# Neurophysiological Correlates of Dynamic Beat Tracking in Individuals With Williams Syndrome

## *Supplemental Information*

## Supplemental Methods and Materials

*Participant details*

Participants with WS were recruited from a residential summer music camp, while TD controls were recruited from the community. Musical skill or interest were not required to attend the music camp. Another three individuals with WS and one TD control completed the EEG paradigm but were excluded from analyses due to comorbid Autism spectrum disorder (n=1) and technical difficulties (n=3).

*Behavioral measures*

The Musical Interest Scale (MIS) consists of items rated on a 6-point scale with a 0 rating corresponding to "Does not describe" and a 5 rating corresponding to "Describes perfectly". Here, we were primarily interested in participants' beat perception skills and thus assessed this with one question from the MIS Skill subtest (Question 11): "My child has a good sense of rhythm". The Sensitivity to Sounds questionnaire assesses how frightened or bothered a child is on five sound dimensions (loudness, suddenness, duration, low-pitched, high-pitched) on a seven-point Likert scale, which are summed to create a total sensitivity to sounds score (1,2).

Williams syndrome (WS) participants also completed the Beat Alignment Test (BAT, (3)). In this test, participants heard beep tracks superimposed on short musical excerpts of various genres and determined whether or not the beeps aligned with the musical beat. On misaligned tracks, beeps were phase shifted by 30% either ahead of or behind the beat. Participants first completed practice items with feedback prior to completing the 16 test items. BAT scores were computed as d-prime (d') recognition scores (Z-score normalizing the proportion of hits minus the proportion of false alarms) for each participant. Hits were correctly identified tracks with "on beat" beeps and false alarms were incorrectly identified tracks with "off beat" beeps (i.e., participant wrongly identified beeps as "on beat"). BAT data was excluded for four participants who did not understand task directions (response bias score of 0).

*EEG data collection procedure*

Auditory stimuli were presented at 75dB via a loudspeaker approximately 60cm above the participants' heads. EEG data were recorded in NetStation software (v.4.4) using a high-density array of 128 Ag/AgCl electrodes embedded in soft sponges (Geodesic Sensor Net, ECI, Inc., Eugene, OR, USA) connected to a high impedance amplifier (NetAmps 200). Data were collected at a sampling rate of 500 Hz with a 0.1-200 Hz filter. Impedance was measured below 40 kΩ before the EEG session.

*EEG preprocessing*

Data were first band-pass filtered from 0.5-100 Hz (zero-phase, non-causal finite impulse response (FIR) filter) and sinusoidal noise at 60 Hz was then removed using the cleanline (65) EEGLAB plugin. Noisy channels were then identified with the Artifact Subspace Reconstruction (ASR) function (4) and subsequently interpolated using spherical spline interpolation. Continuous data were additionally cleaned using ASR (recommended SD threshold of 20) and channels were re-referenced to the average. Independent component analysis (ICA) was conducted to identify and remove components associated with eye movements and cardiac activity, with the aid of the ICLabel tool in EEGLab (5). The threshold for automated artifact component rejection in ICLabel was 80%, and was corroborated by manual inspection of the IC components. For both the Accent1 condition and Accent2 condition, data were epoched from -400ms to 1200 ms from first tone onset and additionally filtered from 0.5-55Hz. Epochs that exceeded a -100/+100 μV threshold were rejected (6). Manual inspection steps were implemented throughout the preprocessing pipeline to ensure fidelity of the cleaned data. An average of 11.24% (*SD*=9.83%) and 7.49% (*SD*=5.69%) of trials were rejected for the WS group and TD control group, respectively[1]. Additional filtering and time-windowing steps were implemented for the time-frequency and ERP analyses.

[1] Two WS participants had higher rates of epoch rejection (39% and 30%) compared to other subjects, but inclusion of their data did not affect results as they still had more than 250 clean trials of data per condition. No other participants had more than 25% of their original data modified, either through channel interpolation or epoch rejection.

*Parameters of cluster based permutation tests*

The two-tailed non-parametric clustering test zeroes out values that do not surpass the t-threshold (cluster level alpha = 0.05). The minimum number of channels to be included in a significant cluster was 2, and the distance between neighboring channels was determined using the Fieldtrip triangulation parameter. We used a Monte Carlo method to test the significance of each cluster compared with clusters made from 1000 random permutations of values drawn from the other conditions/group labels (7)*;* cluster-level *p*-values < 0.05 were considered significant.

*Cluster sum calculations in WS*

To correlate EEG activity with behavioral measures, we summed EEG power over the group-defined significant clusters to obtain a single value per participant (8). Cluster sums were computed for each participant for each frequency band in the evoked time-frequency analyses. Thus, for time-frequency analyses there were 6 cluster sums computed for each participant: alpha, beta, and gamma clusters for the Beat1 and Beat2 effects. We then ran correlations between each of these neural measures and the behavioral measures (MISQ11, Sensitivity to Sounds, BAT d').

*Linear regressions accounting for age, sex, and IQ*

We ran multiple linear regressions using the *lm* function in R to assess whether between group (WS vs. TD) differences in neural variables persisted when accounting for Age and Sex. For ERPs, mean amplitude for each individual was computed over the significant group difference clusters (P1 component, 28-58ms; P2 component, 148-202ms). For time-frequency analyses, mean power for each individual was computed over the significant group difference in the alpha band corresponding to the Beat1 effect (74-254 ms, 31 electrodes). No other time-frequency analyses yielded significant power differences between groups. However, to ensure that the lack of group differences remained when including Age and Sex in the models, we computed the mean power separately for WS and TD individuals for the between condition significant clusters. This was done for the alpha band cluster corresponding to the Beat2 effect as well as both beta and gamma band clusters. Thus, we ran 8 multiple linear regression models with our two ERP (P1, P2 components) and six time-frequency (alpha, beta, gamma activity, Beat1 and Beat2 effects) variables of interest. Group, Age, and Sex were included as independent variables in each model.

Additionally, we conducted separate linear regressions within the WS group with IQ scores as the independent variable and the two ERP and six time-frequency neural measures as dependent variables.

*Exploratory statistical analyses for brain and behavior measures in WS*

We first ran planned correlations between all behavioral measures and our six time-frequency measures (alpha, beta, and gamma evoked activity for Beat1 and Beat2 effects) to assess how neural responses (specifically evoked power in TFRs) to beat patterns are associated with behavioral measures of rhythm perception and auditory sensitivities. From the correlations we then built linear regression models to test the unique contribution of neural measures to the variance in behavioral measures of music/rhythm skills (MISQ11 rhythm item, Sensitivity to Sounds, BAT). KBIT-2 IQ, Age, and Sex were included as potential covariates. We used the *lm* function in R for regression models with continuous dependent variables (BAT, Sensitivity to Sounds) and the “polr” function from the R package *MASS* for the model with the ordinal dependent variable (MISQ11).

## Supplemental Results and Discussion

*Group differences persist when controlling for age and sex*

Group differences for the ERP P1 and P2 components as well as the alpha Beat1 effect were still significant after controlling for Age and Sex. The lack of group differences for the beta and gamma activity, as well as the alpha Beat2 effect, remained non-significant when controlling for Age and Sex. Thus, our results are robust to these variables and Age and Sex do not account for a significant amount of the variance seen in our beat perception task.

For the P1 and P2 components, there was a main effect of Sex (males>females, $p$=0.017 and $p$=0.003). For the alpha and beta Beat1 effects, there was a significant main effect of Age, but this was no longer significant in both cases when excluding one significantly older TD control participant.

*IQ and neural measures within the WS group*

Within the WS group, IQ was associated with only two of our eight neural variables of interest: amplitude of the P1 component for the Beat1 effect ($t$=-2.35, $p$=0.027) and gamma power for the Beat2 effect ($t$=3.25, $p$=0.0033). Individuals with WS who had lower IQ scores had greater amplitude for the P1 component. This parallels a study of children with autism, where lower IQ was associated with reduced suppression of early auditory ERP components (13). A different trend was found for the gamma Beat2 effect; individuals with lower IQ scores had a greater increase in gamma power in response to the second tone. We might have expected lower IQ scores to correlate with less of a switch in the beat percept (i.e., more difficulty with the task, less increase in gamma for the Beat2 effect). This somewhat inconsistent relationship of IQ to neural variables parallels other work investigating relationships between IQ and EEG correlates of auditory and attentional processing in WS (14) and could be a consequence of sample size.

*Individual differences in WS group: Correlating brain and behavior*

The only brain measure that significantly correlated with our behavioral measures of interest was alpha power for the Beat2 effect, i.e., greater alpha power to the second tone in each condition sequence. The only behavioral measure to correlate with this alpha activity was the MISQ11 (parent-reported musical rhythm ability). Thus, in subsequent regression models, alpha power, IQ, Age, and Sex were entered as independent variables for our dependent variable of interest: MISQ11. The results of the models are presented in Table S2 and Figure S3. In a simple ordinal logistic regression model, alpha power for the Beat2 effect was associated with parent-reported musical rhythm ability ($t$=2.05, $p$=0.040). However, when controlling for IQ, Age, and Sex, this association disappeared ($t$=1.84, $p$=0.065).

The simple ordinal logistic regression revealed an association in the opposite direction of the predicted effect: We expected more negative alpha power for the Beat2 effect (i.e. larger distance between blue and red lines in Figure 2 in main text) would correlate *negatively* with MISQ11 scores. This would indicate a more successful switch in the neural response to the beat, which we would expect to correlate with rhythm abilities in WS. Several factors may contribute to this inconclusive finding. First, many parents rated their child at the top of the scale (score of 5), limiting the variability in ratings. Second, several of the adults with WS in this study no longer lived at home with the parent who completed the questionnaire, so parents' reports may not be the most reflective measure of their child's current rhythm abilities. Additionally, the MIS questionnaire relies on parent observation of their child's overt rhythmic movements; beat perception and rhythm production abilities (i.e., movement to beat) may not always align, as evidenced by individuals with beat deafness (9,10). Differences in task demands (implicit, passive listening vs. explicit responses) may also explain the lack of a relationship in the current study between neural measures of beat perception and the Beat Alignment Test (BAT), and may require larger sample sizes, especially when considering the high variability in the WS population on behavioral tests of rhythm perception and production (11,12). In general, quantifying individual differences using EEG power measures is still an evolving area in the field.

## Supplemental Tables and Figures

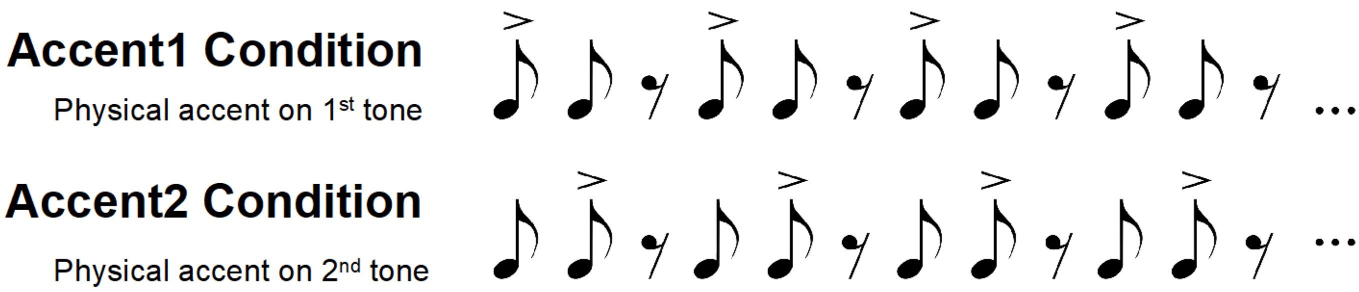


**Figure S1.** Stimuli used in the dynamic attending EEG paradigm. Figure adapted from Iversen et al., 2009.

**Table S1. Linear regression models of group differences (WS vs. TD) controlling for Age and Sex.**

| *Dependent Variable* Independent variables | β | SE | t | p |
|---|---|---|---|---|
| *P1 component* | | | | |
| Group | 0.35 | 0.11 | 2.42 | 0.02* |
| Age | 0.16 | 0.0055 | 1.09 | 0.28 |
| Sex | -0.38 | 0.11 | -2.50 | 0.017* |
| *P2 component* | | | | |
| Group | 0.30 | 0.21 | 2.15 | 0.037* |
| Age | 0.09 | 0.01 | 0.62 | 0.54 |
| Sex | -0.46 | 0.22 | -3.17 | 0.0030* |
| *Alpha, Beat1 effect* | | | | |
| Group | 0.42 | 0.21 | 3.06 | 0.0039* |
| Age | -0.29 | 0.010 | -2.01 | 0.05*+ |
| Sex | -0.01 | 0.21 | -0.066 | 0.95 |

| | | | | | |
|---|---|---|---|---|---|
| *Beta, Beat1 effect* | | | | | |
| | Group | -0.19 | 0.14 | -1.23 | 0.23 |
| | Age | -0.35 | 0.007 | -2.10 | 0.043*+ |
| | Sex | -0.07 | 0.15 | -0.42 | 0.68 |
| *Gamma, Beat1 effect* | | | | | |
| | Group | -0.16 | 0.21 | -0.96 | 0.34 |
| | Age | -0.069 | 0.01 | -0.39 | 0.70 |
| | Sex | -0.12 | 0.22 | -0.71 | 0.48 |
| *Alpha, Beat2 effect* | | | | | |
| | Group | -0.30 | 0.14 | -1.86 | 0.071 |
| | Age | -0.029 | 0.0072 | -0.17 | 0.86 |
| | Sex | -0.11 | 0.15 | -0.66 | 0.51 |
| *Beta, Beat2 effect* | | | | | |
| | Group | 0.13 | 0.13 | 0.75 | 0.46 |
| | Age | 0.023 | 0.0066 | 0.13 | 0.90 |
| | Sex | -0.017 | 0.14 | -0.10 | 0.92 |
| *Gamma, Beat2 effect* | | | | | |
| | Group | 0.06 | 0.24 | 0.39 | 0.70 |
| | Age | 0.28 | 0.01 | 1.62 | 0.11 |
| | Sex | -0.047 | 0.24 | -0.28 | 0.78 |

*Notes.* All β values are standardized. The base code for Group is TD controls and the base code for Sex is males.

* denotes a significant main effect in the model.

+ when excluding one TD control who was significantly older than the rest of the participants (61.67 years), the main effect of Age was no longer significant for both the alpha Beat1 effect (*p*=0.10) and beta Beat1 effect (*p*=0.38).

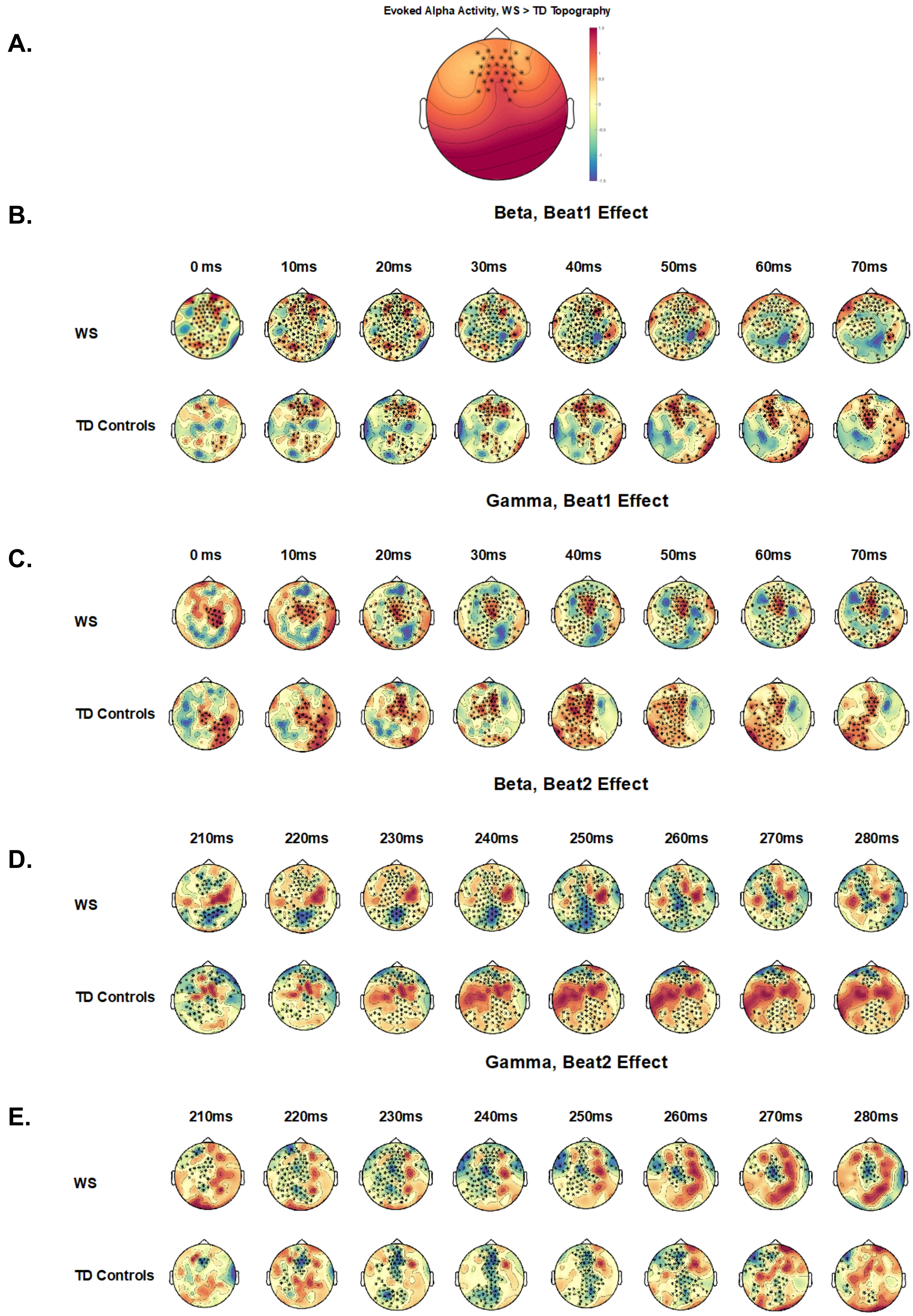
A.
Evoked Alpha Activity, WS > TD Topography
B.
Beta, Beat1 Effect
0 ms
10ms
20ms
30ms
40ms
50ms
60ms
70ms
WS
TD Controls
Gamma, Beat1 Effect
C.
0 ms
10ms
20ms
30ms
40ms
50ms
60ms
70ms
WS
TD Controls
Beta, Beat2 Effect
D.
210ms
220ms
230ms
240ms
250ms
260ms
270ms
280ms
WS
TD Controls
Gamma, Beat2 Effect
E.
210ms
220ms
230ms
240ms
250ms
260ms
270ms
280ms
WS
TD Controls

**Figure S2.** A) Group difference topographies for the alpha Beat1 effect. Individuals with WS exhibited greater activity than TD controls over a 74-254ms window across 31 electrodes, clustered in a fronto-central region. Asterisks denote electrodes contributing to the significant cluster.

B-E) Representative latencies (0-70ms) for the Beat1 effect in participants with WS (top) and TD controls (bottom) in beta (B) and gamma (C) frequency bands. Representative latencies (210-280ms) for the Beat2 effect in participants with WS and TD controls in beta (D) and gamma (E) frequency bands. Topography plots are statistical maps of *t*-values; asterisks denote electrodes contributing to the significant clusters. Based on visual inspection of these topographies, individuals with WS exhibit a somewhat broader scalp distribution compared to TD controls, particularly for the Beat1 effect.

**Table S2. Regression model associated with MISQ11**

| Dependent Variable | $\beta^b$ | SE | t | p | 95% CI |
|---|---|---|---|---|---|
| **MISQ11** | | | | | |
| Alpha Beat2 effect | 0.91 | 0.49 | 1.84 | 0.065 | [-0.004 1.98] |
| IQ | -0.87 | 0.43 | -2.03 | 0.042 | [-1.77 -0.069] |
| Age | -0.63 | 0.44 | -1.42 | 0.15 | [-1.55 0.24] |
| Sex | 0.36 | 0.45 | 0.80 | 0.42 | [-0.51 1.28] |

*Note.* $^b$ $\beta$ estimates are unstandardized.

MISQ11= Music Interest Scale, Question 11 (rhythm item).

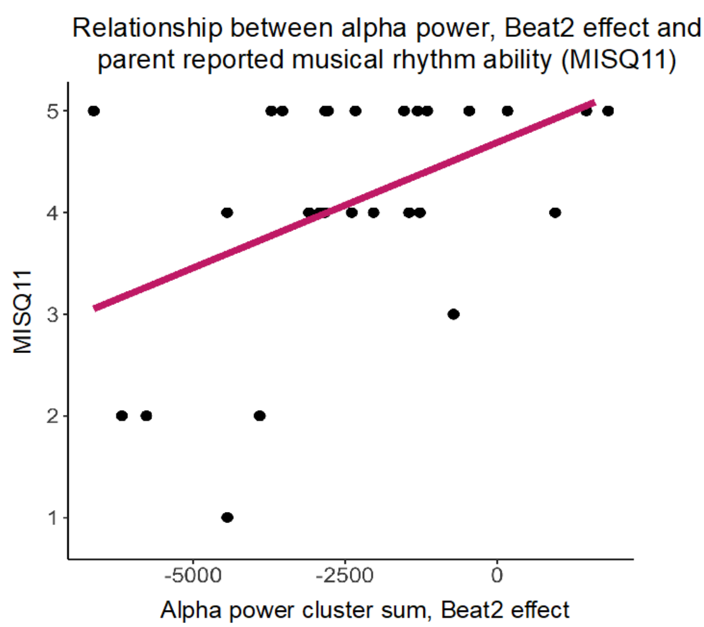


**Figure S3.** Correlation between MISQ11 and alpha power Beat2 effect in the WS group. Negative cluster sum values indicate a greater Beat2 effect. Each point is a participant with WS. This association is not significant when controlling for Age, Sex, and IQ. MISQ11= Musical Interest Scale, Question 11 (rhythm item).

## Supplemental References


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