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Altered neural oscillations in classical galactosaemia during sentence production

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Abstract

Classical galactosaemia (CG) is a hereditary disease in galactose metabolism that despite dietary treatment is characterized by a wide range of cognitive deficits, among which is language production. CG brain functioning has been studied with several neuroimaging techniques, which revealed both structural and functional atypicalities. In the present study, for the first time, we compared the oscillatory dynamics, especially the power spectrum and time–frequency representations (TFR), in the electroencephalography (EEG) of CG patients and healthy controls while they were performing a language production task. Twenty-one CG patients and 19 healthy controls described animated scenes, either in full sentences or in words, indicating two levels of complexity in syntactic planning. Based on previous work on the P300 event related potential (ERP) and its relation with theta frequency, we hypothesized that the oscillatory activity of patients and controls would differ in theta power and TFR. With regard to behavior, reaction times showed that patients are slower, reflecting the language deficit. In the power spectrum, we observed significant higher power in patients in delta (1–3 Hz), theta (4–7 Hz), beta (15–30 Hz) and gamma (30–70 Hz) frequencies, but not in alpha (8–12 Hz), suggesting an atypical oscillatory profile. The time-frequency analysis revealed significantly weaker event-related theta synchronization (ERS) and alpha desynchronization (ERD) in patients in the sentence condition. The data support the hypothesis that CG language difficulties relate to theta–alpha brain oscillations.

KEYWORDS

classical galactosaemia, EEG, neural oscillations, sentence production, spectral analysis, syntactic planning, time–frequency analysis

1 | INTRODUCTION

Classical galactosaemia (CG, OMIM 230400) is a hereditary disease in galactose metabolism caused by a

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deficiency of galactose-1-phosphate uridylyltransferase (GALT, EC 2.7.7.12) enzyme, due to pathogenic variants in the *GALT* gene, and as a consequence, it is characterized by an absent or barely detectable GALT enzyme activity.[1] Despite a lifelong galactose-restricting diet, CG patients suffer from long term complications with a broad range of symptoms and severity,[2–4] among which are neurological and cognitive impairments. In particular, neuroimaging studies observed altered myelination, scattered white matter abnormalities, cerebral and cerebellar atrophy.[5–7] With regard to cognitive functioning, attentional, memory and expressive language impairments have been reported. Whereas receptive language seems to not be affected in CG, patients experience difficulties in articulation, but also in syntactic planning during speech production.[8] In order to mitigate CG language deficit, speech therapy is commonly suggested and a new early communication intervention delivered via telepractice has also been proposed.[9,10]

Nonetheless, a complete understanding of the cause of CG language deficit and, therefore, of the best treatment options is still lacking. Previous neuroimaging studies investigated the anatomical and functional connectivity features of the CG brain. Differences in resting state connectivity and in white matter structure have been reported, suggesting altered information processing.[7,11] With regard to speech production, a similar network of brain regions was observed to be active both in CG patients and healthy controls; however, additional regions (i.e., inferior frontal gyrus and superior temporal gyrus) were active in patients, highlighting the potential recruitment of additional neural resources to compensate for network deficits.[12] Moreover, an event-related potential (ERP) study pointed to differences in amplitude of the P300 component in CG patients and controls,[8] interpreted as patients recruiting additional syntactic planning resources.

Neural oscillations in CG patients have not been investigated yet. Oscillations are informative markers for brain functioning: they allow regions of the brain to communicate with each other by means of phase coherence in certain frequency bands across neuronal ensembles.[13,14] Therefore, differences in oscillations can indicate differences in the brain functional connectivity. Here, we look into brain oscillations in two different ways. One approach is a general power spectrum analysis. It provides insight into very general information on frequency power in the human brain. Higher power values relate to better network connectivity,[17] and have been reported in other patient groups with brain pathologies before.[26] We investigate whether a similar pattern is visible in CG. The other approach is time–frequency (TF) analysis. This approach allows investigating power changes over time, related to a certain event. In our experiment, the event is the onset of the visual animation, which coincides with the onset of the targeted speech planning process. TF, therefore, provides specific frequency and temporal information about neural oscillation involved in speech planning and is sensitive to changes in the task (here to syntactic complexity).

The focus on neural oscillations now is a follow-up on previous brain research in CG reporting atypical white matter structure and ERP P300. Considering that oscillations depend on white matter microstructure and that the P300 is driven by theta oscillations,[15–17] we hypothesize that CG patients neural oscillations differ from controls, especially in the theta frequency range, during language production. For the analysis we used the dataset of Timmers et al.,[8] which was previously analyzed with a focus on the P300 ERP.

Findings on neural oscillations would expand our current understanding of the neural mechanisms of language and CG language deficit.

2 | MATERIALS AND METHODS

2.1 | Provided dataset

The original dataset of Timmers et al.[8] included both EEG recordings and audio recordings of 22 adolescent patients diagnosed with classical galactosaemia and 21 adolescent healthy controls. Participants were native Dutch speakers, they had normal or corrected to normal vision and did not suffer of any relevant health conditions. The ethical clearance for the study was given by The Medical Ethical Committee of Maastricht University Hospital/Maastricht University (azM/UM).

For the present study, three datasets had to be excluded from the analysis (one patient and two healthy controls), due to the presence of excessive artifacts (i.e., both slow drifts and high frequency noise). As a result, 40 participants were included in the analysis: 21 patients (6 males, mean age: 15.0 years, SD 2.2, range 10.8–19.1 years) and 19 controls (6 males, mean age: 14.1 years, SD 1.8, range 11.4–17 years).

2.2 | CG patient characteristics

The patients included in the original study by Timmers et al.[8] were diagnosed at the mean age of 12 days old (range: 0–60) and were introduced to a diet at the mean age of 12 days old (range: 0–60). Their GALT activity was measured at diagnosis and it was on average 0.6% of the mean reference value (range: not detected to 1.83%). All patients adhered to a galactose-restricted diet. The mean urine galactose and galactitol levels (measured in

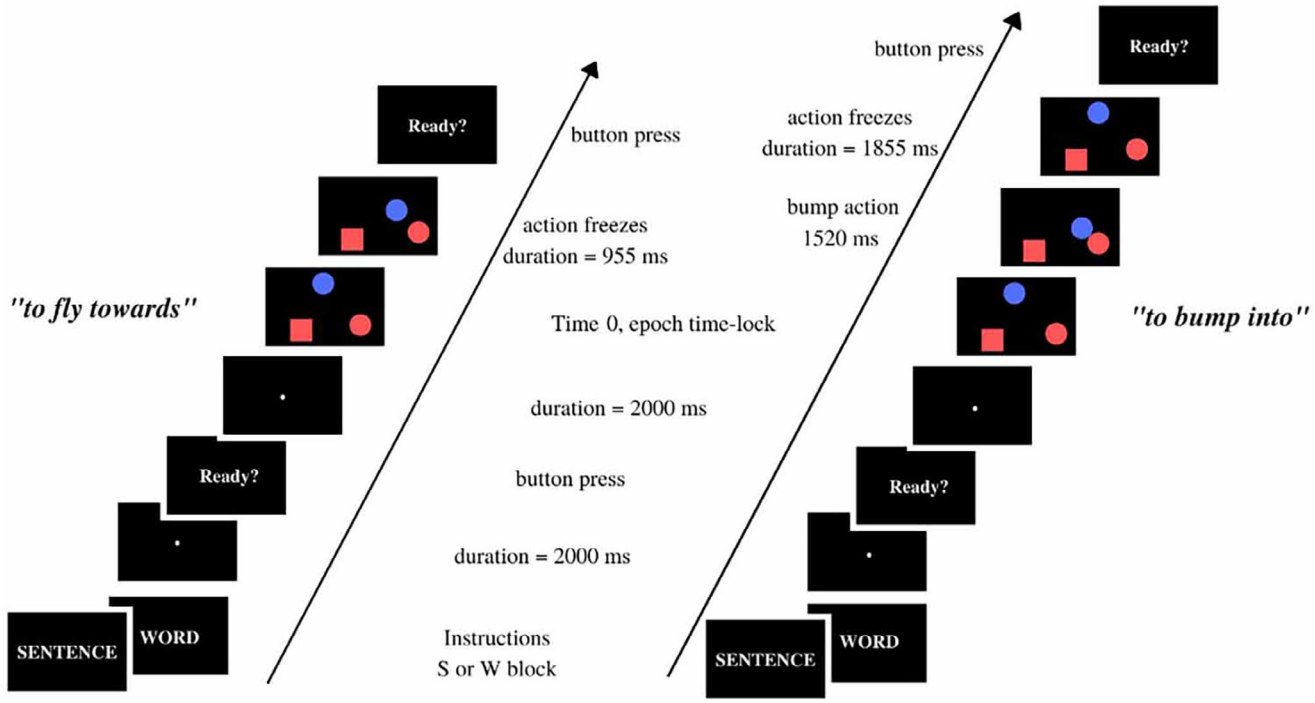

FIGURE 1 Experiment paradigm. Left: timing of the experiment for 'fly towards' and 'bump into' naming trials. Instruction about the type of animated scene description (sentence vs word naming) was presented at the beginning of each block.

μmmol/mmol creatinine, within 3 months of EEG testing) were 12.0 and 132.0, respectively. Finally, 68.2% of the patients received special education, 86.4% received speech therapy and 50% received motor therapy at some point in life. With regards to the *GALT* pathogenic variant, 50% ($n = 10$) of the patients were homozygous for the c.563A>G (p.Gln188Arg) variant, better known as (Q188R/Q188R), 25% was compound heterozygous for this one variant and another pathogenic variant and 25% had other severe pathogenic variants.

With respect to their cognitive abilities, the patients performed three neuropsychological tests to assess their visuo-motor skills, short- and long-term visual memory (The Rey Osterreith Complex Figure), sustained attention (The Bourdon-Vos test) and verbal working memory skills (Digit Span, Forward and Backward). In comparison with the control group, CG patients were slower in the sustained attention test and showed lower performance in the visuo-motor and verbal working memory tests. More details about the participants and the experimental design can be found in Timmers et al.[8]

2.3 | Experimental paradigm

Participants performed a language production task, based on the paradigm introduced by Indefrey et al.,[18] during which they were instructed to describe a visually animated scene with two different levels of syntactic complexity. Each scene consisted of three geometrical shapes (square, triangle, or circle), which could have one of three possible colors (red, blue, or green); during the scene one of the figures performed one of two possible actions ('*fly towards*' or '*bump into*') upon another figure (Figure 1).

In the experiment, participants were asked to describe the presented scenes using single-words ('W'), for instance '*circle*' '*blue*' '*circle*' '*red*' '*to bump into*' (low syntactic complexity), or using sentences ('S'), for instance '*the blue circle bumps into the red circle*' (high syntactic complexity). Importantly, the two conditions of syntactic complexity were visually identical, they only differed in required syntactic planning. In the word condition, lexical resources for single word lexical access were needed (semantic, phonology, articulation). For sentence naming, additional syntactic encoding was required to bind the words into a correct sentence, both on a local noun-phrase level (i.e., inflections of adjectives and verb) and on a sentence level (i.e., assembly of the two noun-phrases in a syntactic phrase).

First, participants performed a practice block, which was followed by the main language task: each participant performed three runs. Each run included two blocks, one per condition, consisting of 32 trials each. Instructions were given to the participants at the beginning of each block. The duration of the animated scenes varied

between action verbs (Figure 1): 955 ms for "*to fly towards*", and 1885 ms for '*to bump into*' type of sentences. The difference was due to a higher number of frames for '*to bump into*' trials. The first 955 ms of the scenes did not differ across animation conditions.

2.4 | EEG recording and behavioral measures

Neural activity was recorded while participants performed the language task using Brain Vision Recorder software (Brain Vision, MedCaT B.V.) with a sampling rate of 500 Hz. The EEG was recorded with an elastic cap (Electro-Cap International (ECI) Inc.) and 32 electrodes were positioned according to the international 10–20 system. Twenty electrodes were used as active leads: F3, Fz, F4, FC3, FCz, FC4, C3, Cz, C4, CP3, CPz, CP4, P3, Pz, P4, O1, Oz, O2, T3 and T4. AFz was used as ground electrode and A1 as reference electrode. Vertical and horizontal eye movements were recorded by four electrodes, respectively at left upper (SO1) and lower ridge (IO1) and on the left (LO1) and right (LO2) canthus. Additionally, both accuracy and reactions times were measured: respectively, the number of errors and self-corrections, voice onset time (VOT) and total speech time (TST) were investigated. As Timmers et al.[8] reported, CG patients made significantly more errors, had significantly longer VOT and TST in comparison with the control group. Additionally, the sentence condition resulted in longer TST and more self-corrections compared to the word condition for both groups.

2.5 | Data analysis

2.5.1 | Pre-processing

The EEG recording of each participant was pre-processed with EEGLAB (version 2019.1).[19] First, the data were band-pass filtered between 0.1 Hz and 100 Hz and bipolar electrooculography (EOG) signals were computed from the four EOG electrodes. Then, the data were re-referenced to the average of A1 and A2 (mastoids), following the same approach of Timmers et al.[8] The data were epoched from −1500 to 3500 ms post stimulus onset and baseline corrected from −1500 to −1400 ms. The epoch length was set to 5000 ms in order to include 3 cycles of the slowest frequency of interest (delta, 1 Hz, 3 s) and included the critical time window,[20] considered as the time between the start of the animation (time = 0) and the voice onset time (VOT, on average, 1850 ms for controls and 2000 ms for patients). Channels showing anomalous and noisy activity across the whole recording were detected and signals were corrected by means of spherical interpolation.

Additionally, the data were corrected for artifacts in two separate steps: first, they were inspected visually for unique and unusual artifacts and the related noisy trials were rejected (on average 10% of the trials). Secondly, an independent component analysis (ICA) was performed to reject artifact patterns (e.g., slow drifts, muscle movement, eye movement). We conducted a mixed ANOVA and a one-way ANOVA to check for differences in the final number of trials between groups and conditions and in the final number of ICA components between groups, respectively. No differences were observed in the number of trials after rejection between groups ($p = 0.345$) and/or conditions ($p = 0.427$, group × condition: $p = 0.207$). Similarly, no differences were observed in the number of included ICA components after rejection between groups ($p = 0.416$).

2.5.2 | Power spectrum analysis

The power spectrum analysis reports the amount of activity in certain frequency bands of the signal, averaged for the duration of each trial, allowing us to observe and compare the overall oscillatory profiles of CG patients and healthy controls. The power spectrum was computed in EEGLAB (version 2022.0)[19] running on MATLAB (version R2022a, MathWorks, Natick, MA) for each frequency band (delta 1–3 Hz, theta 4–7 Hz, alpha 8–12 Hz, beta 15–30 Hz and gamma 30–70 Hz) using a fast Fourier transform (FFT) on each trial. The spectral decomposition was expressed as absolute power values (1 μV^2). In particular, for this analysis the entire epoch time window (−1500 to 3000 ms) was considered, with the result that the spectral power values corresponded to the averaged power across 5000 ms. The same time window was used for the time–frequency analysis.

2.5.3 | Time–frequency analysis

The time–frequency analysis illustrates how the activity in certain frequency bands changes across time, revealing fine grained task-related power changes (known as event-related spectral perturbations, ERSPs) and how these differ between groups. The ERSPs were computed with EEGLAB toolbox (version 2022.0)[19] running on MATLAB (version R2022a, MathWorks, Natick, MA) for the EEG signal from the following channels: F3, Fz, F4, FC3, FCz, FC4, C3, Cz, C4, CP3, CPz, CP4, P3, Pz, P4, O1, Oz and O2.

The ERSPs were calculated on the entire epoch (from −1500 ms to 3000 ms, with a baseline between −1500 ms and 0), in the frequency range between 1 and 70 Hz by using a frequency-dependent Hanning window with a frequency resolution of 0.7 Hz and a time resolution of 22 ms.

2.5.4 | Statistical analyses

In order to test for significant differences in power between groups, we applied cluster-based permutation tests[21] using the Fieldtrip toolbox[22] embedded in the EEGLAB toolbox.[19] In a second step, the same statistical procedure was used to evaluate significant differences in power between naming conditions within groups. Every sample (channel–frequency pair) was compared between groups or between conditions, providing a *t*-value. The samples with a *t*-value above the 95th quantile threshold were selected and clustered on the basis of channels and frequencies. Based on the sum of the *t*-values within each cluster, the cluster statistics were calculated and the maximum value was considered as test statistic, with which the effects of groups and conditions were evaluated. In order to control for multiple comparisons, a clustering method was used by means of the Montecarlo method: 4000 random permutations were generated to form a permutation distribution, which was compared against the observed test statistics. For the time–frequency analysis, we computed the ERSPs per group and condition. Cluster-based permutation tests were used to compare groups and conditions (within each group) following the same procedure as for the power spectrum analysis. In this case, each sample corresponded to a channel–frequency–time triplet and the above-threshold samples were clustered on the basis of channels, frequency and time points. Moreover, the tests were first conducted with an alpha level of $\alpha = 0.05$, and if significant, the tests were repeated at a stricter alpha level ($\alpha = 0.01$).

2.5.5 | Pearson's correlation

In order to test for associations between the group differences in power and time–frequency representations and CG language and cognitive skills, we conducted Pearson's correlations in SPSS (IBM SPSS Statistics for Windows, Version 20.0, IBM Corp., Armonk, NY). As measures of CG cognitive functioning, we used the patients' scores on the Rey Osterreith Complex Figure (Copy subtest) and the Digit Span (Forward and Backward), assessing visuomotor and verbal working memory skills, respectively (for more information on the neuropsychological tests, see Timmers et al.[8]). We selected these neuropsychological tests, as these were the ones with the most notable differences between CG patients and healthy controls in the original study.[8]

In particular, we correlated the patients' general power in delta, theta, beta and gamma frequency bands with behavioral measures of accuracy (number of errors) and reaction times (voice onset time) during the experiment and the patients' scores on the neuropsychological tests.

With respect to the time–frequency representations, we restricted the analysis to the time window, the frequency range and the scalp locations corresponding to the cluster (sentence condition, 300–2000 ms, 3–9 Hz, frontal electrodes: F4 F3 FZ FC4), in which a significant group difference was observed. We extracted the patients' TF values and correlated these with behavioral measures of accuracy (number of errors) and reaction times (voice onset times) during the language experiment in the sentence condition and the patient's scores on the neuropsychological tests.

We applied a Bonferroni correction to account for the multiple comparisons (i.e., multiple frequency bands for the general power and multiple electrodes for the time–frequency representations).

3 | RESULTS

In order to investigate the oscillatory dynamics in CG patients and compare them to the control group, we conducted both a power spectrum and a time–frequency analysis.

3.1 | Power spectrum analysis

The power spectrum analysis revealed a significant group effect. The patients' EEG had higher spectral power in all frequency bands, with the exception of alpha frequency (8–12 Hz). Figure 2 displays the power distribution over the scalp separately for patients and controls as well as significant differences per channel across groups. Figure 3 displays the distribution of power values across frequency bands for each group. The significant effect was observed over fronto-central electrodes in low frequency bands (delta, theta) and over the entire scalp in high frequency bands (beta, gamma). Within both groups, the two different naming conditions did not differ significantly.

No significant correlations were observed between patients' general power in delta, theta, beta and gamma frequency bands and behavioral measures during the language task (reaction times and accuracy) or their

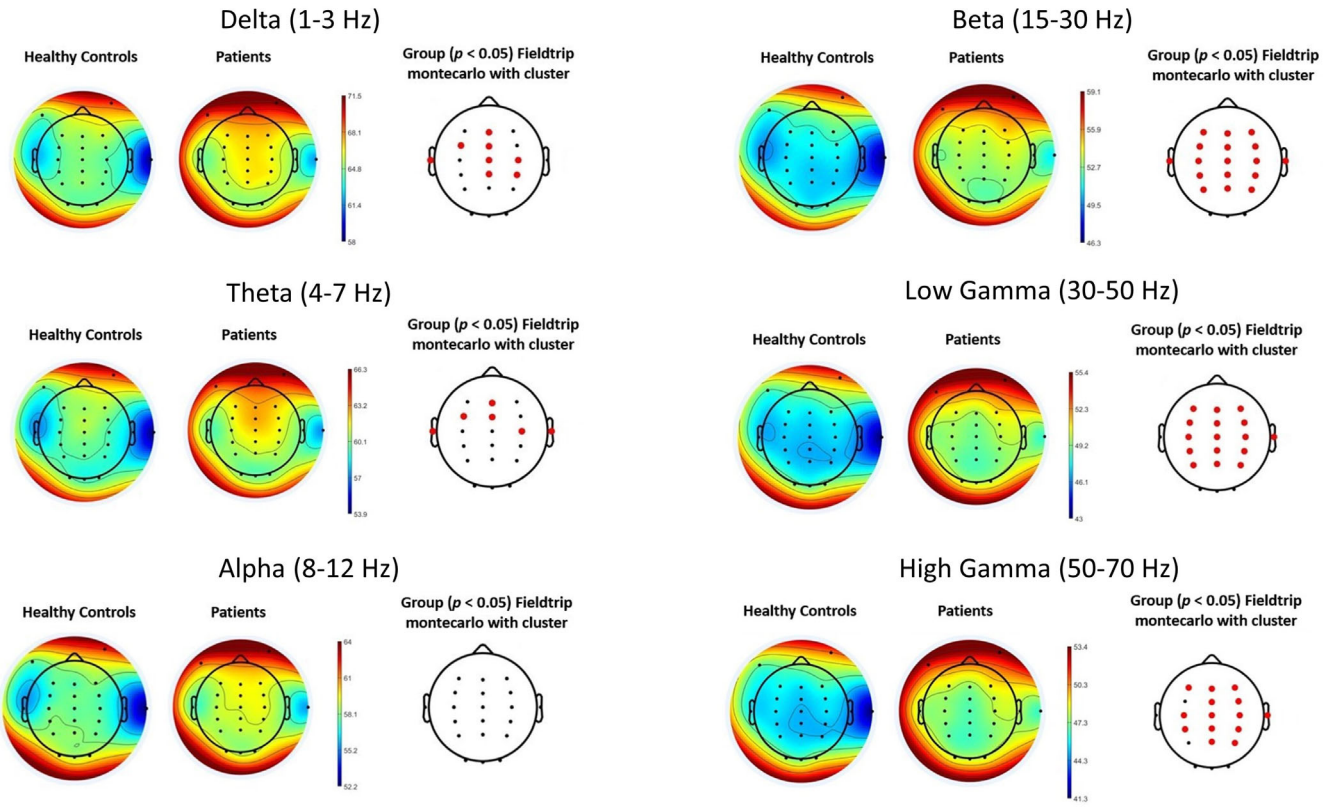

FIGURE 2 Scalp topography of EEG power spectrum differences across groups. For each frequency band, the control group is displayed on the left, the patient group in the middle and statistically significant group differences across electrodes in red. The patients had higher power values in all frequency bands, except for alpha.

visuo-motor and verbal working memory skills ($p > 0.01$, α-corr = 0.01, Table S1).

3.2 | Time–frequency analysis

We first computed the ERSPs plots for both factors, group and condition, separately for each channel to visually inspect the plots (left and middle columns in Figure 4). The ERSPs show the changes in spectral power over time from scene onset on (0–3000 ms), relative to a pre-stimulus baseline. An increase in spectral power typically indicates neuronal synchronization whereas a decrease in spectral power indicates neural desynchronization. We therefore refer to increases in spectral power as event-related synchronization (ERS) and to decreases in spectral power as event-related desynchronization (ERD).

By visually inspecting the ERSPs, we observed alpha–beta ERD and theta ERS. The alpha–beta ERD was most prominent in the time range of 300–3000 ms in both groups. In the patient group, the ERD was more widespread and not confined to this frequency range, and also involved the theta frequency in the time range between 500 and 1000 ms. It was stronger over frontal channels. In higher frequency bands (15–70 Hz), the ERD was visible from stimulus onset to approximately 1500 ms, and stronger in the control group, especially over parietal channels.

Theta ERS were observed between 250 and 550 ms and after 1500 ms in the control group: the effect was strongest over frontal channels. Notably, the ERS was observed in the patient group as well, but it was weaker and mostly observed over frontal and central channels. The group difference was observed in the time preceding overt naming (before 1850 or 2000 ms, respectively), indicating atypical speech planning processes and motor preparation in the patients. These last until the end the overt naming (here not displayed, as the total speech time of patients was 5.1 s, and of controls 4.3 s[8]).

The findings based on visual inspection were confirmed by cluster-based permutation tests. The statistical analyses revealed a significant group effect in the higher syntactic complexity condition (sentence), corresponding to clusters displayed in Figure 4, *right column* (only channels within significant clusters are displayed). The effect was localized over frontal channels in theta–alpha range (3–9 Hz, $p < 0.01$). For the low syntactic condition (words), we did not observe significant differences

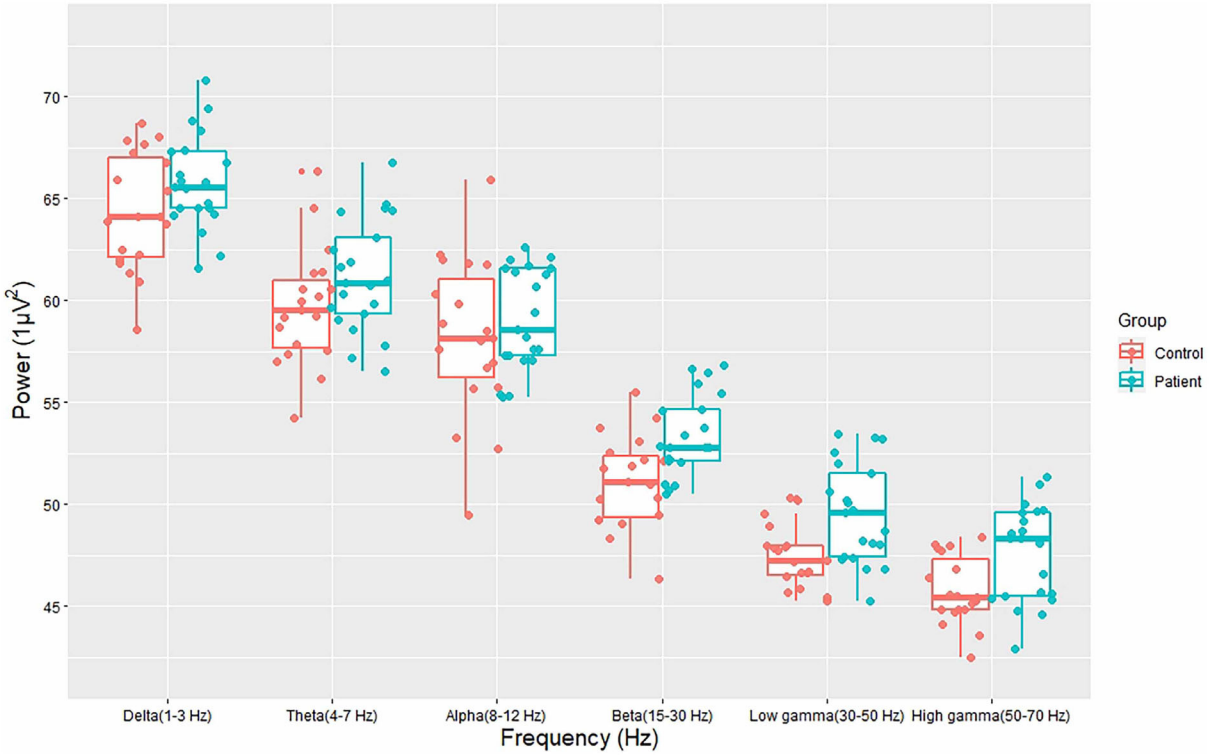

FIGURE 3 Spectral EEG power values of CG patients (in blue) and healthy controls (in red) across frequency bands, showing higher values for the patients. The box plot illustrates the distribution of power values for each frequency band and group, including the interquartile range (white box), the median (horizontal line) and the minimum and maximum values (vertical bars). Each dot represents one participant.

between groups. The same holds for a comparison of naming conditions within groups (no difference between word and sentence naming).

By means of Pearson's correlation, we tested the presence of a relation between the time-frequency modulation in the sentence condition and behavioral and neuropsychological measures within the patient group. A negative correlation was observed between the theta–alpha time–frequency representations at electrode F4 and voice onset times ($r = -0.550$, $p = 0.010$, α-corr $= 0.012$, Table S2): lower time–frequency values (i.e., stronger ERD) were associated to longer voice onset times. No other significant correlations were observed.

4 | DISCUSSION

The aim of the present study was to investigate the oscillatory power and time-frequency profile of CG patients during sentence production and to compare it with that of healthy controls. A second aim was to compare different syntactic complexity (sentence vs. word naming) within each group. We focused on language production (speaking) because expressive language deficits have been frequently observed in CG patients,[4,23] with a negative effect on the quality of life of the patients. Language, like any other cognitive process, engages functional brain networks that are specific to this process.[24] These specialized networks require a certain anatomical and functional characteristics to operate optimally. One relevant feature of these networks is neural oscillations. Oscillations engage networks, and connect brain areas via phase coherence in a highly dynamic fashion.[25] In CG, the language network operates sub-optimally. This was shown by previous studies using (f)MRI[7,11,12] as well as EEG/ERP in the patients.[8] Unknown is which oscillatory frequency bands might play a role in this. The previous ERP work suggested theta as a potential target frequency. We hypothesized that the oscillatory activity of patients and controls would differ in theta power (global power) and time–frequency representation (TFR, power modulation over time). With regard to behavior, reaction times showed that patients were slower, reflecting the language deficit. In the global power spectrum, we observed significant higher power in patients in delta (1–3 Hz), theta (4–7 Hz), beta (15–30 Hz) and gamma (30–70 Hz) frequencies, but not in alpha (8–12 Hz), suggesting an atypical oscillatory profile. The time-frequency analysis revealed significantly weaker event-related theta synchronization (ERS) and stronger alpha desynchronization (ERD) over

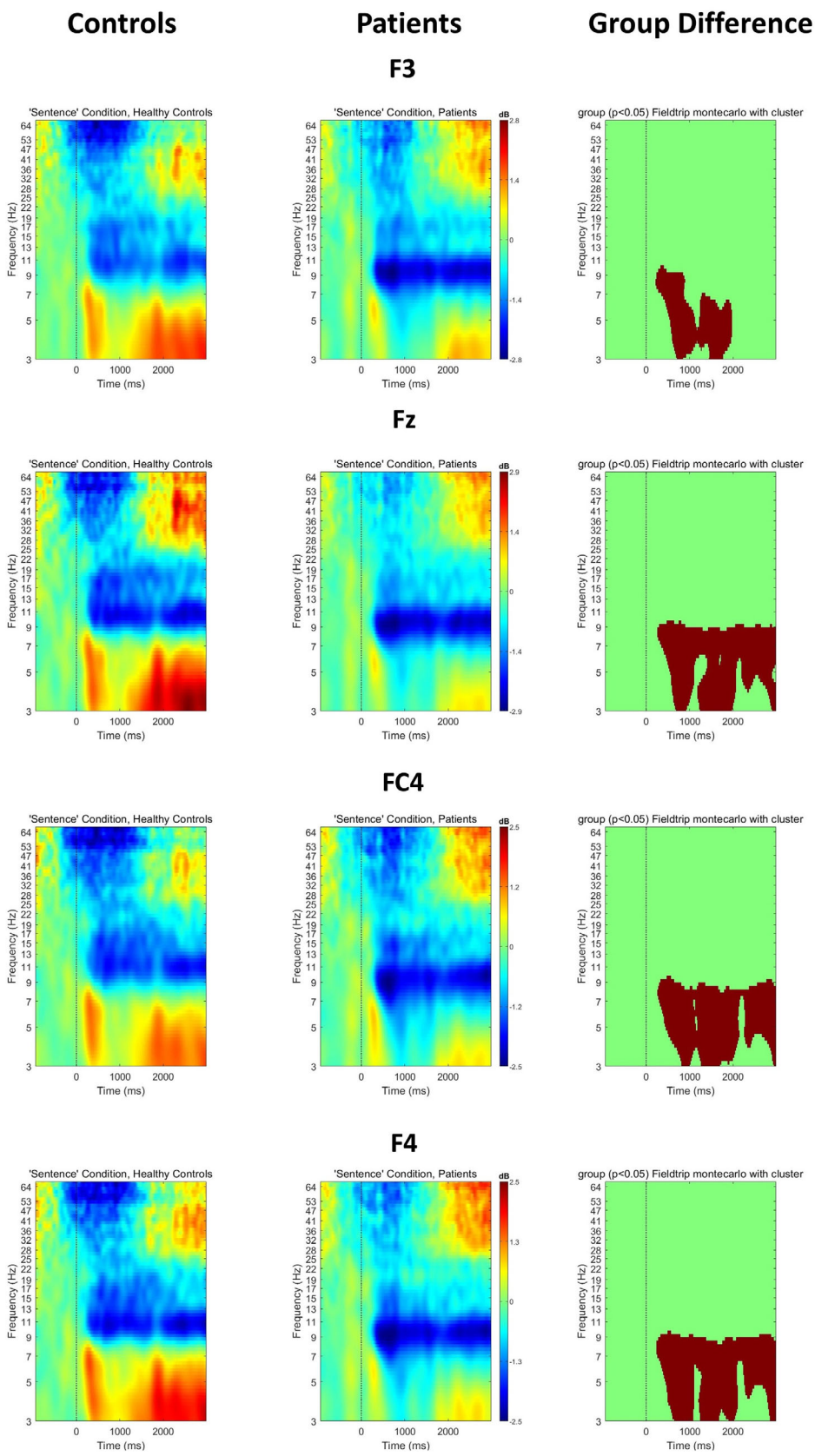

FIGURE 4 Significant event related spectral perturbation (ERSP) differences between groups in the sentence naming (high syntactic complexity) condition. Right: control group. Middle: patient group. Left: Significance plots (in red), revealing a group effect within the theta-alpha frequency range. ERSPs show power changes of EEG brain oscillation of different frequency bands over time. These changes are evoked by the stimulus, in this case by the onset of the animated scene and the speech planning process (at 0 ms).

frontal regions in patients in the sentence condition from 300 ms post scene-onset lasting until speech-onset. This time-frequency modulation over right frontal regions (electrode F4) was shown to be associated with slower reaction times (i.e., longer voice onset time) within the patient group. The data support the hypothesis that CG

language difficulties relate to theta–alpha oscillations. Here we discuss and interpret the results in more detail.

4.1 | Oscillatory power profile of CG patients

Global power is a measure of general brain oscillations strength. Importantly, higher power change is driven by synchronized neuronal activation, which has been proposed as an important measure of network connectivity.[14,25] We observed an overall increase of power in delta, theta, beta and gamma frequencies in the patient group in comparison with healthy controls (Figures 2 and 3). The higher power was found over fronto-central electrodes in the low frequencies and over the entire scalp in the high frequencies (Figure 2). We interpret this widespread pattern of increased power in CG patients as reflecting the recruitment of additional neural resources to perform the task in comparison with the control group. Recruiting more resources might be a compensatory mechanism within a language network with compromised connectivity.[7,11] The increased power in multiple frequency bands might reflect the engagement of larger populations of neurons. This interpretation is in line with findings of our previous fMRI study.[12] With fMRI, using the same naming task, we observed in CG patients the activation of an extended network of regions over the left frontal cortex and the recruitment of additional areas, among which the superior temporal sulcus. Our finding is also in line with previous studies reporting altered delta activity as marker of cognitive dysfunction: increased delta power has been previously reported in several disorders and pathologies, among which aphasia, dyslexia, ADHD (for a review see Güntekin and Başar[26]).[27–29] Similarly, increased power in theta frequency has been found in children with learning disabilities and has been suggested to relate to suboptimal cortical network activation.[30]

Beta frequency power decreases have been commonly related to retrieval of contextual and lexical information from memory[31] and to movement preparation. The task we used here required participants to retrieve lexical information from memory to describe the animated scene (i.e., shapes, colors and verbs) and to prepare and execute the articulatory movements during speaking. The observed difference in beta power and the functional interpretation of beta suggests an impairment in lexical retrieval of syntactic information and/or execution of speech movements in CG patients.[7,8]

Gamma frequency is involved in unimodal and multimodal sensory binding.[32,33] Naming animated scenes, similar to sensory binding, requires binding of perceptual and linguistic information at different levels (visual, conceptual, semantic, syntactic, phonological and articulatory information). Language production requires the coactivation and interactions of different brain regions and several cognitive stages,[23,34] most likely via two neural routes in analogy to dual route models for auditory language processing[35] and for reading.[36] Gamma frequency might have a role in bottom-up binding of linguistic information across these two language routes. In this view, CG patients seem to require additional resources to engage the language network, as represented by the increased gamma power pattern compared to controls. The same might hold for theta and delta frequencies.

We did not observe power difference in alpha frequency between groups. We interpret this result as indication of typical attention processing in CG because alpha oscillations are associated with attentional processing that facilitate transmission of top down predictions to visual cortex.[37–39] Alpha frequency also promotes the neural network communication between frontal and posterior brain regions more generally, as well as maintaining ongoing perceptual states.[38]

4.2 | Time-frequency modulation during speech planning in CG

We studied the TFR because the TF analysis reveals dynamic power changes over time, separately per frequency band, indicating brain network functioning. TF profiles of patients should always be compared to healthy controls. Differences can then be interpreted as differences in oscillatory neural network dynamics. Based on previous work on functional connectivy[11] and ERP,[8] we expected a difference in theta between groups. Elevation of power at a given moment, also referred to as ERS relates to engaging a network at this moment, in our case the language network during the preparation to speak. Decrease in power, referred to as desynchronization (ERD), relates to active inhibition of non-relevant areas or neural populations in a cognitive task, related to attentional focus.

The time-frequency analysis revealed a significant group effect in the sentence condition (higher syntactic complexity), corresponding to a cluster in the theta–alpha (3–9 Hz) frequency range. In this frequency range, CG patients showed a reduced ERS. The groups did not differ in the word naming conditions, nor was there a significant difference within the groups for sentence versus word conditions. The reduced ERS at electrode F4 in the patient group was associated with slower reaction times (longer voice onset times), suggesting that this

time–frequency modulation is relevant for language planning in patients. This is in line with previous literature on the role of theta ERS in language processes. Increases in theta activity have been previously related to memory processes[39]: in particular, theta oscillations have been proposed to act as gating mechanism for information processing in (verbal) working memory, and have a relevant role in connecting brain regions necessary for the task.[40] The observed theta activity can be categorized as an early theta ERS and a late theta ERS, with an onset at approximately 250 and 1500 ms, respectively (Figure 4). These ERS relate to language processing, as this was the task of the participants and what the correlation results suggest. We cannot be sure at this point, but would like to suggest functional specification of these two ERS in some more detail. The early theta ERS could reflect information encoding of the stimulus characteristics (such as location)[41] and matching processes between incoming (animation) and stored information (do I recognize the objects) in memory. This type of information is necessary input for the syntactic planning process. The late theta ERS might relate to linguistic information retrieval, such getting access to lexical information of words (type of word, type of tense, case, etc.),[42] or syntactic unification (binding two noun phrases together),[43] but also to maintenance processes that help manage task-related cognitive load (keep the first noun phrase in mind while planning the second).[44,45] The late ERS could reflect cognitive processes of syntactic planning after initiation of the entire speech plan, it could also relate to motor preparation. Both time windows are before actual speech onset indicating speech planning and not execution of speech.

The observed weaker theta synchronization in patients as compared to healthy controls suggests that theta synchronization is hampered. In light of the function of brain oscillations, this means that the language network is less well engaged, resulting in syntactic planning deficits. These are then visible in behavior in terms of elongated naming latencies and higher amount of speech errors. This interpretation is in line with previous ERP studies suggesting a lexical retrieval and syntactic impairment at the basis of CG patients' language difficulties.,[8,12] but hints now towards an important role of theta in language processing.

In the sentence conditions, we also observed higher alpha desynchronization in patients as compared to healthy controls. Neural desynchronization represents successful memory retrieval and information representation.[46] The observed task-related stronger desynchronization in patients may reflect increased effort to retrieve and maintain the same information. Alpha suppression is also observed during sensorimotor preparation[47] and attentional processes,[31,48] hence individuals with CG may require higher levels of alpha suppression to successfully keep focus during sentence production.

We did not observe a group effect in the word condition. This condition did require only limited syntactic planning, but very similar processes of visual perception (identical animated scenes across tasks), object recognition, and lexical access of words as the sentence condition. The lack of a group difference in word production can be interpreted as evidence for a typical perception and lexical access process of single words in CG patients.

To investigate syntactic complexity, we introduced sentence naming (syntactic complex planning) and word naming (not syntactically complex), with the aim to extract TF modulation for words versus sentence. We looked into this in two ways, between groups and within groups. Between groups a complexity effect was found as we observed a group effect for sentence production but not for word production. We interpret this as an indication that patients have problems whenever syntactic planning is involved. They do not have problems in single word access. The non-significant finding in the word condition is in line with similar findings in ERP by our own group. In the within-group comparison, there was no significant difference between sentence and word condition. A priori, we expected a modulation with syntactic complexity, as we observed this in the ERP studies before, especially in healthy controls.[8] The lack of a sentence vs word condition effect in the time–frequency analysis could mean that the present study was underpowered. This seems unlikely, as we found significant group differences in the sentence condition. Another reason could be that there is no difference in the cognitive process of sentence naming and word naming. This we can rule out too, based on the significant difference in behavioral data, in which sentence naming is slower compared to word naming within each group. A third reason could be that our time–frequency analysis is sensitive to language processing in general but not sensitive to differences in sentence and word planning whereas ERP was sensitive to it. This is possible as ERP and time–frequency show different aspects of neural oscillations. ERPs capture only phase-locked activity, time–frequency analysis measures both phase-locked and non-phase locked activity.[20] Syntactic processing (as in sentence planning: structure of sentence and relation of words to each other) or a lack of it (as in word naming) might modify these aspects differently. Future research is required to understand this lack of within-group comparison better. The main finding in the present study is the observed atypical frequency power, and atypical ERS and desynchronizations in theta and alpha frequency bands during sentence planning in the CG patients. The study provides a next step in

unraveling the mechanisms behind the CG clinical language deficit.

4.3 | Limitations

It should be noted that the current study investigated oscillatory dynamics during sentence production in a sample of adolescent participants (age range: 10–19 years old). Additionally, our patient group was not selected based on reported language and speech impairments and it may be the case that including patients with a more severe language deficit may result in more sustained differences across groups. Future research could consider and overcome these limitations, to exclude age-specific effects in our findings and to generalize these to adult CG patients, including information on the severity of their language impairment. Additionally, we interpreted the observed oscillatory dynamics in CG patients in light of our experimental manipulations and previous literature on the role of neural oscillations in human cognition and language.

5 | CONCLUSION

The present study provided two major findings. Firstly, the benchmarking of the oscillatory dynamics of language production in CG patients. Higher power in delta, theta, beta and gamma frequency bands were found in CG patients in comparison with healthy controls, highlighting the recruitment of additional neuronal resources and/or impaired information processing. Secondly, a reduced event-related spectral synchronization was observed in CG patients in the high syntactic complexity condition in theta–alpha range, supporting the hypothesis of a syntactic planning deficit in CG. These results underline a new aspect of CG neural impairment and suggest that their language deficits relate to altered neural oscillations, complementing the previous ERPs and (f)MRI findings. In particular, our results on neural oscillations open the possibility of investigating the causal relation between the altered oscillatory rhythms and CG language skills by means of non-invasive brain stimulation (NIBS). NIBS enables the modulations of atypical intrinsic oscillatory rhythms and has already been investigated as a possible treatment option in several cognitive disorders.[49–51]

AUTHOR CONTRIBUTIONS

Sara Mazzini wrote the research proposal, conducted the analysis, prepared data visualization, wrote and revised the manuscript. **Sai Yadnik** wrote the research proposal, conducted the analysis with specific expertise on cluster-based permutation testing and prepared data visualization. **Inge Timmers** designed the experiment, recruited the participants, and collected the data. **Estela Rubio-Gozalbo** is one of the PIs of the research line: she provided funding, access to patients and expertise in CG, she supervised the project and revised the manuscript. **Bernadette M. Jansma** is one of the PIs of the research line: she co-designed the experiment, provided funding and expertise in EEG data analysis, she supervised the project and revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

Sara Mazzini, Sai Yadnik, Inge Timmers, Estela Rubio-Gozalbo and Bernadette M. Jansma all declare that they have no competing interests with this work.

DATA AVAILABILITY STATEMENT

Anonymized data can be shared upon request.

ETHICAL APPROVAL

The experiment has been approved by the Medical Ethical Committee of Maastricht University Hospital / Maastricht University (azM/UM).

INFORMED CONSENT

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients, and in case of minors their parents, for being included in the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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