our sample spanning a wide

age range, even though it was significant using only one of the two methods of correcting for multiple comparisons. Notably, the tendencies observed in our study were significantly larger in females compared to males and exhibited a maximum at approximately 13.5 Hz, in line with our previous results about the sexually dimorphic relationship between sleep spindles and IQ<sup>15–17</sup>. However, this association was only significant according to the bootstrapping method for multiple comparisons correction, and not using the Ruger areas. The Ruger area is imperfectly suited to disentangle separate effects which smoothly morph together along both the frequency and the spatial domain as it was the case here, evidenced by the presence of two separate areas (alpha and sigma) of association using the bootstrapping method. NREM associations must be interpreted very carefully due to the lack of agreement on their significance across correction methods.

**Sleep quality.** Tentatively, one may assume that the significant association between IQ and REM beta power and the tendency-level association with NREM alpha power are both indicative of the same phenomenon: a decrease in sleep quality. High frequency activity in both NREM and REM sleep is generally interpreted as a sign of poor sleep quality<sup>51</sup> or a sensitive marker of sleep fragility and environmental awareness during sleep<sup>52</sup>, and it was found in patients with insomnia<sup>53,54</sup> or fibromyalgia<sup>55,56</sup>. However, the function and significance of NREM alpha activity may depend on its topography<sup>51</sup>, and REM beta has also been associated with positive outcomes, that is, lower nightmare severity and more benign PTSD symptoms<sup>57</sup>. Furthermore, low-frequency and beta activity in REM sleep are inversely associated<sup>44–46</sup>, and a pattern of less low frequency and more beta activity, like we observed in the present study, is associated with better functioning in Alzheimer’s disease, potentially reflecting more intact cholinergic pathways<sup>47,49,58</sup>. It is notable that sleep macrostructure parameters were not significantly correlated with RES in either sex and with or without correcting for the effects of age. In sum, there is little evidence that higher NREM alpha and REM beta and lower REM delta in more intelligent female subjects is a sign of poor quality, but it can be speculated that it is associated with an information processing network which is also affected in neurodegenerative diseases. Unfortunately, the lack of previous studies describing the functional importance of the non-sigma elements of the sleep EEG fingerprint associated with intelligence hinders a more detailed interpretation of our findings.

**General perspective.** Despite its excellent psychometric properties<sup>59–61</sup> and importance for a great variety of life outcomes not limited to the cognitive domain<sup>62–64</sup> the physiological underpinnings of general intelligence remain elusive. Some of the generally replicated physiological parameters associated with intelligence are head/brain size<sup>65</sup>, neural efficiency<sup>20</sup>, sleep spindle measures<sup>15</sup> and structural and functional imaging properties of widespread cerebral areas<sup>5</sup>, including connectivity patterns<sup>66</sup>, in approximately descending order of the reliability of association. The elusive nature of general intelligence is perhaps best highlighted by genetic studies, which are important not only because they explain the difficulty of finding a single physiological mechanism behind intelligence, but also because they tend to have the greatest statistical power with sample sizes typically in the tens or hundreds of thousands.

General intelligence is very strongly heritable<sup>3,67</sup>, with twin study heritability estimates for adult intelligence of 0.6–0.8. This high heritability indicates that genetically regulated biological functions are a good target for finding putative mechanisms behind general intelligence. However, genome-wide association studies (GWAS) only revealed statistically significant SNPs associated with intelligence<sup>68,69</sup> or the strongly correlated years in education<sup>70,71</sup> when extremely large sample sizes were used, indicating that even the strongest single genetic variants have very small effects. Genome-wide complex trait analysis (GCTA)<sup>72–75</sup> confirms the strong heritability of intelligence, but also the fact that this heritability is the largely additive total effect of many genetic variants with extremely small individual effects, including family-specific rare genetic variations with negative effects<sup>76–78</sup>. Furthermore, the genetic variants associated with intelligence are highly pleiotropic, evidenced by the strong genetic correlation between intelligence and phenotypically correlated traits, such as LDL cholesterol levels, the risk of diabetes and cardiovascular conditions, poverty, obesity, depression, anxiety and schizophrenia (negative correlations) and HDL cholesterol levels, household income, years in education, height and head size (positive correlations)<sup>79,80</sup>. Little is known about the precise effects of the associated SNPs (or those that they are in linkage with), although they are preferentially expressed in the central nervous system<sup>69,70</sup>. Two studies<sup>73,74</sup> established a connection between the FNBPII gene and general intelligence. The plexin gene family, implicated in axon guidance during neural growth, was implicated in extremely high intelligence<sup>81</sup> but this effect was not replicated in the general population. The importance of neurogenesis-promoting genetic variants for general intelligence has been confirmed by a recent highly powered study<sup>68</sup>, which is well in line with the observed effect of intelligence in longitudinal cerebral development<sup>82</sup>, the stabilization of intelligence by the end of adolescent development<sup>3,67</sup> and the strong genetic correlation between childhood and adult general intelligence<sup>83,84</sup>.

Unfortunately, if general intelligence is primarily determined by a large number of highly pleiotropic genetic variants with small individual effects, then the prospects of finding well-delineated physiological mechanisms underlying intelligence are poor in studies with sample sizes typical for behavioral neuroscience ( $N < 1000$ ). However, measures which themselves reflect the functioning of complex neural systems might be exceptions as they capture the end product of complicated genetic pathways involving complementary and possible substitutable mechanisms. The sleep EEG is a good candidate for such a measure, given its high individual stability<sup>24,27,85</sup>, strong genetic determination<sup>27,32,86</sup> and the fact that it reflects the events in large, functionally connected neural assemblies free from contamination by wakeful mentation and movement artifacts.

Our results confirm that activity in the sleep spindle-related sigma frequency range is related to intelligence. Sleep spindles are among the most genetically determined parts of the sleep EEG spectrum<sup>86</sup>, therefore, this association is unsurprising. However, reductions in sleep spindles are observed in a very wide variety of neurological and psychiatric conditions as well, including schizophrenia<sup>87,88</sup> and Alzheimer’s disease<sup>89</sup>, indicating that sleep spindles resemble a non-specific marker of the integrity of the central nervous system. Future studies with

available sleep EEG, intelligence and genetic data may investigate whether common variants associated with years in education<sup>70</sup> or cognitive ability<sup>69</sup> are also associated with sleep spindles, which would indicate that one of the effects of these variants is promoting a more efficient form of thalamocortical communication and thus propose a genetically mediated physiological mechanism of general intelligence. Alternatively, if sleep spindles are negatively associated with rare genetic variants<sup>76–78</sup> then a more likely explanation is that mutational load is similar to neurological and psychiatric disease as a non-specific reducer of sleep spindle activity, and the association between sleep spindles and intelligence is also due to non-specific genetic effects. Little is known, however, about the generating mechanisms of the other oscillations we found to be associated with intelligence, therefore, their further study is recommended in order to elucidate their potential contributing mechanism to cognitive ability

## Conclusions

Overall, our results suggest that 1.) a wide range of spectral features in the sleep EEG are associated with intelligence, suggesting that the relationship between sleep EEG and IQ go well beyond sleep spindles and 2.) just like sleep spindles, other spectral characteristics of the sleep EEG are also associated with IQ in a sexually dimorphic manner, suggesting that sleep oscillations in general are more related to cognitive performance in women than men. Arguably, the vast majority of scalp EEG studies in healthy human subjects have focused on either slow waves or sleep spindles. Our results demonstrate that the potential functional relevance of other oscillations, most notably REM beta oscillations<sup>50</sup>, which are also trait-like and thus possible markers of individual differences, might have been underestimated. Since much research is still needed in order to understand why less-researched NREM or REM oscillations reflect individual differences, it would be important to conduct studies aimed to either replicate these findings or to elucidate the precise neurophysiology behind NREM alpha or REM beta oscillations. Similarly, future analyses are suggested for finding the potential correlates of intelligence in the sleep EEG of males. While power spectral density is not correlated with intelligence in males, other measures of sleep EEG may be. In line with wake EEG results<sup>22,90</sup>, EEG phase locking, coherence and regional asymmetries are suggested as candidate measures. However, our results suggest that intelligence – even if measured by the same tests – has different neural substrates in males and females.

## References

- Allport, G. W. What is a trait of personality? *The Journal of Abnormal and Social Psychology* **25**, 368 (1931).
- Chen, G., Gully, S. M., Whiteman, J. A. & Kilcullen, R. N. Examination of relationships among trait-like individual differences, state-like individual differences, and learning performance. *J Appl Psychol* **85**, 835–847 (2000).
- Plomin, R. & Deary, I. J. Genetics and intelligence differences: five special findings. *Mol Psychiatry* **20**, 98–108 (2015).
- Haier, R. J. *et al.* Gray matter and intelligence factors: Is there a neuro-g? *Intelligence* **37**, 136–144 (2009).
- Jung, R. E. & Haier, R. J. The Parieto-Frontal Integration Theory (P-FIT) of intelligence: converging neuroimaging evidence. *Behav Brain Sci* **30**, 135–154 (2007).
- Colom, R., Jung, R. E. & Haier, R. J. Distributed brain sites for the g-factor of intelligence. *NeuroImage* **31**, 1359–1365 (2006).
- Geiger, A. *et al.* The sleep EEG as a marker of intellectual ability in school age children. *Sleep* **34**, 181–189 (2011).
- Hoedlmoser, K. *et al.* Slow sleep spindle activity, declarative memory, and general cognitive abilities in children. *Sleep* **37**, 1501–1512 (2014).
- Gruber, R. *et al.* The association between sleep spindles and IQ in healthy school-age children. *International Journal of Psychophysiology* **89**, 229–240 (2013).
- Chatburn, A. *et al.* Sleep spindle activity and cognitive performance in healthy children. *Sleep* **36**, 237–243, <https://doi.org/10.5665/sleep.2380> (2013).
- Schabus, M. *et al.* Sleep spindle-related activity in the human EEG and its relation to general cognitive and learning abilities. *Eur J Neurosci* **23**, 1738–1746, <https://doi.org/10.1111/j.1460-9568.2006.04694.x> (2006).
- Lustenberger, C., Maric, A., Durr, R., Achermann, P. & Huber, R. Triangular relationship between sleep spindle activity, general cognitive ability and the efficiency of declarative learning. *PLoS one* **7**, 21 (2012).
- Fogel, S. M., Nader, R., Cote, K. A. & Smith, C. T. Sleep spindles and learning potential. *Behav Neurosci* **121**, 1–10, <https://doi.org/10.1037/0735-7044.121.1.1> (2007).
- Bódizs, R. *et al.* Prediction of general mental ability based on neural oscillation measures of sleep. *Journal of sleep research* **14**, 285–292, <https://doi.org/10.1111/j.1365-2869.2005.00472.x> (2005).
- Ujma, P. P. *et al.* Sleep spindles and intelligence: evidence for a sexual dimorphism. *J Neurosci* **34**, 16358–16368 (2014).
- Bódizs, R., Gombos, F., Ujma, P. P. & Kovács, I. Sleep spindling and fluid intelligence across adolescent development: sex matters. *Frontiers in Human Neuroscience* **8**, <https://doi.org/10.3389/fnhum.2014.00952> (2014).
- Ujma, P. P., Sandor, P., Szakadat, S., Gombos, F. & Bódizs, R. Sleep spindles and intelligence in early childhood-development and trait-dependent aspects. *Dev Psychol* **52**, 2118–2129 (2016).
- Jaušovec, N. Differences in EEG alpha activity related to giftedness. *Intelligence* **23**, 159–173 (1996).
- Jaušovec, N. & Jaušovec, K. Sex differences in brain activity related to general and emotional intelligence. *Brain Cogn* **59**, 277–286 (2005).
- Neubauer, A. C. & Fink, A. Intelligence and neural efficiency: Measures of brain activation versus measures of functional connectivity in the brain. *Intelligence* **37**, 223–229 (2009).
- Neubauer, A. C., Fink, A. & Schrausser, D. G. Intelligence and neural efficiency: The influence of task content and sex on the brain-IQ relationship. *Intelligence* **30**, 515–536 (2002).
- Thatcher, R. W., North, D. & Biver, C. Intelligence and EEG current density using low-resolution electromagnetic tomography (LORETA). *Hum Brain Mapp* **28**, 118–133 (2007).
- Bódizs, R., Gombos, F. & Kovács, I. Sleep EEG fingerprints reveal accelerated thalamocortical oscillatory dynamics in Williams syndrome. *Research in Developmental Disabilities* **33**, 153–164 (2012).
- De Gennaro, L., Ferrara, M., Vecchio, F., Curcio, G. & Bertini, M. An electroencephalographic fingerprint of human sleep. *NeuroImage* **26**, 114–122 (2005).
- Ambrosius, U. *et al.* Heritability of sleep electroencephalogram. *Biol Psychiatry* **64**, 344–348 (2008).
- Buckelmuller, J., Landolt, H. P., Stassen, H. H. & Achermann, P. Trait-like individual differences in the human sleep electroencephalogram. *Neuroscience* **138**, 351–356 (2006).
- De Gennaro, L. *et al.* The electroencephalographic fingerprint of sleep is genetically determined: a twin study. *Annals of neurology* **64**, 455–460 (2008).
- Landolt, H. P. Genetic determination of sleep EEG profiles in healthy humans. *Prog Brain Res* **193**, 51–61 (2011).



29. Tan, X., Campbell, I. G., Palagini, L. & Feinberg, I. High internight reliability of computer-measured NREM delta, sigma, and beta: biological implications. *Biol Psychiatry* **48**, 1010–1019 (2000).
30. Merica, H. & Gaillard, J. M. Statistical description and evaluation of the interrelationships of standard sleep variables for normal subjects. *Sleep* **8**, 261–273 (1985).
31. Linkowski, P., Kerkhofs, M., Hauspie, R., Susanne, C. & Mendlewicz, J. EEG sleep patterns in man: a twin study. *Electroencephalogr Clin Neurophysiol* **73**, 279–284 (1989).
32. Adamczyk, M. *et al.* Genetics of rapid eye movement sleep in humans. *Transl Psychiatry* **7**, 85 (2015).
33. Tan, X., Campbell, I. G. & Feinberg, I. Internight reliability and benchmark values for computer analyses of non-rapid eye movement (NREM) and REM EEG in normal young adult and elderly subjects. *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology* **112**, 1540–1552 (2001).
34. Potari, A. *et al.* Age-related changes in sleep EEG are attenuated in highly intelligent individuals. *NeuroImage* **23**, 30519–30515 (2016).
35. Iber, C., Ancoli-Israel, S., Chesson, A. & Quan, S. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specification*. 1st edn, (American Academy of Sleep Medicine, 2007).
36. Vasko, R. C. *et al.* Power spectral analysis of EEG in a multiple-bedroom, multiple-polygraph sleep laboratory. *International journal of medical informatics* **46**, 175–184 (1997).
37. Duncan, J. *et al.* A Neural Basis for General Intelligence. *Science* **289**, 457–460, <https://doi.org/10.1126/science.289.5478.457> (2000).
38. Prokosh, M. D., Yeo, R. A. & Miller, G. F. Intelligence tests with higher g-loadings show higher correlations with body symmetry: Evidence for a general fitness factor mediated by developmental stability. *Intelligence* **33**, 203–213 (2005).
39. Cattell, R. B. *Culture fair intelligence test: (a measure of "g")*. (Institute for Personality and Ability Testing, 1973).
40. Abt, K. Descriptive data analysis: a concept between confirmatory and exploratory data analysis. *Methods Inf Med* **26**, 77–88 (1987).
41. Duffy, F. H. *et al.* Quantified neurophysiology with mapping: statistical inference, exploratory and confirmatory data analysis. *Brain Topogr* **3**, 3–12 (1990).
42. Simor, P., Horváth, K., Ujma, P. P., Gombos, F. & Bódizs, R. Fluctuations between sleep and wakefulness: Wake-like features indicated by increased EEG alpha power during different sleep stages in nightmare disorder. *Biological Psychology* **94**, 592–600 (2013).
43. Groppa, D. M., Urbach, T. P. & Kutas, M. Mass univariate analysis of event-related brain potentials/fields I: a critical tutorial review. *Psychophysiology* **48**, 1711–1725, <https://doi.org/10.1111/j.1469-8986.2011.01273.x> (2011).
44. Uchida, S., Maehara, T., Hirai, N., Kawai, K. & Shimizu, H. Theta oscillation in the anterior cingulate and beta-1 oscillation in the medial temporal cortices: a human case report. *Journal of clinical neuroscience: official journal of the Neurosurgical Society of Australasia* **10**, 371–374, [https://doi.org/10.1016/s0967-5868\(03\)00025-0](https://doi.org/10.1016/s0967-5868(03)00025-0) (2003).
45. Uchida, S., Maehara, T., Hirai, N., Okubo, Y. & Shimizu, H. Cortical oscillations in human medial temporal lobe during wakefulness and all-night sleep. *Brain Research* **891**, 7–19 (2001).
46. Uchida, S., Maloney, T. & Feinberg, I. Beta (20–28 Hz) and delta (0.3–3 Hz) EEGs oscillate reciprocally across NREM and REM sleep. *Sleep* **15**, 352–358 (1992).
47. Brayet, P. *et al.* Quantitative EEG of Rapid-Eye-Movement Sleep: A Marker of Amnesic Mild Cognitive Impairment. *Clinical EEG and Neuroscience* **47**, 134–141, <https://doi.org/10.1177/1550059415603050> (2016).
48. Montplaisir, J., Petit, D., Lorrain, D. & Gauthier, S. Sleep in Alzheimer's disease: further considerations on the role of brainstem and forebrain cholinergic populations in sleep-wake mechanisms. *Sleep: Journal of Sleep Research & Sleep Medicine* (1995).
49. Petit, D., Montplaisir, J., Lorrain, D. & Gauthier, S. Spectral analysis of the rapid eye movement sleep electroencephalogram in right and left temporal regions: a biological marker of Alzheimer's disease. *Annals of neurology* **32**, 172–176 (1992).
50. Vijayan, S., Lepage, K. Q., Kopell, N. J. & Cash, S. S. Frontal beta-theta network during REM sleep. *eLife* **6**, e18894, <https://doi.org/10.7554/eLife.18894> (2017).
51. Pivik, R. T. & Harman, K. A reconceptualization of EEG alpha activity as an index of arousal during sleep: all alpha activity is not equal. *Journal of sleep research* **4**, 131–137, <https://doi.org/10.1111/j.1365-2869.1995.tb00161.x> (1995).
52. McKinney, S. M., Dang-Vu, T. T., Buxton, O. M., Solet, J. M. & Ellenbogen, J. M. Covert Waking Brain Activity Reveals Instantaneous Sleep Depth. *PLoS one* **6**, e17351, <https://doi.org/10.1371/journal.pone.0017351> (2011).
53. Perlis, M. L., Smith, M. T., Andrews, P. J., Orff, H. & Giles, D. E. Beta/Gamma EEG activity in patients with primary and secondary insomnia and good sleeper controls. *Sleep* **24**, 110–117 (2001).
54. Krystal, A. D., Edinger, J. D., Wohlgemuth, W. K. & Marsh, G. R. NREM sleep EEG frequency spectral correlates of sleep complaints in primary insomnia subtypes. *Sleep* **25**, 630–640 (2002).
55. Branco, J., Atalaia, A. & Paiva, T. Sleep cycles and alpha-delta sleep in fibromyalgia syndrome. *The Journal of rheumatology* **21**, 1113–1117 (1994).
56. Horne, J. A. & Shackell, B. S. Alpha-like EEG activity in non-REM sleep and the fibromyalgia (fibrositis) syndrome. *Electroencephalography and Clinical Neurophysiology* **79**, 271–276 (1991).
57. Mellman, T. A., Pigeon, W. R., Nowell, P. D. & Nolan, B. Relationships between REM sleep findings and PTSD symptoms during the early aftermath of trauma. *Journal of Traumatic Stress* **20**, 893–901, <https://doi.org/10.1002/jts.20246> (2007).
58. Montplaisir, J., Petit, D., Gauthier, S., Gaudreau, H. & Decary, A. Sleep disturbances and eeg slowing in alzheimer's disease. *Sleep Res Online* **1**, 147–151 (1998).
59. Strauss, E., Sherman, E. M. S. & Spreen, O. *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*. (Oxford University Press, 2006).
60. Neisser, U. *et al.* Intelligence: Knowns and unknowns. *American Psychologist* **51**, 77–101, <https://doi.org/10.1037/0003-066x.51.2.77> (1996).
61. Mackintosh, N. J. *IQ and human intelligence*. (Oxford University Press, 2011).
62. Batty, G. D., Mortensen, E. L. & Osler, M. Childhood IQ in relation to later psychiatric disorder: evidence from a Danish birth cohort study. *Br J Psychiatry* **187**, 180–181 (2005).
63. Batty, G. D., Der, G., Macintyre, S. & Deary, I. J. Does IQ explain socioeconomic inequalities in health? *Evidence from a population based cohort study in the west of Scotland*. Vol. 332 (2006).
64. Marmot, M. & Kivimäki, M. *Social inequalities in mortality: a problem of cognitive function?* Vol. 30 (2009).
65. Gignac, G., Vernon, P. A. & Wickett, J. C. Factors influencing the relationship between brain size and intelligence. *The scientific study of general intelligence: Tribute to Arthur R. Jensen*, 93–106 (2003).
66. Penke, L. *et al.* Brain white matter tract integrity as a neural foundation for general intelligence. *Mol Psychiatry* **17**, 1026–1030, <https://doi.org/10.1038/mp.2012.66> (2012).
67. Bouchard, T. J. Jr. & McGue, M. Genetic and environmental influences on human psychological differences. *Journal of neurobiology* **54**, 4–45, <https://doi.org/10.1002/neu.10160> (2003).
68. Hill, W. D., Davies, G., McIntosh, A. M., Gale, C. R. & Deary, I. J. A combined analysis of genetically correlated traits identifies 107 loci associated with intelligence. *bioRxiv* (2017).
69. Sniekers, S. *et al.* Genome-wide association meta-analysis of 78,308 individuals identifies new loci and genes influencing human intelligence. *Nat Genet* **22** (2017).
70. Okbay, A. *et al.* Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. *Nat Genet* **48**, 624–633, <https://doi.org/10.1038/ng.3552> (2016).

71. Rietveld, C. A. *et al.* GWAS of 126,559 Individuals Identifies Genetic Variants Associated with Educational Attainment. *Science (New York, N.Y.)* **340**, 1467–1471, <https://doi.org/10.1126/science.1235488> (2013).
72. Davies, G. *et al.* Genome-wide association study of cognitive functions and educational attainment in UK Biobank (N = 112 151). *Mol Psychiatry* **21**, 758–767 (2016).
73. Davies, G. *et al.* Genome-wide association studies establish that human intelligence is highly heritable and polygenic. *Mol Psychiatry* **16**, 996–1005 (2011).
74. Benyamin, B. *et al.* Childhood intelligence is heritable, highly polygenic and associated with FBNP1L. *Mol Psychiatry* **19**, 253–258, <https://doi.org/10.1038/mp.2012.184> (2014).
75. Robinson, E. B. *et al.* The genetic architecture of pediatric cognitive abilities in the Philadelphia Neurodevelopmental Cohort. *Molecular psychiatry* **20**, 454–458, <https://doi.org/10.1038/mp.2014.65> (2015).
76. Ganna, A. *et al.* Ultra-rare disruptive and damaging mutations influence educational attainment in the general population. *Nature neuroscience* **19**, 1563–1565, <https://doi.org/10.1038/nn.4404> (2016).
77. Hill, W. D. *et al.* Genomic analysis of family data reveals additional genetic effects on intelligence and personality. *bioRxiv* (2017).
78. Yeo, R. A., Gangestad, S. W., Liu, J., Calhoun, V. D. & Hutchison, K. E. Rare copy number deletions predict individual variation in intelligence. *PLoS one* **6**, e16339, <https://doi.org/10.1371/journal.pone.0016339> (2011).
79. Hagenaars, S. P. *et al.* Shared genetic aetiology between cognitive functions and physical and mental health in UK Biobank (N = 112[thinsp]151) and 24 GWAS consortia. *Mol Psychiatry* **21**, 1624–1632, <https://doi.org/10.1038/mp.2015.225> (2016).
80. Hill, W. D. *et al.* Molecular Genetic Contributions to Social Deprivation and Household Income in UK Biobank. *Current Biology* **26**, 3083–3089, <https://doi.org/10.1016/j.cub.2016.09.035> (2016).
81. Zabaneh, D. *et al.* A genome-wide association study for extremely high intelligence. *Mol Psychiatry*, <https://doi.org/10.1038/mp.2017.121> (2017).
82. Shaw, P. *et al.* Intellectual ability and cortical development in children and adolescents. *Nature* **440**, 676–679 (2006).
83. Deary, I. J. *et al.* Genetic contributions to stability and change in intelligence from childhood to old age. *Nature* **482**, 212–215, <https://doi.org/10.1038/nature10781> (2012).
84. Trzaskowski, M., Yang, J., Visscher, P. M. & Plomin, R. DNA evidence for strong genetic stability and increasing heritability of intelligence from age 7 to 12. *Molecular Psychiatry* **19**, 380–384, <https://doi.org/10.1038/mp.2012.191> (2014).
85. Finelli, L. A., Achermann, P. & Borbély, A. A. Individual ‘fingerprints’ in human sleep EEG topography. *Neuropsychopharmacology* **25**, S57–62 (2001).
86. Purcell, S. M. *et al.* Characterizing sleep spindles in 11,630 individuals from the National Sleep Research Resource. **8**, 15930 (2017).
87. Ferrarelli, F. Sleep in patients with schizophrenia. *Curr Sleep Med Rep* **1**, 150–156 (2015).
88. Manoach, D. S., Pan, J. Q., Purcell, S. M. & Stickgold, R. Reduced Sleep Spindles in Schizophrenia: A Treatable Endophenotype That Links Risk Genes to Impaired Cognition? *Biol Psychiatry* **14**, 00818–00815 (2015).
89. Gorgoni, M. *et al.* Parietal Fast Sleep Spindle Density Decrease in Alzheimer’s Disease and Amnesic Mild Cognitive Impairment. *Neural plasticity* **2016**, 10, <https://doi.org/10.1155/2016/8376108> (2016).
90. Thatcher, R. W., North, D. & Biver, C. EEG and intelligence: relations between EEG coherence, EEG phase delay and power. *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology* **116**, 2129–2141 (2005).

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P.P.U., R.B. and M.D. designed research; P.P.U., B.N.K., P.S., L.G., M.P., R.B. and M.D. acquired data; F.G. and A.P. contributed analytic tools; P.P.U. analyzed data; P.P.U., R.B. and M.D. wrote the first draft of the manuscript; P.P.U., B.N.K., P.S., F.G., A.P., L.G., M.P., A.S., R.B. and M.D. discussed the results and critically revised the manuscript.

## Additional Information

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