Figures and figure supplements

Sleep EEG in young people with 22q11.2 deletion syndrome: A cross-sectional study of slow-waves, spindles and correlations with memory and neurodevelopmental symptoms

Nicholas A Donnelly *et al*

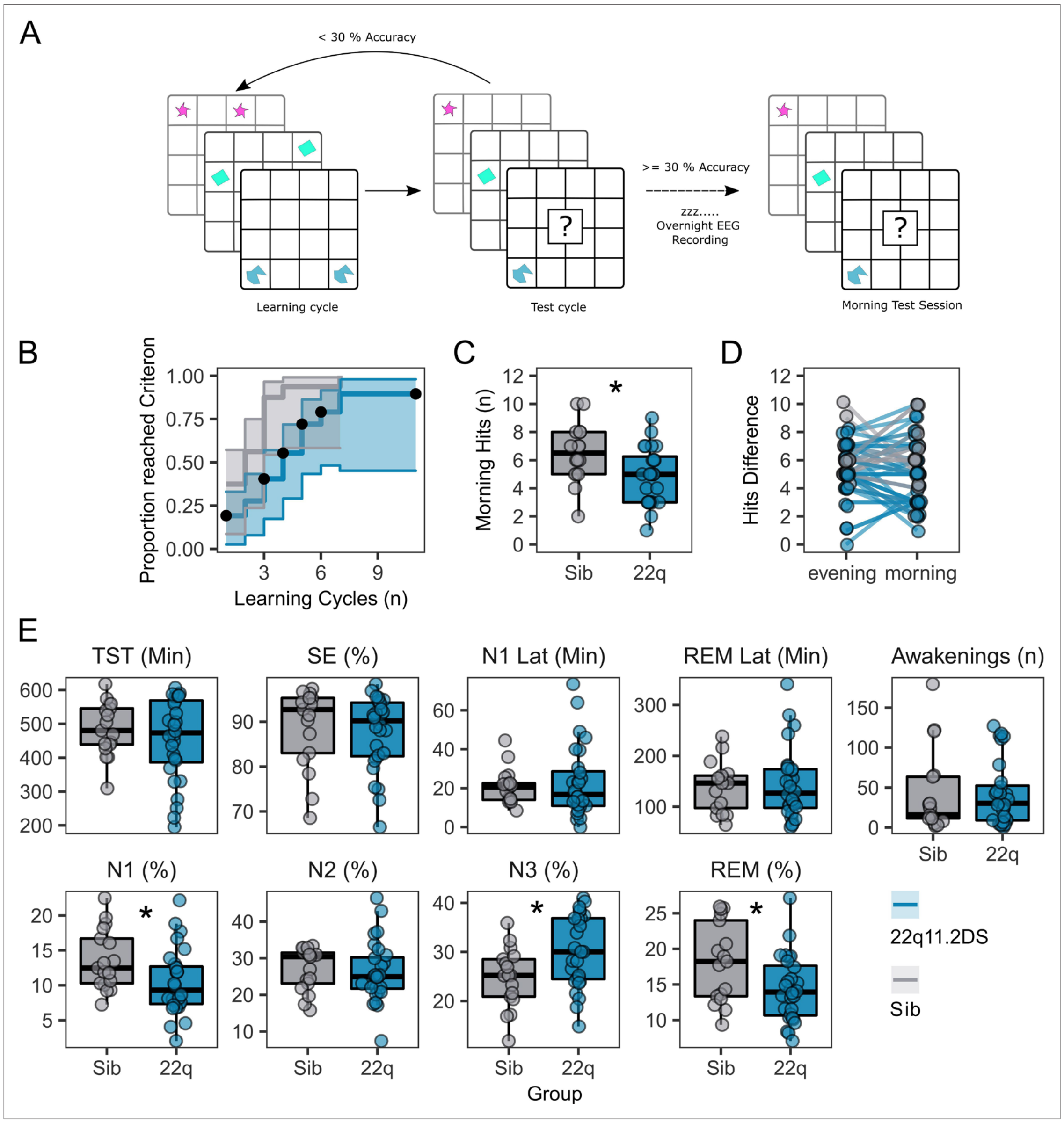

Figure 1. Memory task performance and sleep architecture features of 22q11.2DS.

(**A**): Schematic of the 2D object location task. The evening before sleep EEG recordings, participants first were sequentially presented with pairs of images on a 5 x 6 grid. In a subsequent test cycle, they were presented with one image of the pair, and were required to select the grid location of the other half of the pair. If the participant did not achieve > 30% accuracy, they would have another learning cycle. In the morning a single test cycle was undertaken. (**B**): Plot of performance in acquiring the 2D object location task, showing the proportion of participants in each group reaching the 30% performance criterion after each learning cycle. Shaded areas represent the 95% confidence interval. Black dots show when participants were right-censored due to stopping the task prior to reaching the 30% criterion. (**C**): Box plots of performance in the morning test session, where participants had one cycle of the memory task. Number of correct responses is out of a possible 15. Asterix indicate the group difference is statistically significant, generalised linear mixed model, p<0.05 (see ***Table 2*** for full statistics). (**D**): Plots of change in performance between the final evening learning session and the morning test session. Each participant is represented as a point, with a line connecting their evening and morning performance. Points have been slightly jittered to illustrate where multiple participants had the same score. (**E**): Box and whisker plots showing sleep architecture features: Total sleep time (TST) in minutes, Sleep efficiency (SE) as a percentage, Latency to N1 sleep (minutes), Latency to first REM sleep (minutes), Number of awakenings after sleep onset (n), Percentage of hypnogram in N1 sleep, Percentage of hypnogram in N2 sleep, Percentage of hypnogram in N3 sleep, and Percentage of hypnogram in REM sleep. Asterixes indicate the group difference is statistically significant, linear mixed model, *P*<0.05 (see ***Table 1*** for full statistics). Boxes represent the median and IQR, with the whiskers representing 1.5 x the IQR. Individual participant data are shown as individual points. Points have been slightly jittered in the x direction only to illustrate where multiple participants had similar results.

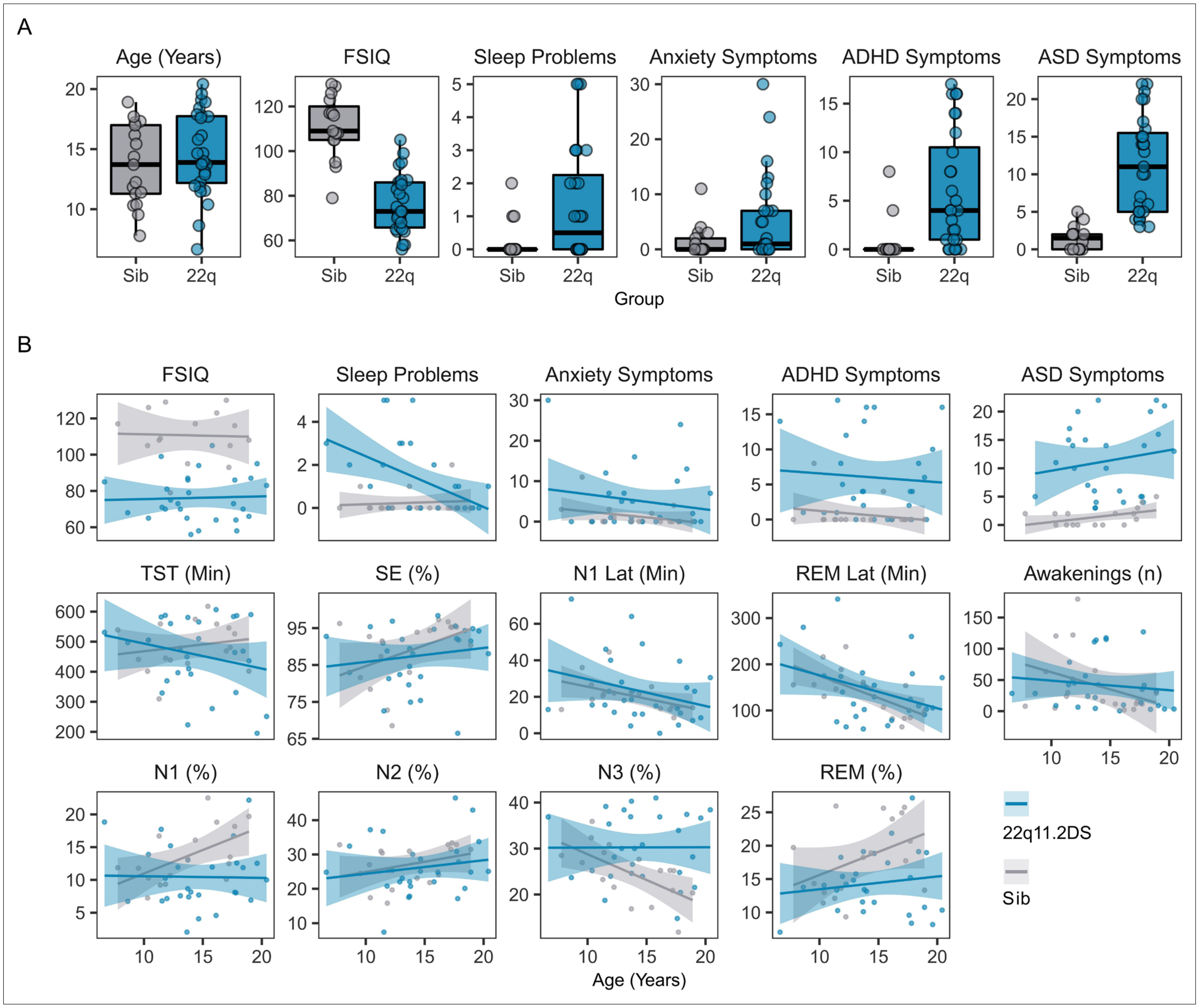

Figure 1—figure supplement 1. Individual Psych Hypno Data. (**A**) Boxplots and overplotted individual data for participant age, Full Spectrum IQ (FSIQ) and psychiatric symptoms. ADHD = Attention Deficit Hyperactivity Disorder symptoms, from the CAPA interview; ASD = Autism Spectrum Disorder symptoms, from the SCQ interview. Boxes represent the median and IQR, with the whiskers representing 1.5 x the IQR. Individual participant data are shown as individual points. Points have been slightly jittered in the x direction only to illustrate where multiple participants had similar results. (**B**) Line plots and overplotted individual data for FSIQ, psychiatric and hypnographic measures, plotted against participant age at the time of EEG. Lines of best fit and 95% confidence intervals are derived from linear models. Acronyms: TST = Total Sleep Time (in minutes); SE = Sleep Efficiency (%); N1 Lat = Latency to reach first N1 sleep epoch, (in minutes); REM Lat = Latency to reach first REM sleep epoch (in minutes); N1 = Percentage of night in N1 sleep; N2 = Percentage of night in N2 sleep; N3 = Percentage of night in N3 sleep; REM = Percentage of night in REM sleep.

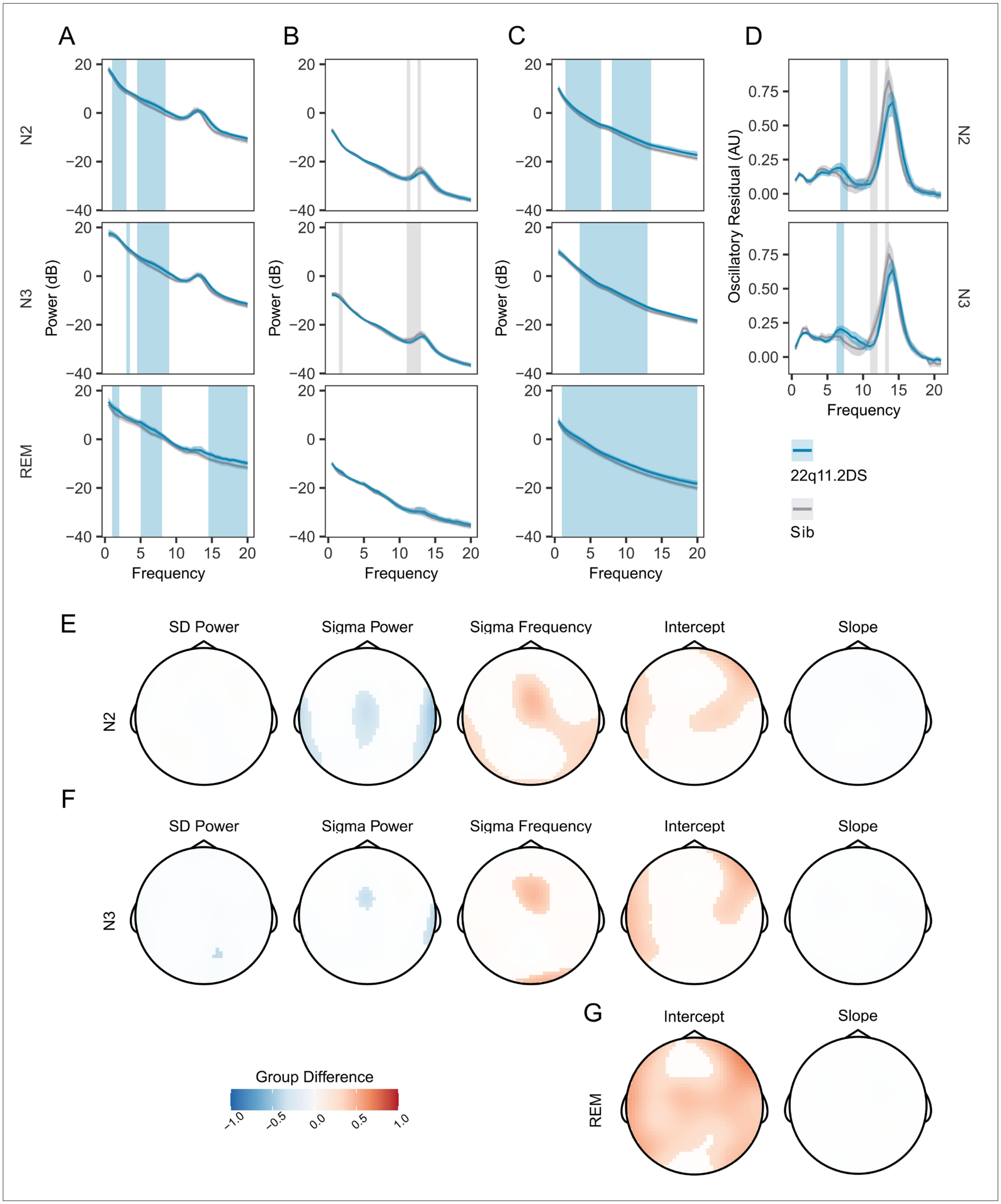

Figure 2. Increased PSD power and Sigma Frequency in 22q11.2DS. (**A**) *Raw Welch Power Spectral Density (PSD, in decibels, 10 * log_{10} of the PSD) on electrode Cz across Stage N2, N2, and REM sleep. Lines show group mean power (blue = 22q11.2DS, gray = Sibling), with bootstrapped 95% confidence intervals of the mean. Patches show regions of significant (cluster corrected) difference between groups (blue = 22q11.2DS >Sibling; grey = 22q11.2DS <Sibling), with 22q11.2DS being associated with increased power at lower frequencies.* (**B**) *Welch PSD of Z-Scored EEG signals*

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*on electrode Cz, as in (**A**); with 22q11.2DS being associated with lower power in the sigma frequency band (10–16 Hz) (**C**) Fractal (1 /f) component of EEG signal processed using the IRASA method on electrode Cz, conventions as (**A**). Higher power across a wide frequency range in 22q11.2DS. (**D**) Oscillatory component of the EEG signal processed using the IRASA method on electrode Cz, conventions as (**A**). (**E**) Topoplots of group difference calculated from multilevel generalized additive models fit to the full 60 channel dataset for the five measures (mean Slow Delta power, mean Sigma power and peak Sigma frequency, 1 /f Intercept and 1 /f Slope) recorded in N2 sleep. Positive differences represent z score group differences indicate 22q11.2DS >Sibling (red colors); negative group differences (blue colors) indicate 22q11.2DS <Sibling. Only regions were where the probability of direction statistic for group difference was >0.995 are colored. (**F**) As in (**E**), for N3 sleep. (**G**) As in (**F**), for REM sleep. Note as REM sleep lacks prominent oscillatory activity, we have not calculated models for SD or sigma related measures in REM as these would not be meaningful.*

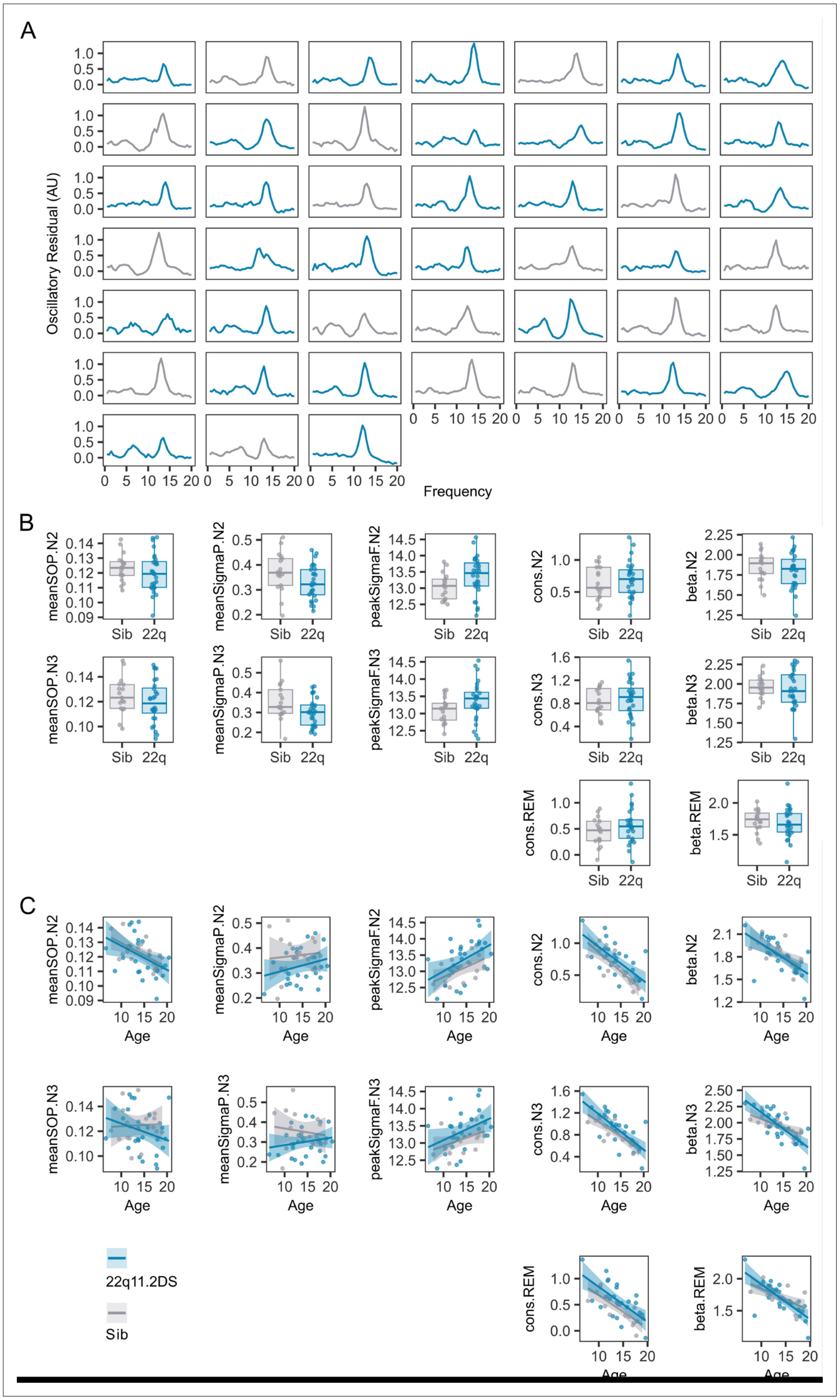

Figure 2—figure supplement 1. Individual PSDs. (**A**)*Plots of the oscillatory signal component of the EEG for each individual in stage N2 (each plot is the average PSD for a single participant). Plots are colored by genotype; grey = sibling, blue = 22q11.2DS.* (**B**) *Boxplots and overplotted individual data for spectral measures derived from N2, N3 and REM epochs. Boxes represent the median and IQR, with the whiskers representing 1.5 x the IQR. Individual*

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participant data are shown as individual points. Points have been slightly jittered in the x direction only to illustrate where multiple participants had similar results. (**C**) *Line plots and overplotted individual data for spectral measures derived from N2, N3, and REM epochs, plotted against participant age at the time of EEG. Lines of best fit and 95% confidence intervals are derived from linear models.*

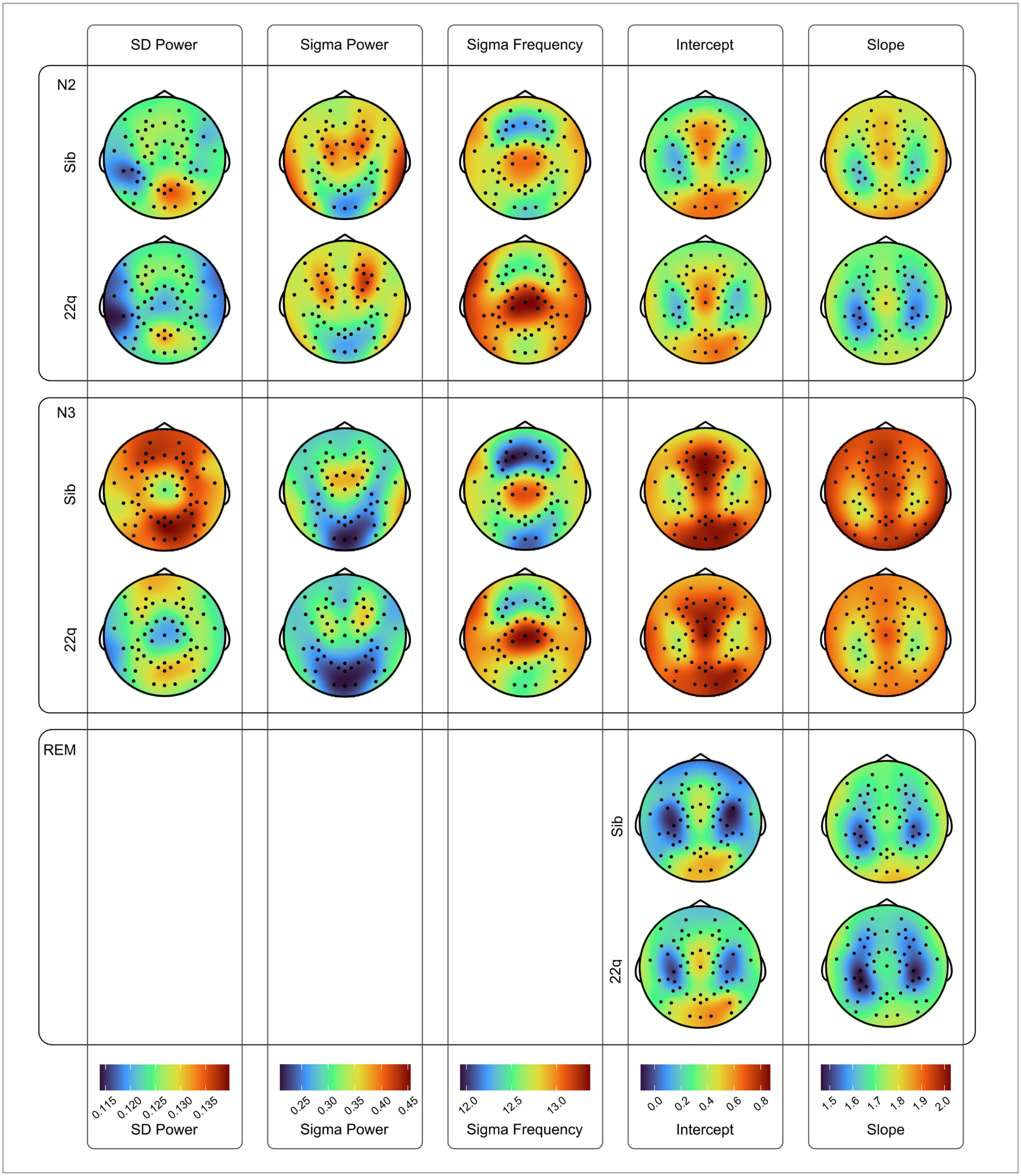

Figure 2—figure supplement 2. Group PSD Topos. Topoplots of group average values for spectral EEG measures (slow delta power, sigma power, peak sigma frequency, 1 /f signal component intercept and 1 /f signal component slope), across N2, N3, and REM epochs. Topoplots in the same column are on the same color scale (color scale shown at the bottom of each column).

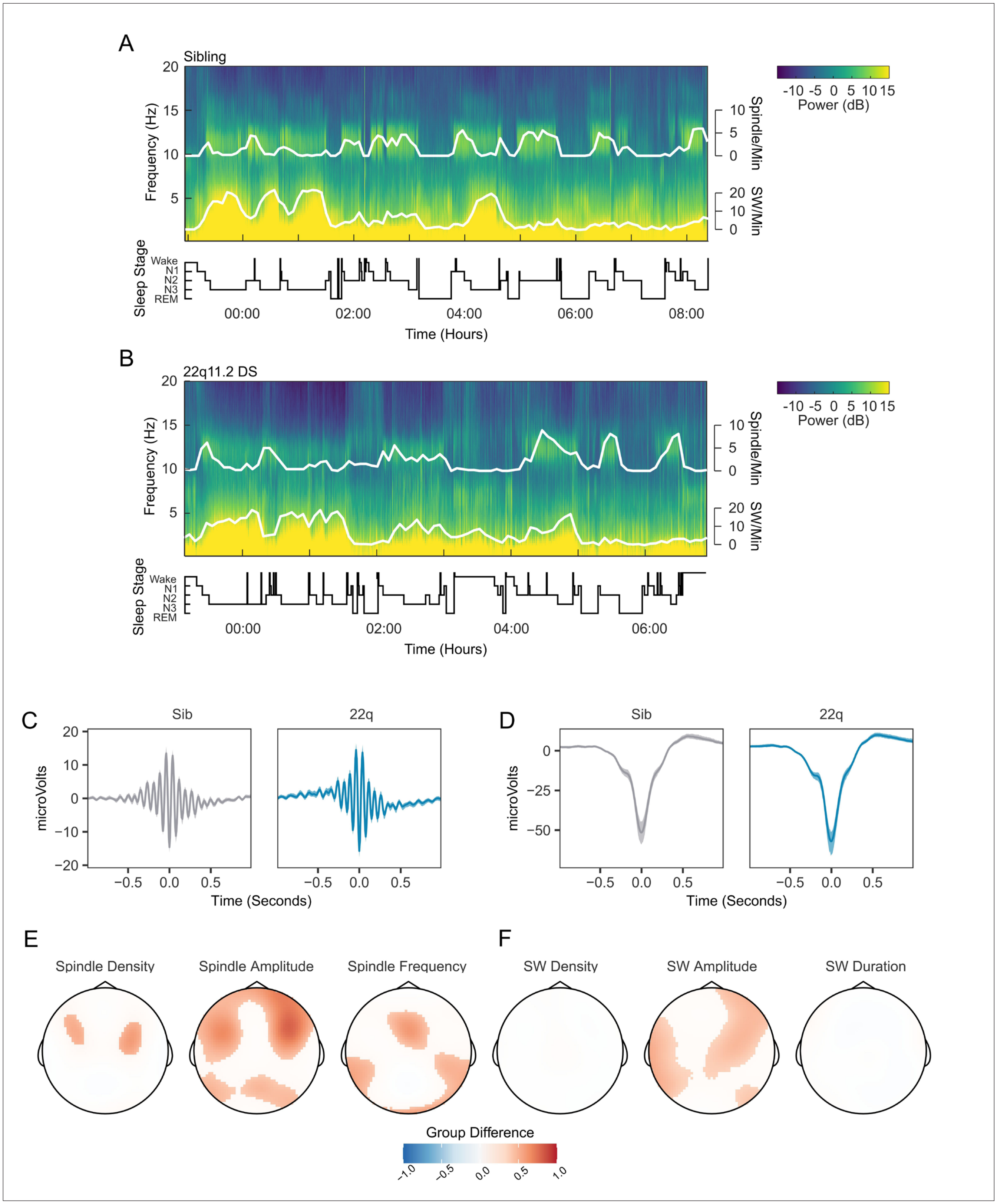

Figure 3. Spindles and slow waves in 22q11.2DS. (**A**) *Example spectrogram of a whole night EEG recording from electrode Cz for an example sibling. The associated hypnogram is displayed below the spectrogram in black, detected spindle and slow wave events are overplotted in white. The co-occurrence of spindle events with epochs of N2 sleep, and of SW events and N3 sleep can be observed.* (**B**) *Example spectrogram of a whole night EEG recording from electrode Cz for an example participant with 22q11.2DS, sibling of the participant illustrated in A* (**C**) *Average spindle waveforms*

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detected on electrode Cz for siblings (left, gray), and 22q11.2DS (right, blue). For each individual the average spindle waveform at Cz was calculated, these averaged waveforms were then calculated for all siblings or all participants with 22q11.2DS. Shaded areas highlight the bootstrapped 95% confidence interval of the mean. (**D**) *Average SW waveforms detected on electrode Cz, same conventions as C* (**E**) *Topoplots of group differences in spindle density, amplitude and frequency, Z-transformed, across all 60 electrodes, from GAMM analyses. Only regions with significant group differences are highlighted. Red colors indicate values of the parameter of interest are greated in 22q11.2DS; blue color that the parameter of interest is greater in siblings* (**F**) *Topoplots of group differences in SW density, amplitude and duration, conventions as in E.*

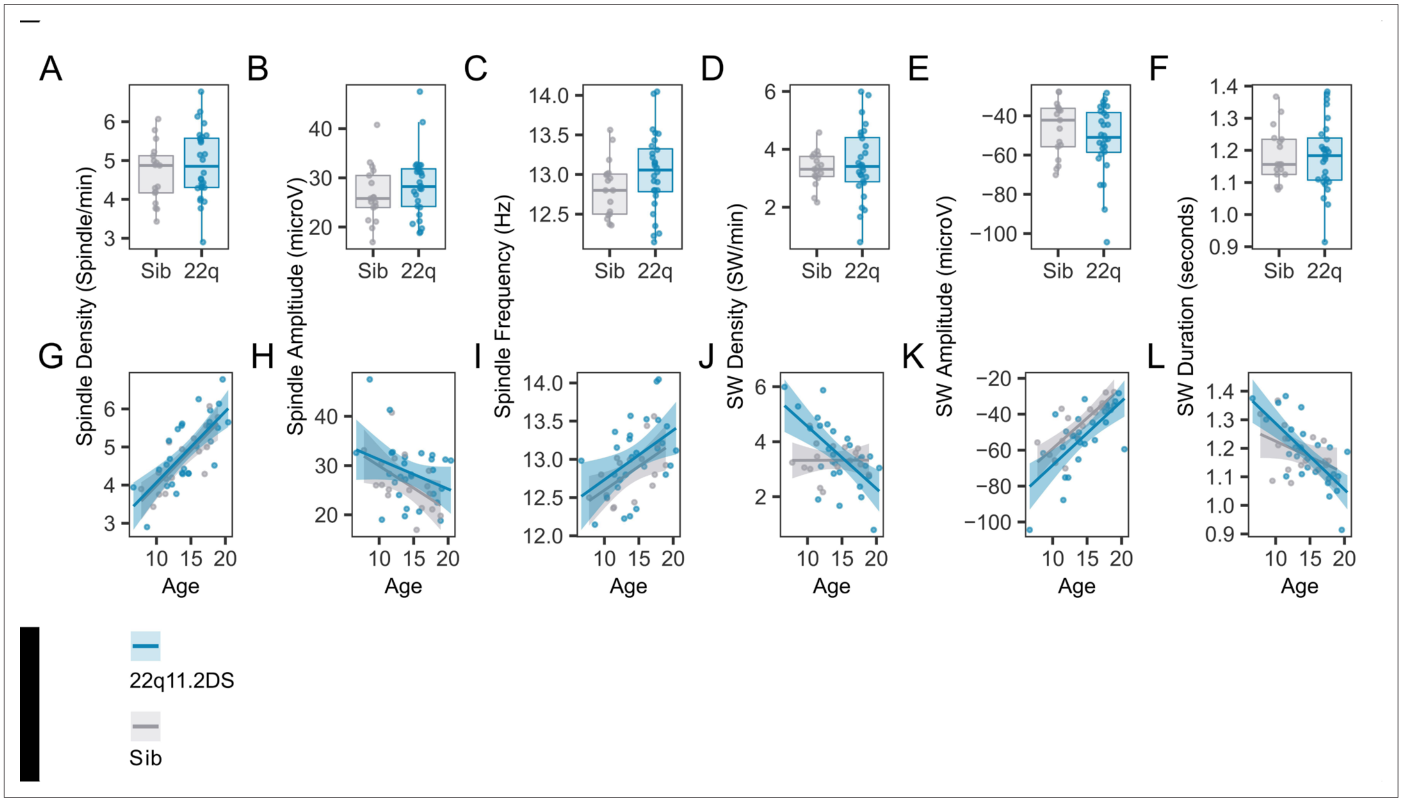

Figure 3—figure supplement 1. Individual event data. (**A**)*Boxplots and overplotted individual data for spindle and SW measures. Boxes represent the median and IQR, with the whiskers representing 1.5 x the IQR. Individual participant data are shown as individual points. Points have been slightly jittered in the x direction only to illustrate where multiple participants had similar results.* (**B**) *Line plots and overplotted individual data for spindle and SW measures, plotted against participant age at the time of EEG. Lines of best fit and 95% confidence intervals are derived from linear models.*

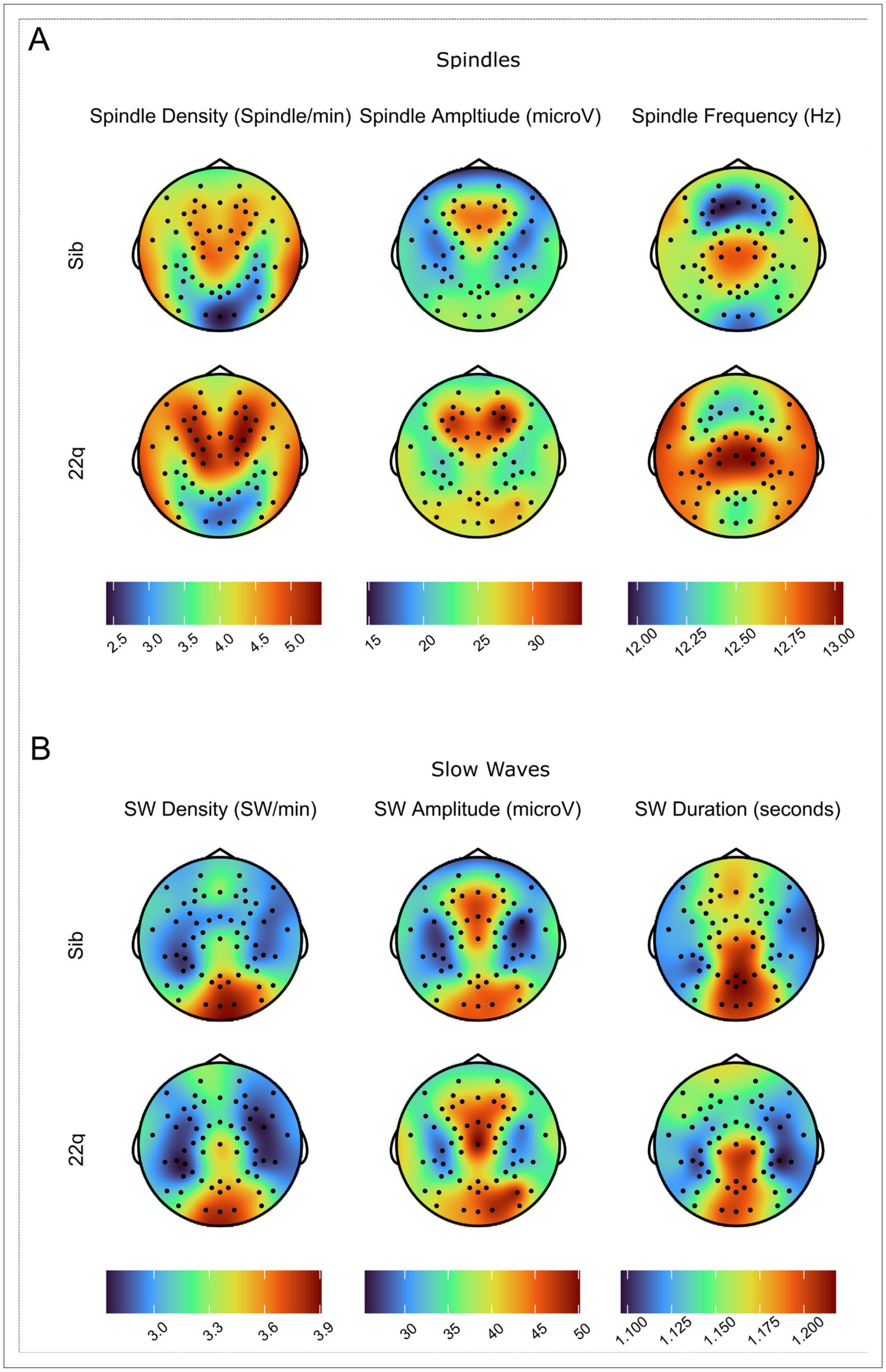

Figure 3—figure supplement 2. Group event topoplots. (**A**)*Topoplots of group average values for spindle measures (density, amplitude, and frequency). Topoplots in the same column are on the same color scale (color scale shown at the bottom of each column).* (**B**) *Topoplots of group average values for SW measures (density, amplitude, and duration). Topoplots in the same column are on the same color scale (color scale shown at the bottom of each column).*

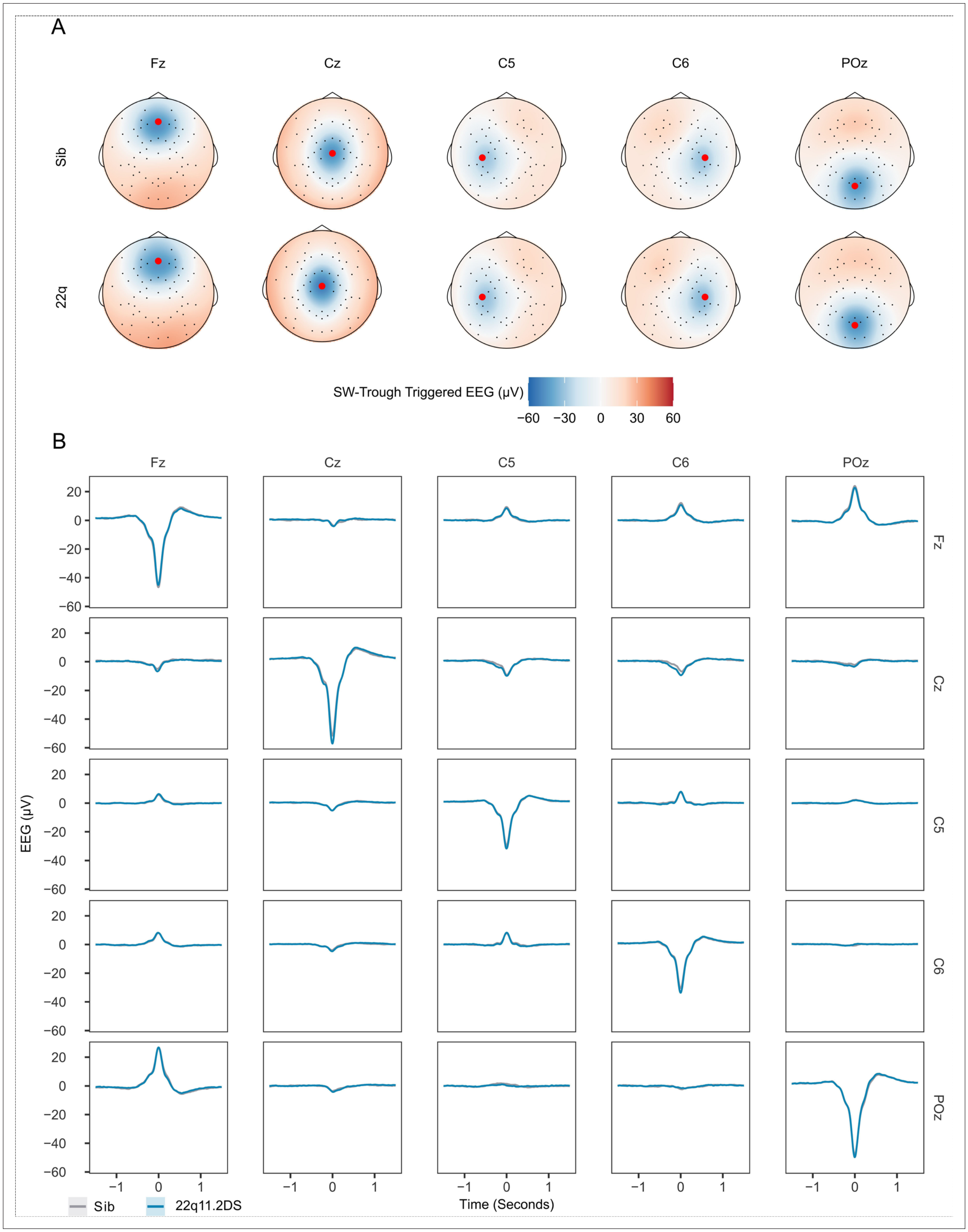

Figure 3—figure supplement 3. SW-triggered potentials. (**A**) The panels show topographical representations of the voltage (in microVolts) recorded at all electrodes at the negative trough of a SW detected at 5 seed electrodes (Fz, Cz, C5, C6 and POz, seed electrode locations are highlighted with red dots.). Each panel shows the average over all SWs detected on that electrode for each group. (**B**) Average SW waveforms across the same set of seed electrodes as in (**A**), with the average waveform at the time of the SW trough at the seed electrode (trigger, columns) shown at all other seed

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electrodes (target, rows) This demonstrates that when negative SW troughs are detected on a given electrode, negative potentials are also recorded on adjacent electrodes, and positive potentials are detected on distant electrodes, reflecting volume conduction and the average reference applied during pre-processing. Note that only negative SWs were detected on each electrode for further analysis, and we performed no cross-electrode analysis (e.g. coherence) in the present study.

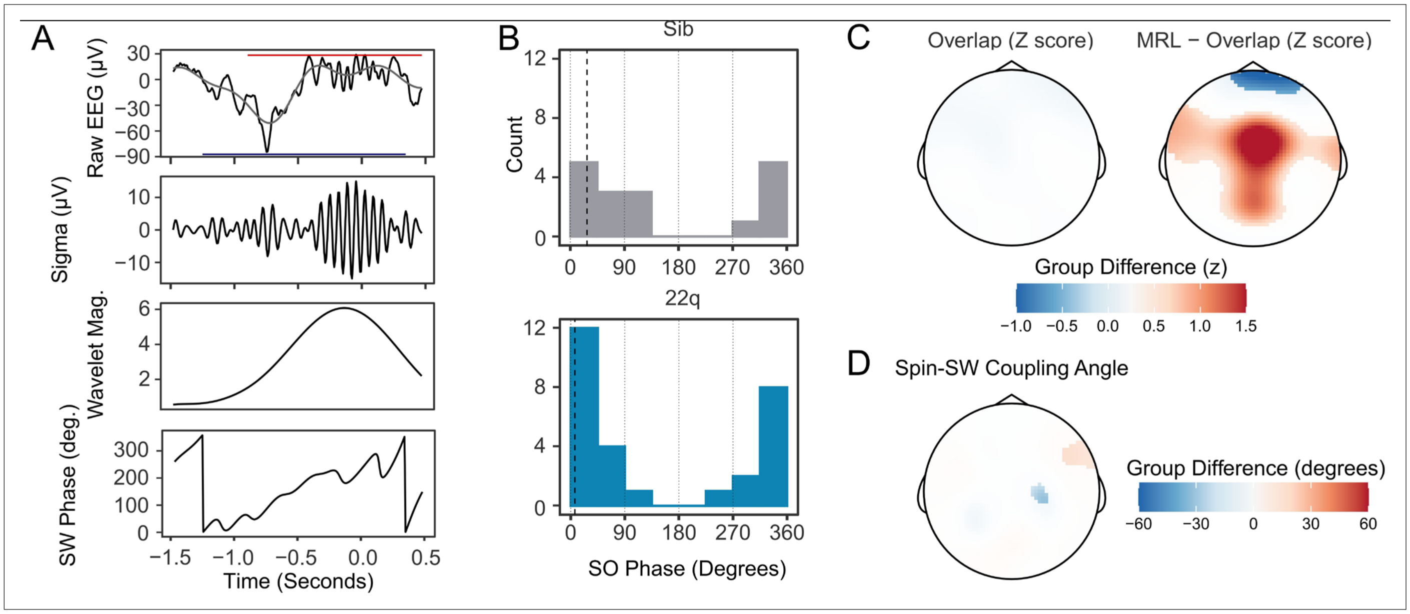

Figure 4. Increased spindle-SW coupling in 22q11.2DS. (**A**) *Illustrative plot of a single spindle and SW recorded at electrode Cz in a control sibling. From top to bottom, panels show the raw EEG (black) with Slow-Wave frequency (0.25–4 Hz) filtered data superimposed (gray) and with the detected boundaries of the spindle and SW highlighted with a red and blue horizontal bar, the sigma-filtered raw signal (10–16 Hz); the magnitude of the continuous wavelet transform of the signal (center frequency 13 Hz); and the SW phase (in degrees*). (**B**) *Histograms of the mean SW phase angle of spindles detected overlapping an SW for all participants at electrode Cz. The SO phase angles are as defined in* (**A**). *Black vertical dashed lines indicate the mean coupling phase angle for each group* (**C**) *Topoplots of group difference in spindle-SW coupling properties: z-transformed spindle-SW overlap (left), and z-transformed mean resultant length (right). The color represents the difference in z-score between groups where a multilevel generalized additive model fit to each dataset predicts a difference between group.* (**D**) *Topoplots of mean Spindle-SW coupling phase angle, where a multilevel generalized additive model fit to each dataset predicts a difference in coupling phase angle between groups.*

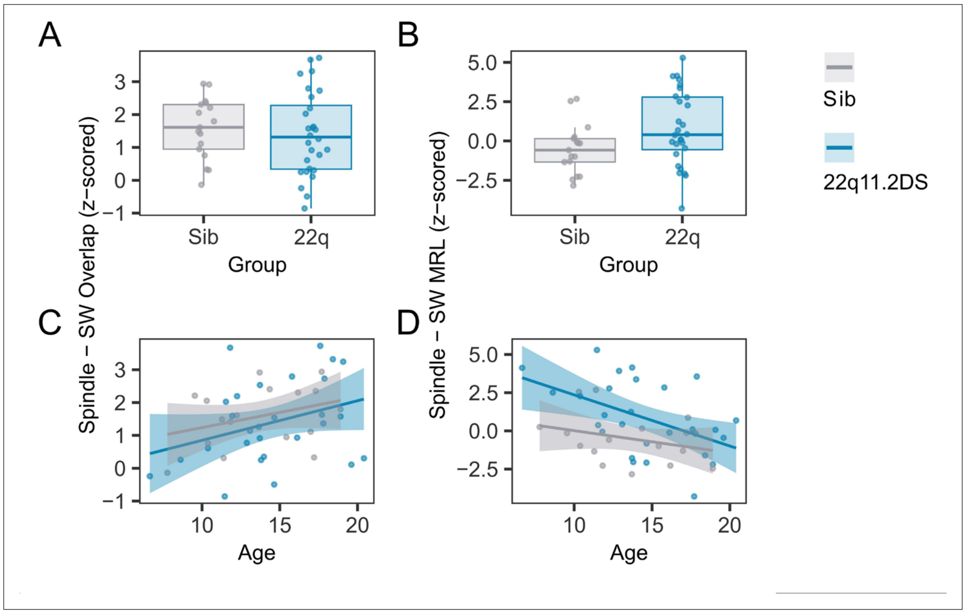

Figure 4—figure supplement 1. Individual coupling data. (**A**) *Boxplots and overplotted individual data for spindle - SW overlap. Boxes represent the median and IQR, with the whiskers representing 1.5 x the IQR. Individual participant data are shown as individual points. Points have been slightly jittered in the x direction only to illustrate where multiple participants had similar results.* (**B**) *Boxplots and overplotted individual data for spindle - SW MRL, conventions as A.* (**C**) *Line plots and overplotted individual data for spindle - SW overlap, plotted against participant age at the time of EEG. Lines of best fit and 95% confidence intervals are derived from linear models.* (**D**) *Line plots and overplotted individual data for spindle - SW MRL, conventions as C.*

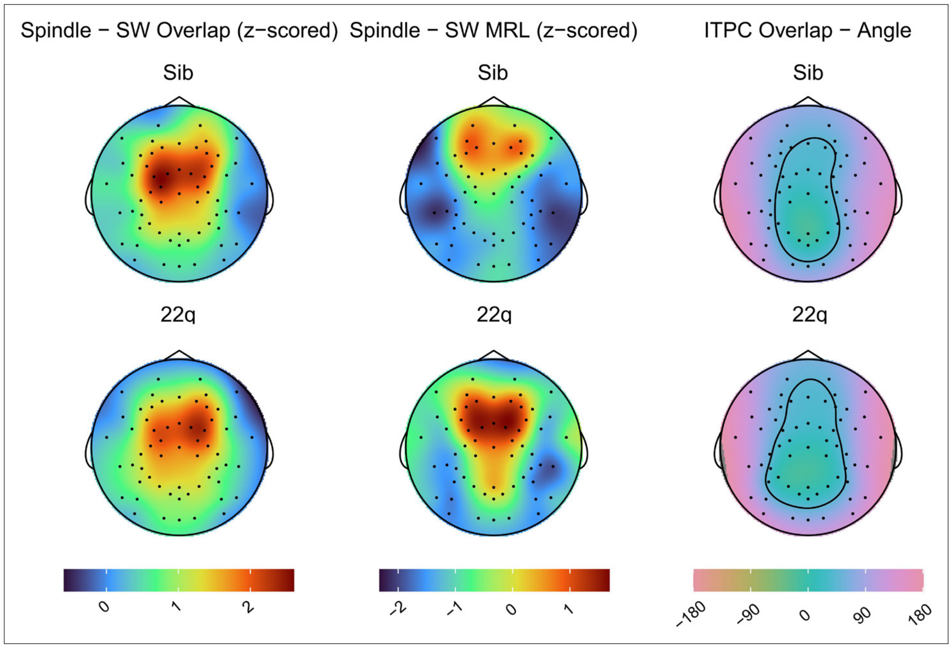

Figure 4—figure supplement 2. Topoplots of group average values for spindle – SW coupling measures (overlap, MRL and mean angle). Topoplots in the same column are on the same color scale (color scale shown at the bottom of each column), note the Angle Measure is in degrees.

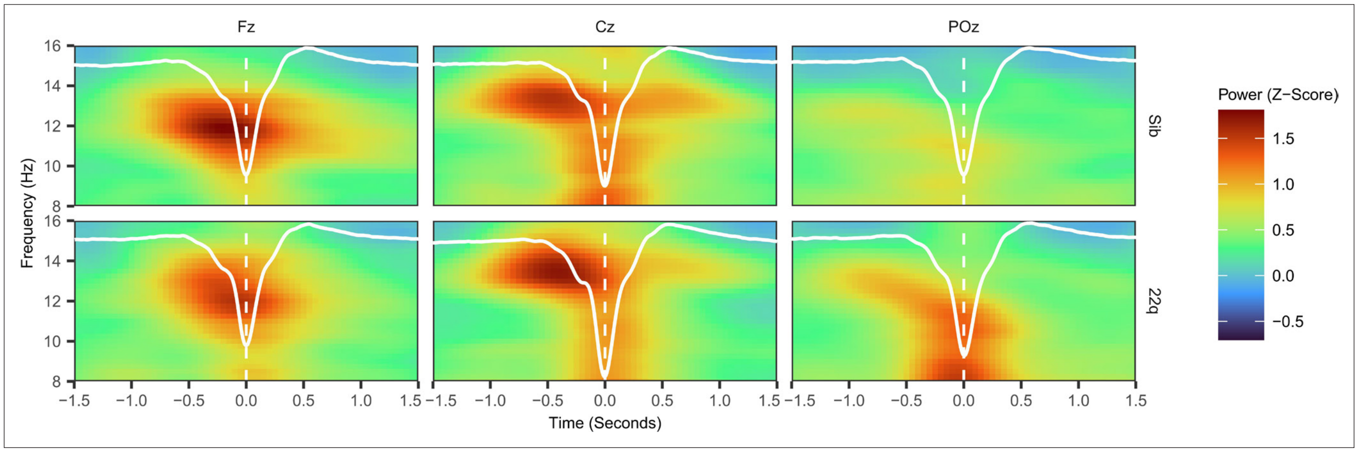

Figure 4—figure supplement 3. SW-Triggered Scalograms. This plot shows the average peri-SW scalogram (time-locked to the SW trough) recorded on electrodes Fz, Cz and POz, with average SW waveforms recorded o the same electrodes superimposed in white. This time-frequency representation is normalised to the average scalogram of the 2 – 1.5 seconds prior to the SW trough and therefore is a z-score. Note that power in the spindle frequency range appears to peak prior to the SW trough, particularly on electrode Cz.

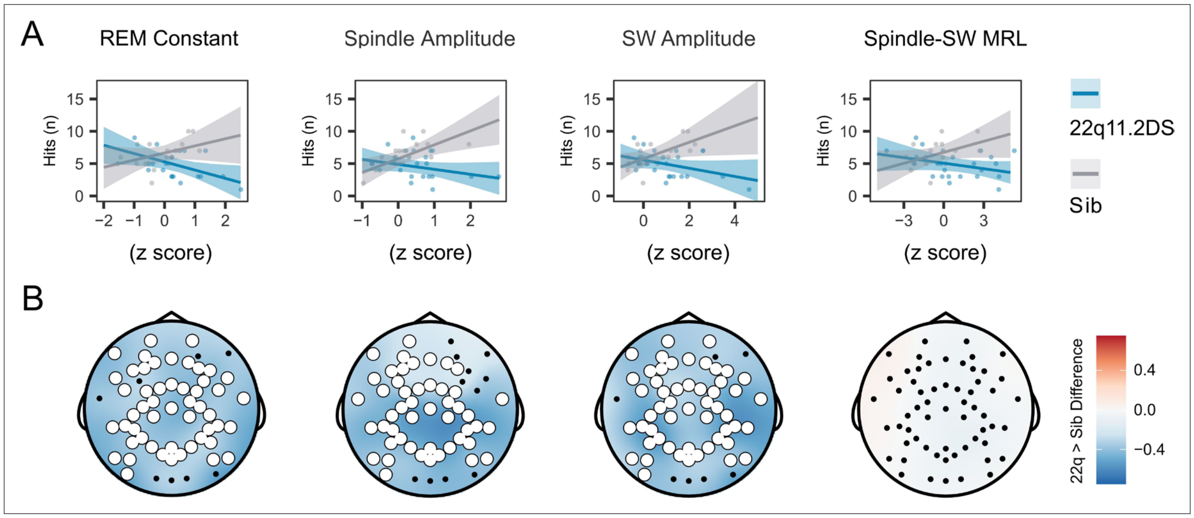

Figure 5. EEG signatures of sleep dependent memory consolidation. (**A**) Scatter plot of the relationship between EEG measures (recorded on electrode Cz) and hits in the memory task test session, by group. Lines represent predicted mean values, with 95% confidence interval, from linear mixed model. (**B**) Topoplots of the value of the group*EEG feature interaction term, for models fit to hits in the morning test session. Electrodes highlighted in white indicate a significant interaction for an EEG measure detected on that channel, after correction for multiple comparisons. Note all topoplots are on the same color scale.

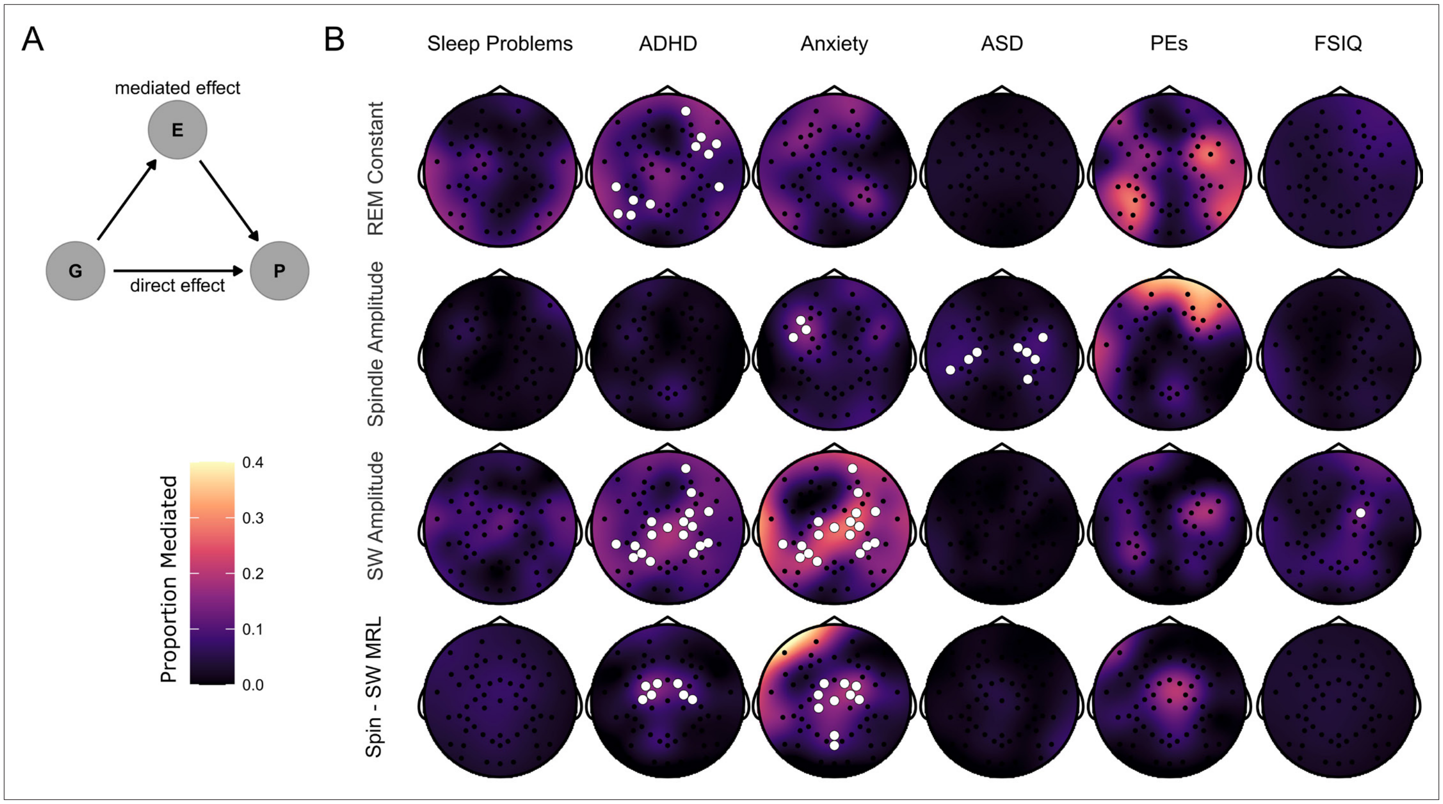

Figure 6. Mediation of psychiatric symptoms and FSIQ by sleep EEG features. (**B**) Topoplots of the proportion of the effect of genotype on psychiatric measures and FSIQ mediated by one of four NREM sleep EEG features (REM constant spindle amplitude, SW amplitude and spindle-SW MRL). Fill color represents the Proportion Mediated. Electrodes are highlighted in white where a mediation model fit on data from that electrode had a significant mediated effect and a significant total effect, corrected for multiple comparisons by the cluster method. (**A**) Directed acyclic graph describing the mediation model fit to EEG data. The effect of Group (**G**) on psychiatric measures and FSIQ (**P**) was hypothesized to be mediated by (**E**) – sleep EEG features.