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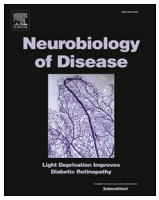

Altered cortical network dynamics during observing and preparing action in patients with corticobasal syndrome

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ABSTRACT

Corticobasal syndrome (CBS) is characterized not only by parkinsonism but also by higher-order cortical dysfunctions, such as apraxia. However, the electrophysiological mechanisms underlying these symptoms remain poorly understood.

To explore the pathophysiology of CBS, we recorded magnetoencephalographic (MEG) data from 17 CBS patients and 20 age-matched controls during an observe-to-imitate task. This task involved observing a tool-use video (action observation), withholding movement upon a Go cue (movement preparation), and subsequently imitating the tool-use action. We analyzed spectral power modulations at the source level.

During action observation, event-related beta power (13-30 Hz) suppression was weaker in CBS patients compared to controls. This reduction was evident bilaterally in superior parietal, primary motor, premotor and inferior frontal cortex. During movement preparation, beta power suppression was also reduced in CBS patients, correlating with longer reaction times. Immediately prior to movement onset, however, beta suppression was comparable between groups.

Our findings suggest that action observation induces beta suppression, likely indicative of motor cortical disinhibition, which is impaired in CBS patients. This alteration may represent a neural correlate of disrupted visuo-motor mapping in CBS. The altered timing of beta suppression to the Go cue suggests deficits in learning the task's temporal structure rather than in movement initiation itself.

1. Introduction

The corticobasal syndrome (CBS) is a rare neurodegenerative disease that rapidly progresses, with no causal treatment options available to this day (Armstrong et al., 2013). The cardinal clinical features are parkinsonism, cognitive decline, and apraxia, i.e. the inability to enact skilled movements despite intact primary sensory and motor function (Park, 2017), often asymmetrically presented at disease onset (Armstrong et al., 2013). At first clinical presentation, CBS is frequently misdiagnosed due to its variable symptomology (Osaki et al., 2004; Joutsa et al., 2014; Alexander et al., 2014; Aiba et al., 2023). The cardinal neuropathological hallmark is the accumulation of misfolded tau-protein in neurons and glia cells, followed by their degeneration (Höglinger et al., 2018). The protein-pathology presumably begins subcortically in the basal ganglia and spreads to various cortical sites, with widespread effects on the frontal, parietal and temporal lobes (Leuzy et al., 2019). Especially motor areas like peri-rolandic, premotor and supplementary motor regions are frequently mentioned as cortical hubs of tau pathology (Pardini et al., 2019; Cho et al., 2017; Kikuchi et al., 2016; Smith et al., 2017) and degeneration (Huey et al., 2009; Josephs et al., 2010; Whitwell et al., 2010; Dutt et al., 2016; Matsuda et al., 2020).

The electrophysiology of CBS is not well investigated. Electroencephalography (EEG) and magnetoencephalography (MEG) studies hint towards widespread spectral slowing of brain activity at rest (Tashiro et al., 2006; Barcelon et al., 2019; Krösche et al., 2023), pronounced in

Abbreviations: CBS, Corticobasal Syndrome; HC, Healthy controls; MRI, Magnetic resonance imaging; EEG, Electroencephalography; MEG, Magnetoencephalography; VBM, Voxel-based Morphometry; PET, Positron Emission Tomography.

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frontal and parietal sites (Krösche et al., 2023). The clinical consequences of these alterations, however, remain unclear. Among various cognitive functions, frontoparietal networks are implicated in the processes of action observation (Molenberghs et al., 2012; Hardwick et al., 2018), motor imagery (Caspers et al., 2010; Hétu et al., 2013; Hardwick et al., 2018) and action execution (Jeannerod, 2001; Hardwick et al., 2018). All of these processes are associated with a desynchronization of motor rhythms in the alpha and beta range (Schnitzler et al., 1997; McFarland et al., 2000; Caetano et al., 2007; Fairhall et al., 2007; Eaves et al. 2016). On a cellular level, these functions are presumably supported by mirror neurons, i.e. neurons that discharge similarly during execution and observation of goal-directed movements (Di Pellegrino et al., 1992; Gallese et al., 1996; Rizzolatti et al., 1996). Mirror neurons were first described in nonhuman primates in frontal and parietal regions (Di Pellegrino et al., 1992; Gallese et al., 1996; Fogassi et al., 2005) before their discovery in humans (Mukamel et al., 2010). Their activity represents the observed action in a motoric neuronal code (Rizzolatti et al., 1996; Rizzolatti et al., 2009; Heyes and Catmur, 2022). Damage to the mirror neuron system may lead to deficits in performing and perceiving goal-directed movements in CBS.

In line with this concept, neuropathology studies demonstrated that cortical degeneration in frontoparietal areas is related to apraxia (Gross and Grossman, 2008; Park, 2017). The same areas show disease-related structural changes in CBS (Huey et al., 2009). On the electrophysiological level, a previous study found pathologically increased left parietal to right premotor beta-band coherence (13-30 Hz) prior to tool-use pantomime in three CBS patients with apraxia (Wheaton et al., 2008). While these observations align well with the established role of frontoparietal networks in goal-directed movement, there is not enough data available to draw firm conclusions on how activity in these networks relates to CBS symptoms.

To help fill this knowledge gap, the current study investigated the association between oscillatory activity and deficits in action observation and movement preparation in a comparably large sample of CBS patients. We made use of an observe-to-imitate task engaging frontoparietal networks, which are presumed to be dysfunctional in CBS patients.

2. Methods

2.1. Participants

In total, 17 CBS patients and 20 healthy controls performed the imitation task. Data from two control participants were discarded. One participant was taking antidepressants and another one had aphantasia i.e. was impaired in motor imagery (Dupont et al., 2022). Four patients of the CBS group were excluded. Two patients did not follow the task instructions and two further patients were diagnosed with Progressive Supranuclear Palsy or Multisystem Atrophy later during clinical follow-up. Consequently, the data of 13 CBS patients and 18 control subjects were used for analysis. The groups did not differ in age (see Table 1.; $t(29) = -1.628$, $p = 0.114$). In the patient group, we performed several neuropsychological / neurological tests to evaluate cognitive impairment, parkinsonism, and apraxia. We used the Montreal Cognitive Assessment (MoCA) to evaluate cognitive impairment (Nasreddine et al., 2005), the UPDRS-III for the severity of parkinsonism (Goetz et al., 2008), the Goldenberg's Apraxia Test (Goldenberg, 1996) and the Test of Upper Limb Apraxia (Vanbellingen et al., 2010) for apraxia. We report relative test scores for cognitive impairment as physical disabilities prevented testing items on visuospatial orientation reliably in two patients. The MoCA scores were normalized by dividing the achieved score by the maximal score, considering only scorable items. The local ethics committee approved the study (study-number: CBS: 2019–447-andere) and every participant gave written informed consent prior to participation, in accordance with the Declaration of Helsinki.

2.2. Trial design

We made use of an observe-to-imitate task, i.e. the observation of an action, followed by a delayed request to imitate that same action (Fig. 1). Each trial began with the display of a fixation cross (variable stimulus duration: 1–3 s) followed by a 2 s video displaying a person using a hammer or a screwdriver, either with the left or with the right hand, in first-person view. This was followed by text instructing the participants to withhold movement (*"do not move yet"*) until a Go cue appeared (movement preparation phase, duration: 5 s). The Go cue was on screen for 4 s. Meanwhile, participants imitated the action with the cued hand until a Stop cue was presented (stimulus duration: 1 s).

Following 10 practice trials, maximally 4 blocks of 40 trials (21 screwdriver, 19 hammer trials in random order) were recorded per participant. In each block, participants were requested to respond with the right hand or with the left hand only (first block randomized, hand switch after each subsequent block). We recorded at least one right hand block and one left hand block in all but one patient, who completed only one left hand block (median: 4 blocks; Range: 1–4; Supplementary Table 1). All healthy controls completed all four blocks.

2.3. Recordings

Brain activity was recorded with a 306-sensor MEG system (VectorView, MEGIN, Espoo, Finland) in a magnetically shielded room, with a sampling rate of 1000 Hz. During the recordings, participants were sitting in upright position with their arms positioned on a table in front of them. Electromyograms were recorded from both forearms and accelerometers were attached to the left and right index finger to track upper limb motion. In addition, we recorded a vertical and a horizontal electrooculogram.

2.4. Data preprocessing

2.4.1. Data cleaning

Data analysis was performed with MATLAB 2018a (MathWorks, Natick, MA), Python 3.9.1, and the Fieldtrip toolbox (version 18.01.2023, Oostenveld et al., 2011). After discarding bad channels, we applied temporal Signal Space Separation (*tSSS*, Taulu and Simola, 2006) to attenuate the interference of sources from outside the MEG helmet (MNE-Python Toolbox 1.3.1, Gramfort et al., 2013). Next, we filtered the *tSSS*-cleaned data with the spectral interpolation algorithm (Leske and Dalal, 2019) to remove line noise and its harmonics and applied a high-pass filter with a cut-off frequency of 0.5 Hz before resampling the data to 250 Hz. Next, we screened the data, removed periods of movement artifacts and sensor noise, and applied independent component analysis. Independent components of non-brain origin, e.g. heartbeat and eye movements, were discarded (median number of

Table 1
Summary data of the study cohorts.

Group	Mean (Std.) age (years)	Gender (f/m)	Diagnosis (poss./prob.)	Mean (Std.) UPDRS-III (sum)	Mean (Std.) MoCA (normalized)	Mean (Std.) Goldenberg (sum)	Mean (Std.) TULIA (sum)
CBS	65.23 (9.27)	6/7	5/8	35.92 (22.03)	0.66 (0.21)	56 (21.73)	18.25 (5.86)
HC	69.17 (3.82)	10/8	–	–	–	–	–

CBS: Corticobasal Syndrome, HC: Healthy controls.

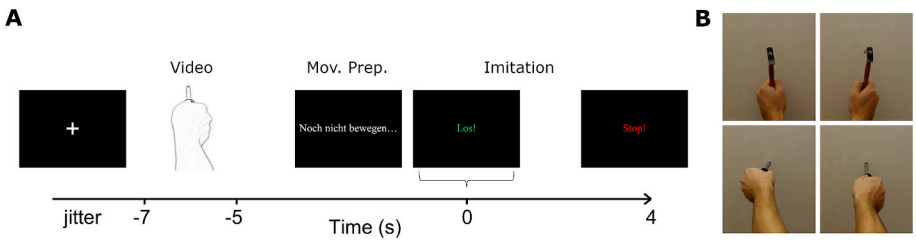

Fig. 1. Trial design. A) Following the display of the fixation cross (1–3 s), a 2 s tool-use video was displayed involving either a hammer or a screwdriver, operated with the left or right hand, depending on the experimental block. This was followed by the instruction to withhold movement ("Noch nicht bewegen…"; 5 s) and a Go cue ("Los!"; 4 s). Patients were to imitate the action displayed earlier until presentation of a Stop cue (1 s). A trial lasted between 13 s and 15 s. B) A screenshot of each of the four videos used in the task. Mov. Prep.: Movement preparation.

ICs removed: 2.5, range: 1 – 5).

2.4.2. Trial definition

The preprocessed time series were segmented into trials of 14 s, centered on the Go cue (-10 to +4 s), encompassing baseline (-7.75 s to -7 s), video (-7 s to -5 s), and movement preparation phase (-5 s to 0 s). Although the extracted trials contained the movement phase, we did not analyze this phase, but limited all analyses to events preceding movement onset.

The choice of the baseline period (-7.75 s to -7 s) was motivated by the need for a pre-stimulus period that was both close in time to the events of interest and distant in time from the movement carried out in the previous trial. When defining trials, we additionally included some seconds prior to baseline to exclude trials with pre-baseline movement, which might result in post-movement beta rebounds contaminating the baseline period (see section *Trial selection*).

2.4.3. Trial selection

We screened all trials and discarded trials containing movement artifacts, particularly when artifacts occurred within or just before the baseline period. To detect outliers in the baseline period, we applied a semi-automatic procedure involving a threshold applied to the first principal component of the smoothed accelerometer signals (±2.33 SD). If ≥100 ms of data within or prior to the baseline period (-9 s to -7 s) were marked as outliers the trial was considered invalid. The results were visually checked and corrected if necessary. This meticulous screening procedure served to ensure that the data analyzed here do not contain movement artifacts.

In total, 22.89 % of trials were removed (CBS: 27.27 %, HC: 20.43 %). The average number of trials after denoising and pooling hammer and screwdriver trials was 86.46 for the CBS group (std: 34.45; range: 28–132) and 124.39 for the HC group (std: 21.21; range: 87–159). In all analyses, spectra were excluded if they were based on less than 25 trials. Supplementary Table S1 provides more detailed information on the available trials per subject.

2.4.4. Movement onset detection

The Teager Kaiser Energy Operator (TKEO, Solnik et al., 2010) was computed to determine movement onset in the accelerometer signals. TKEO was z-normalized, using the mean of a movement-free reference period (-3 to -1 s with respect to the Go cue), and a threshold was applied to determine movement onset (>200 SD TKEO of non-moving hand). Movement onset estimates were visually inspected and corrected if necessary. Reaction times were determined by computing the difference between movement onset and Go cue onset.

2.5. Source reconstruction

T1-weighted magnetic resonance imaging (MRI) scans (Siemens Magnetom Tim Trio, 3-T MRI scanner, Munich, Germany) were used to compute individualized, single-shell head models (Nolte, 2003). Individual MR-images were available for all CBS patients and for 15 of 19 healthy controls. For the remaining participants, we used a template brain (Holmes et al., 1998). The coordinate systems of the MEG and the MRI data were aligned based on anatomical landmarks sampled with a digitizer system (Isotrak, Polhemus, Colchester, Vermont, USA) prior to the MEG recordings. Trials were cut into non-overlapping segments of 1 s length, and we computed one covariance matrix per experimental block. Based on the gradiometer covariance, we estimated source activity for 567 positions on the cortical surface in Montreal Neurological Institute (MNI) space, using a Linearly Constrained Minimal Variance beamformer and a regularization parameter of 5 % (van Veen et al., 1997). Subsequently, we applied singular value decomposition to the x-, y-, and z-components of the resulting dipoles and kept the vector with the largest eigenvalue. Source reconstruction was based on gradiometers only.

2.6. Spectral analysis

Time-frequency decomposition of the source-reconstructed trial data was done via Morlet wavelets for frequencies ranging between 4 Hz and 90 Hz, in 1 Hz steps. The number of cycles for the wavelets ranged from 4 to 15, increasing as a function of frequency in logarithmic space. Wavelets were shifted in steps of 32 ms with respect to the signal. Time-frequency spectra were baseline-corrected by subtracting the temporal mean of the baseline period (-7.75 to -7 s) from each time-frequency bin and dividing the difference by that same value (percent change). Note that the baseline was frequency-specific.

2.7. Statistical analysis

We applied two-tailed cluster-based permutation tests with Monte-Carlo sampling to quantify between-group effects (Maris and Oostenveld, 2007). In short, the dependent variable was shuffled across groups ≥50,000 times. Each time, a cluster-forming threshold was applied, *t*-values were summed for each cluster and the largest sum was kept, contributing to the empirical null distribution. Clusters in the original (non-shuffled) data were considered significant if their cluster sum fell within the extreme 5 % of the null distribution.

As we did not observe differences between hammer and screwdriver trials, we pooled trials across tools for statistical analysis. Similarly, we pooled right hand and left hand trials after mirroring the activity recorded in left hand trials across the midsagittal plane. Both steps served to increase the signal-to-noise ratio.

2.7.1. Estimating the rate of beta power suppression

We used linear regression to estimate the rate of beta event-related desynchronization per participant. More specifically, we averaged the baseline-corrected time-frequency spectra across the beta band (13-30 Hz), resulting in one beta power value per time step (32 ms) for the interval -3.5 s to -0.48 s relative to Go cue onset. The last 480 ms before Go cue onset were omitted because this epoch contained overt movement in the HC group (Fig. 2A). Beta power was smoothed with a moving-average filter to denoise the signal (width: 160 ms) and

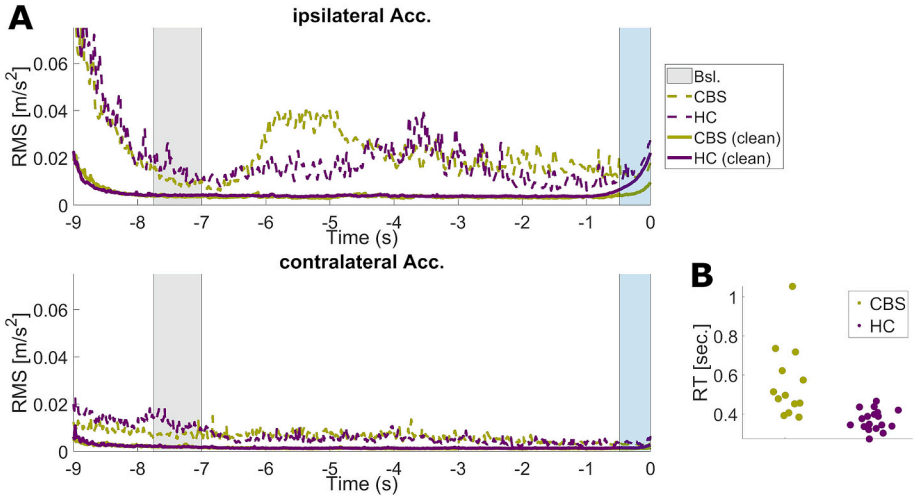

Fig. 2. CBS patients reacted slower than healthy controls (HC). A) Root mean square (RMS) accelerometer data for the moving (ipsilateral) and the non-moving (contralateral) hand before (dashed lines) and after (solid lines) cleaning. HC presented larger RMS values than patients within the [-0.48 s to 0 s] interval (blue shading), with 0 s indicating Go cue onset. B) Distribution of trial median reaction time per participant for CBS (median: 0.496 s, range: 0.384 s to 1.054 s) and HC (median: 0.362 s, range: 0.272 s to 0.466 s). Bsl.: Baseline; CBS: Corticobasal Syndrome; HC: Healthy controls; RT: Reaction time. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

regressed on time to obtain the slope. Slope estimates were compared between groups with independent sample *t*-tests at an alpha-error rate of 5 %. When relating the beta slopes to reaction time, we pooled values across groups and computed Pearson partial correlation coefficients to control for possible group differences in slope.

2.7.2. Bayesian statistics

We applied a Bayesian Analysis of Variance to assess the presence vs. absence of group effects in different phases of the trial. The analysis was performed with R (version 4.4.0) using the BayesFactor package (version 0.9.12–4.7). The model included *group* (HC vs. CBS), *hemisphere* (contralateral vs. ipsilateral) and *trial phase* (action observation, motor preparation, movement initiation) as fixed effects, alongside *participant* (participant ID) as a random effect to account for within-subject variability. The reported Bayes Factors (BF) quantify the evidence for (H1) or against (H0) a group difference per trial phase. They result from post-hoc pairwise comparisons, conducted with Bayesian, independent sample t-tests, after confirming a *group* x *trial phase* interaction. The reporting of evidence follows the recommendations of Andraszewicz et al. (2015).

3. Results

3.1. Behavioral results

All patients were able to imitate hammer and screwdriver use, with large variability in the quality of imitation. Rather than addressing imitation per se, we focused on pre-movement brain activity.

In the pre-movement phase, both groups revealed slight hand motion in some of the trials, despite being instructed to withhold movement until Go cue presentation. This motion was successfully removed in data cleaning (Fig. 2). After data cleaning, the accelerometer data were largely similar for CBS and HC except for the period immediately preceding the Go cue (cluster at -480 ms to 0 s: $t_{sum} = -527.109$, $p = 0.005$; Fig. 2A). Around this time, controls, but not CBS patients, had already initiated their response. Accordingly, controls reacted faster to the Go cue than CBS patients ($t(29) = 4.124$, $p < 0.001$, Fig. 2B).

3.2. Action observation

Action observation was associated with a decrease in alpha/beta power (9-30 Hz), henceforth referred to as event-related desynchronization (ERD). The ERD occurred predominantly in sensorimotor and parietal areas, and, with lower amplitude, in temporal and occipital areas (Fig. 3). It was bilaterally distributed, with a slight emphasis on the hemisphere contralateral to movement, particularly in controls. The desynchronization outlasted the video by ~800 ms in both groups (Fig. 3).

The ERD associated with action observation was more pronounced in controls than CBS patients, for whom the ERD had a more posterior localization. Specifically, pre- and postcentral gyri as wells as the middle frontal gyrus, and parts of the inferior frontal gyrus showed a weaker desynchronization bilaterally in CBS patients (Fig. 4B; contralateral cluster: $t_{sum} = 165.263$, $p = 0.041$; ipsilateral cluster: $t_{sum} = 193.029$, $p = 0.034$). The grid points contained in these clusters served as regions of interest (ROI) in the following. The effect was specific to the beta band, covered the entire observation phase and outlasted it by about 300 ms (Fig. 4C; contralateral cluster $t_{sum} = 2496.215$, $p = 0.017$; ipsilateral cluster $t_{sum} = 2479.829$, $p = 0.017$). Group differences in the alpha (8-12 Hz) and gamma band (60-90 Hz) were not significant.

3.3. Movement preparation

In the 5 s following video offset, participants were waiting for the Go cue signaling imitation start. In this phase, we observed a second alpha/beta ERD, intensifying over time (Fig. 3). The pattern of desynchronization was more focal in comparison to action observation, with a clear peak in sensorimotor cortex contralateral to movement. This second ERD was again smaller in the CBS group, provided that trials were anchored to Go cue onset. Differences emerged in the pre-and post-central gyri and middle frontal gyri contralateral to the response hand (Fig. 4B; cluster $t_{sum} = 121.356$, $p = 0.039$). As for action observation, the group difference occurred the beta band specifically (Fig. 4C; contralateral cluster $t_{sum} = 1471.227$, $p = 0.039$; *time range: -1.488 s to 0 s*). No significant differences emerged in the alpha or in the gamma range. We note that part of the effect might have been mediated by differences in overt movement shortly before Go cue onset (Fig. 2A). When excluding the last 480 ms of the trial, the statistical effect reduced to a trend (cluster $t_{sum} = 90.431$, $p = 0.053$).

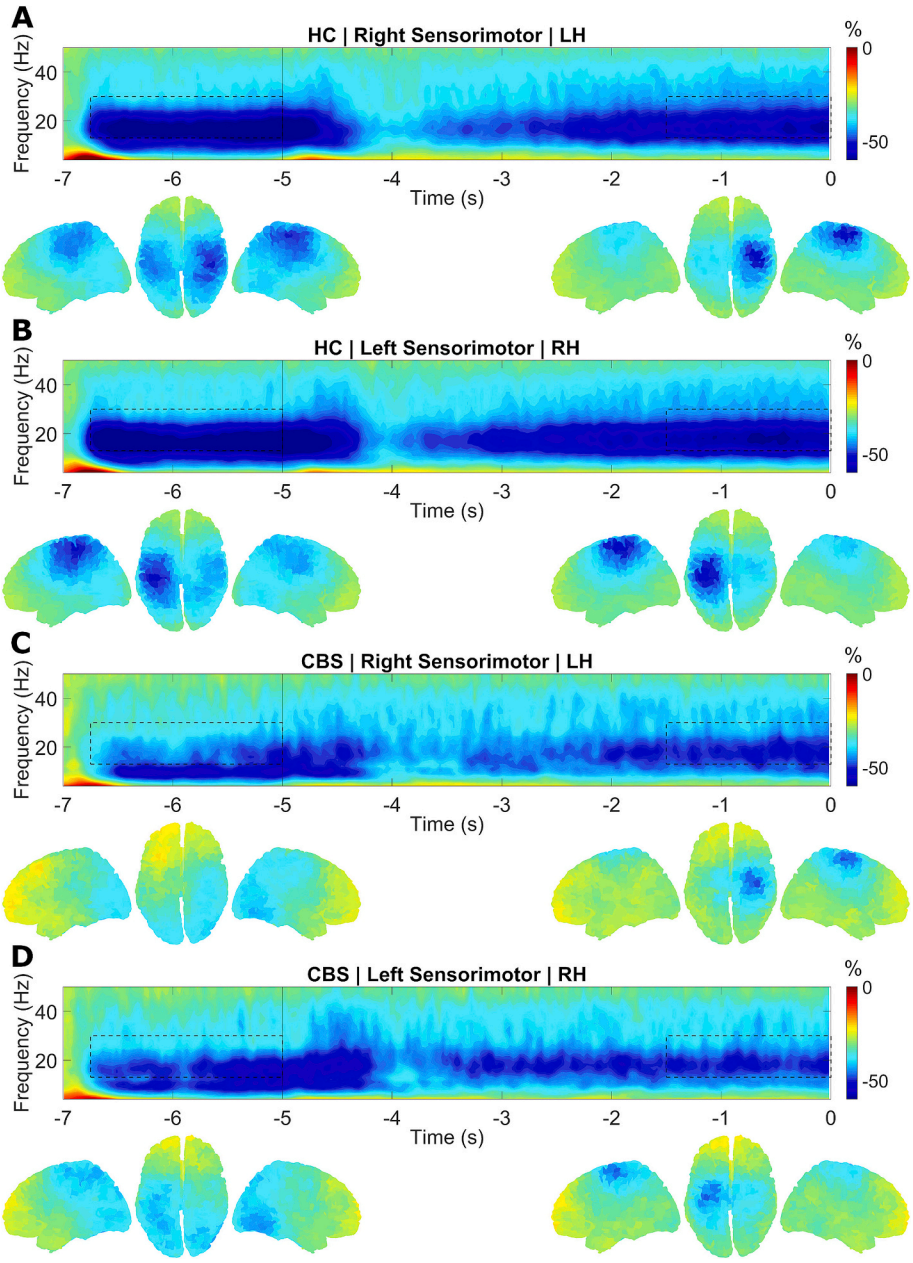

Fig. 3. Action observation and movement preparation were associated with a decrease of beta power in sensorimotor cortex. Spectra: group-average time-frequency spectra of sensorimotor cortex contralateral to imitation bodyside. Relative power change with respect to baseline (-7.75 s to -7 s) is color-coded. The dashed boxes indicate the time-frequency selection used in the source plots below. Left: action observation. Right: movement preparation. Video: -7 s to -5 s. Go cue onset: 0 s. Vertical line at -5 s: video offset. A) Healthy controls ($N = 18$), left hand imitation. B) Healthy controls (N = 18), right hand imitation. C) CBS patients ($N = 11$), left-hand imitation. D) CBS patients (N = 11), right-hand imitation. C) and D): two recordings were excluded because spectra were based on less than 25 trials. HC: Healthy controls; CBS: Corticobasal Syndrome.

3.4. Trial phase comparison

Interestingly, the differences observed immediately before movement onset (-0.5 s to 0 s) vanished when trials were centered on movement onset rather than Go cue onset (Fig. 5; cluster $t_{sum} = 8.87$, $p = 0.411$). In fact, the movement-locked ERD was remarkably similar for HC (Fig. 5A) and CBS (Fig. 5B) with respect to spatial extent, strength, and dynamics, indicating that movement initiation might not be altered in CBS patients.

In order to corroborate the absence of a group difference, we conducted a Bayesian analysis, assessing group effects on beta ERD in the three different trial phases. Specifically, we averaged baseline-corrected power across beta frequencies (13-30 Hz), across locations within the ipsilateral and within the contralateral ROI, separately, and across the following time intervals: +0.25 s to +2 s relative to video onset (action observation), -1.5 s to 0 s relative to Go cue onset (movement preparation) and -0.5 s to 0 s relative to movement onset (movement initiation). This analysis yielded strong evidence for an interaction between trial phase and group ($BF_{10} = 19.761$). Post-hoc comparisons yielded no evidence for a group difference during movement initiation ($BF_{10;contra.} = 0.727$; $BF_{10;ipsi.} = 0.697$), but strong evidence for action observation ($BF_{10;contra.} = 29.399$; $BF_{10;ipsi.} = 25.704$) and moderate evidence for movement preparation ($BF_{10;contra.} = 8.751$; $BF_{10;ipsi.} = 3.603$). The difference in effect size is illustrated in Fig. 5C.

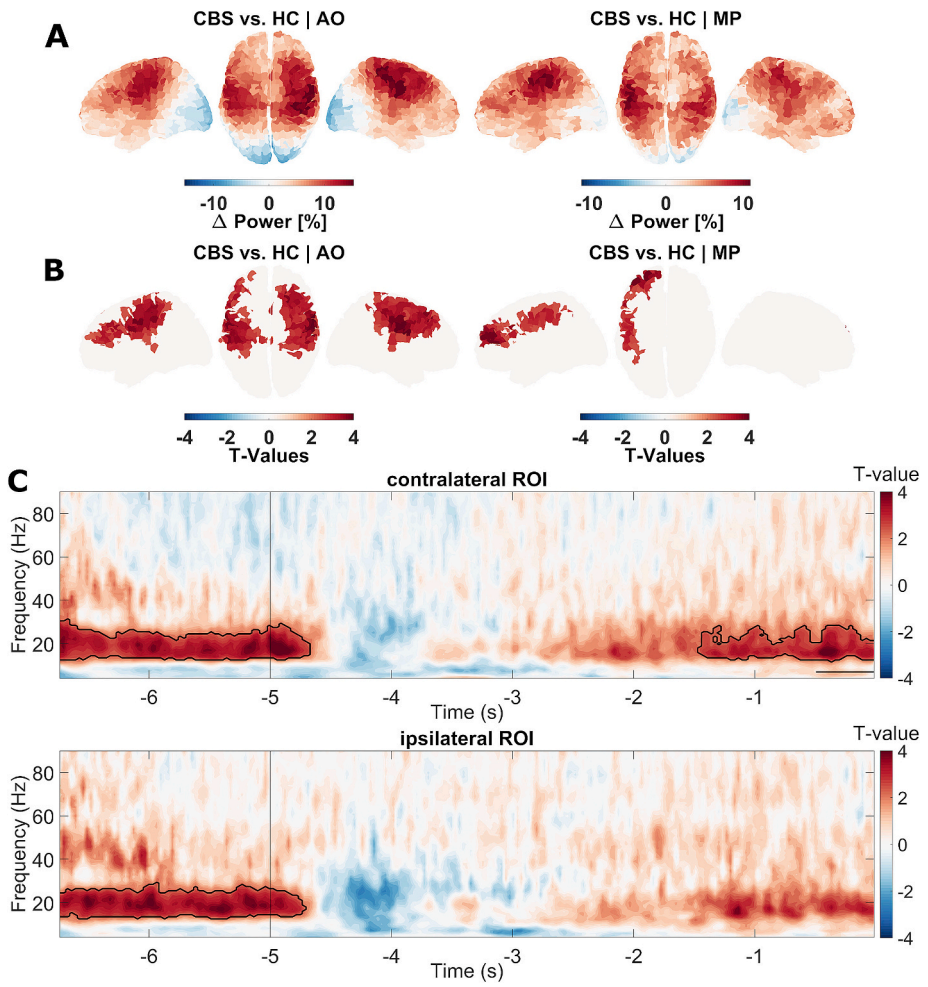

Fig. 4. Comparison of event-related beta power desynchronization between CBS patients and healthy controls. A) Difference in group-average baseline-corrected beta-power (13-30 Hz) for action observation (-6.75 s to -5 s) and movement preparation (-1.5 s to 0 s). Warmer colors indicate weaker event-related beta desynchronization (beta ERD) in patients. Left- and right-hand trials were pooled after mirroring the activity of left-hand trails across the sagittal plane (left hemisphere: contralateral to imitation). B) Whole-brain statistical comparison, beta ERD in CBS patients vs. HC. Non-significant changes masked. Highlighted areas in the left column of B) served as regions of interest (ROI). C) Statistical comparison of time-frequency maps for the contralateral ROI (B, left column, left hemisphere) and for the ipsilateral ROI (B, left column, right hemisphere). Significant differences indicated by solid black contour. The black horizontal line marks the epoch containing movement in HC (see Fig. 2A). Vertical line at -5 s: video offset. AO: Action observation; MP: Movement Preparation. CBS: Corticobasal Syndrome; HC: Healthy controls.

3.5. Go cue anticipation

The above analysis suggests that CBS patients and controls did not differ in motor cortical beta power suppression before moving (Fig. 5). Nevertheless, we observed group differences in beta ERD in the movement preparation phase (Fig. 4). We hypothesized that these findings can be reconciled by accounting for the difference in reaction time. CBS patients reacted slower than controls, which presumably went along with a slower suppression of beta power. In order to test this idea, we estimated the linear decay rate of beta power (beta slope) in the movement preparation phase and compared it across groups.

The estimated slopes of the beta ERD were smaller in the CBS group than in controls (Fig. 6A; contralateral ROI: $t(29) = 3.103$, $p = 0.004$; ipsilateral ROI: $t(29) = 3.761$, $p < 0.001$). Furthermore, the slope estimates of the contralateral hemisphere correlated with reaction times, confirming that steeper beta slopes are related to faster reaction times (Fig. 6B; Pearson partial correlation; contralateral ROI: $r_{Beta \times RT|Group} = 0.417$, $p = 0.022$; ipsilateral ROI: $r_{Beta \times RT|Group} = 0.212$, $p = 0.26$). The correlations remained significant when excluding the outlier with RT > 1 s. These findings suggest that CBS patients were less oriented in time, resulting in insufficient suppression of beta power at Go cue onset and longer reaction times.

3.6. Correlations between beta ERD and CBS symptoms

In CBS patients, we found no correlation (Spearman's ρ) between the beta ERD in the contra- or ipsilateral region of interest and test scores quantifying apraxia (TULIA: $|\rho| < 0.375$, $p > 0.23$; Goldenberg: $|\rho| < 0.396$, $p > 0.182$), cognitive impairment (MoCA: $|\rho| < 0.385$, $p > 0.194$), or parkinsonism (UPDRS III: $|\rho| < 0.251$, $p > 0.409$). We neither found correlations between test scores and beta slope estimates ($|\rho| < 0.509$, $p > 0.076$).

4. Discussion

Little is known about the patho-electrophysiolgy of CBS. In this paper, we provide a comprehensive characterization of the electrophysiological differences between CBS patients and healthy age-matched controls in an observe-to-imitate task, requiring functions believed to be impaired in CBS, such as visuo-motor mapping and motor preparation. We found that action observation and GO cue anticipation were associated with beta power desynchronization in motor and

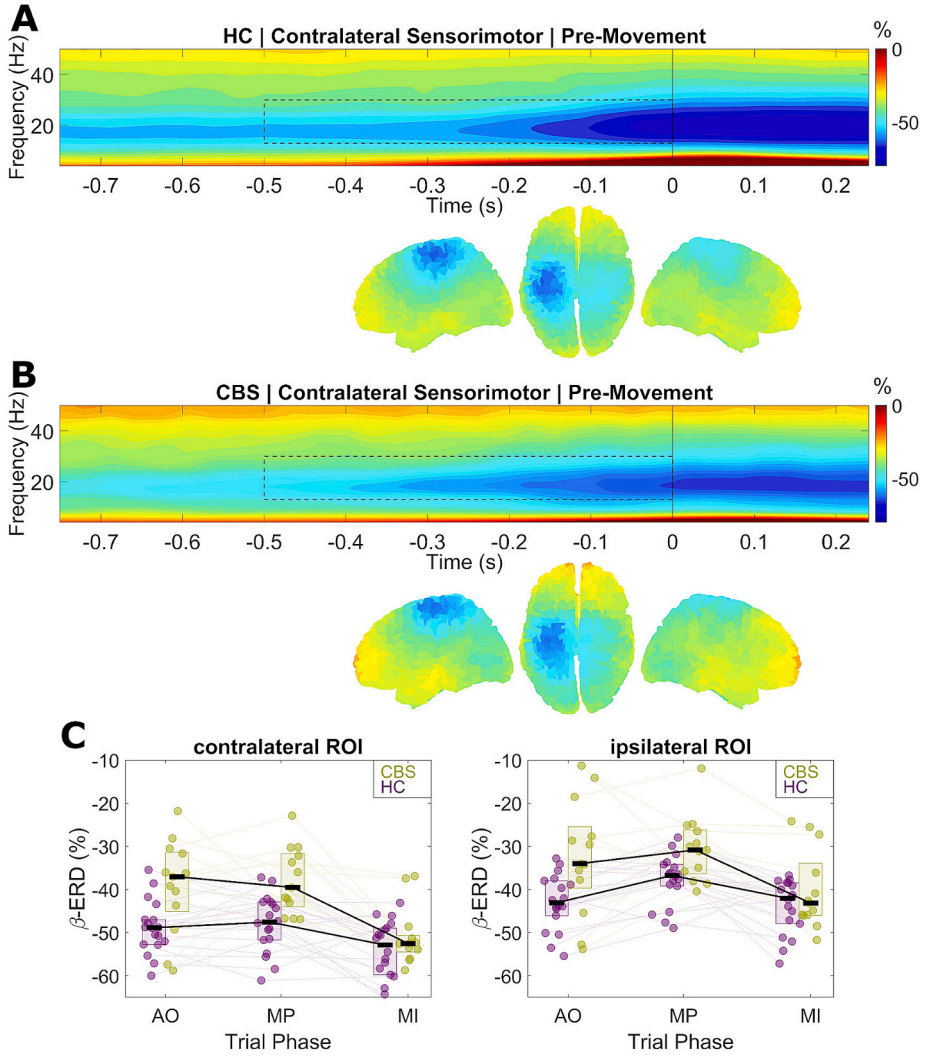

Fig. 5. Beta power dynamics were similar for CBS patients and healthy controls immediately before movement onset. A) HC and B) CBS patients. Group-average time-frequency spectrum of sensorimotor cortex contralateral to imitation bodyside, anchored to movement onset (0 s). Relative power change with respect to baseline (-7.75 s to -7 s) is color-coded. The dashed boxes indicate the time-frequency selection used in the source plots below. Left- and right-hand trials were pooled after mirroring the activity of left-hand trails across the sagittal plane (left hemisphere: contralateral to imitation). C) Baseline-corrected power, averaged across beta frequencies, time points within the respective trial phase, and grid points contained within the two regions of interest (Fig. 4B, left column). HC: Healthy controls; CBS: Corticobasal Syndrome; ROI: Region of interest; AO: Action observation; MP: Movement preparation; MI: Movement initiation. ERD: Event-related desynchronization.

parietal areas. These modulations, timed to action-relevant, visual information presented before movement onset, were weaker in CBS patients than in controls. The degree of beta power suppression immediately before movement onset, in contrast, was not different between patients and controls, suggesting that the effects observed here are neural correlates of selective deficits in visuo-motor mapping and implicit learning of temporal structure, respectively, rather than of impaired movement initiation.

4.1. Action observation

Functional magnetic resonance studies revealed a comprehensive brain network encompassing both subcortical and cortical regions engaged in the observation of meaningful actions. Subcortically, activation occurs in the cerebellum (Gazzola and Keysers, 2009; Molenberghs et al., 2012), in the basal ganglia (Errante and Fogassi, 2020; Errante et al., 2023), and in the thalamus (Errante and Fogassi, 2020; Errante et al., 2023). Cortically, frontal regions such as premotor and precentral cortex are involved, alongside the supplementary motor area, primary somatosensory cortex, parietal and occipital cortex (Caspers et al., 2010; Molenberghs et al., 2012; Hardwick et al., 2018; Errante and Fogassi, 2020; Errante et al., 2023).

On the electrophysiological level, action observation is associated with a suppression of beta oscillations in sensorimotor areas (Cochin et al., 1998; Hari et al., 1998; Babiloni et al., 2002; Muthukumaraswamy and Johnson, 2004; Caetano et al., 2007; Sebastiani et al., 2014; Pavlidou et al., 2014b; Pavlidou et al., 2014a; Kilner et al., 2009). In agreement with the current study, a previous study localized this beta desynchronization to frontoparietal areas, and primary sensorimotor areas in particular (Sebastiani et al., 2014). Concerning the lateralization of beta desynchronization during action observation there is conflicting evidence. One study reported bilateral desynchronization (Babiloni et al., 2002) while another study reports contralateral desynchronization with respect to the target stimulus (Kilner et al., 2009). In our study, we found that beta desynchronization during action observation shows a mild contralateral predominance, which might have resulted from the need to imitate the observed, unilateral hand movement later in the trial.

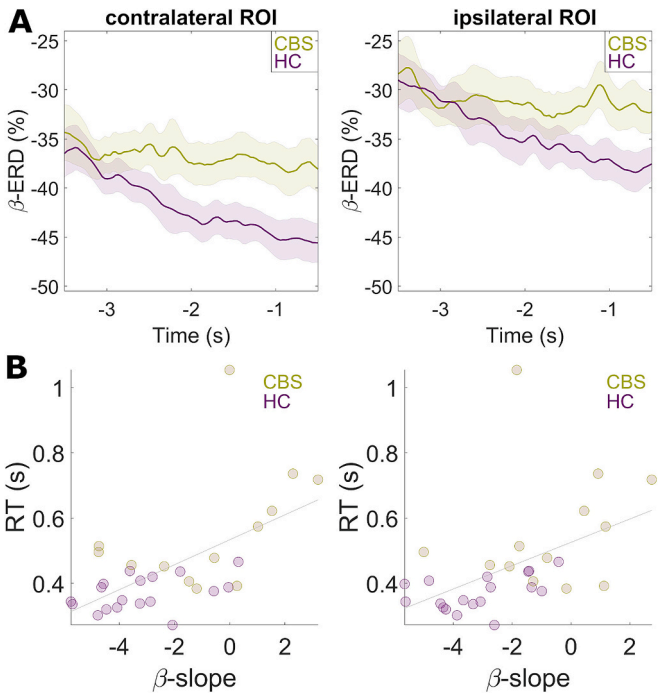

Fig. 6. The rate of beta power suppression prior to the Go cue differed between CBS patients and healthy controls and correlated with reaction time. A. Beta power dynamics before Go cue presentation (0 s). The group means are displayed as colored lines, and the standard error is indicated by shaded areas. B. Linear decay rate of beta power (beta slope) vs. trial-median reaction time. Note that we omitted the last 480 ms of the trial in this analysis because it contained hand movement (Fig. 2A). CBS: Corticobasal Syndrome; HC: Healthy controls; ROI: Region of interest; RT: Reaction time.

Providing movement context is known to affect the beta desynchronization associated with action observation, although the nature of these effects is not fully understood. Muthukumaraswamy and Johnson (2004), for example, found that the observation of meaningless movements leads to less beta suppression than the observation of goal-directed movements. Pavlidou et al. (2014b), in contrast, found that biologically implausible movement is associated with a stronger ERD than plausible movement, which was attributed to a difference in effort when matching visual information onto motor representations. These reports imply that beta modulations emerging during action observation are related to cognitive processes rather than being limited to movement parameters.

4.2. Similarities between action observation, motor imagery, and movement execution

The electrophysiological signature of action observation is remarkably similar to that of movement execution and motor imagery. Before participants begin to move (Toro et al., 1994; Fairhall et al., 2007), or imagine a movement (Pfurtscheller and Neuper, 1997; Schnitzler et al., 1997; McFarland et al., 2000; Eaves et al. 2016), beta power decreases in primary sensorimotor areas. Given the substantial evidence supporting an inhibitory role of beta oscillations in motor control, stemming from studies on Parkinson's disease (Kühn et al., 2004; Swann et al., 2011; Alegre et al., 2013; Toledo et al., 2014) and response inhibition (Swann et al., 2012; Picazio et al., 2014; Schaum et al., 2021), this beta power suppression likely reflects a transient disinhibition of primary sensorimotor cortex, which is otherwise constantly inhibited by the response inhibition network, including pre-supplementary motor area (Swann et al., 2012; Picazio et al., 2014; Schaum et al., 2021), inferior frontal cortex (Swann et al., 2012; Picazio et al., 2014; Schaum et al., 2021) and the subthalamic nucleus (Kühn et al., 2004; Alegre et al., 2013; Chen et al., 2020). Notably, this transient disinhibition does not necessarily result in overt movement. It rather reflects an "active network state" (Pogosyan et al., 2009; Little et al., 2019; Muralidharan and Aron, 2021) common to action observation, motor imagery and movement execution. In line with this interpretation, a recent meta-analysis of fMRI studies has demonstrated that the activation maps of action observation, motor imagery, and motor execution considerably overlap in premotor, sensorimotor, and rostral parietal areas (Hardwick et al., 2018).

4.3. Differences between action observation, motor imagery, and movement execution

Besides the abovementioned similarities, several differences have been identified between action observation, motor imagery, and motor execution. Notably, movement execution engages a rather focal cortical network centered on primary sensorimotor areas, with a limited activation of premotor and inferior parietal regions (Hardwick et al., 2018). Action observation and motor imagery, in contrast, recruit a more extended network, including premotor, pre-SMA and various parietal areas (Hardwick et al., 2018). These additional frontoparietal regions might be required for visuo-motor mapping, i.e. the integration of the visual percept and the motor representation of an action, which is particularly important in observe-to-imitate tasks.

Substantial parts of the frontoparietal network are affected by pathological changes in CBS, likely explaining why we observed the strongest CBS-related alterations in the action observation phase. Pathological alterations include both gray matter degeneration (Huey et al., 2009; Josephs et al., 2010; Whitwell et al., 2010; Dutt et al., 2016; Matsuda et al., 2020) and damage to white matter tracts that link frontal with parietal cortices and/or subcortical regions, such as the superior longitudinal fasciculus (Ferrea et al., 2022; Uchida et al., 2023). The subcomponents of the superior longitudinal fasciculus linking parietal and frontal regions (Makris et al., 2005; Nakajima et al., 2020), in particular, might facilitate visuo-motor mapping during action observation (Hecht et al., 2013).

4.4. Movement preparation

The disinhibition of motor cortex during action observation, reflected by the first beta ERD in our task, was likely a direct consequence of action observation, and thus largely independent of learning. The ERD timed to the Go cue, in contrast, was presumably contingent on learning the trial's temporal structure, including the constant interval between video offset and Go cue onset. Previous literature has demonstrated that beta power adapts to the timing of a predictable, upcoming target stimulus (van Ede et al., 2011; Heideman et al., 2018). In line with these studies, Tzagarakis et al. (2010) demonstrated that beta desynchronization is modulated by response uncertainty. Thus, the reduced pre-Go beta modulation in the CBS cohort is likely the result of uncertainty regarding the onset of the Go stimulus. The fact that patients have a slower ERD might thus be indicative of an impairment in learning temporal structure. In line with this idea, beta desynchronization correlated with reaction time, confirming previous reports (Perfetti et al., 2011; Tzagarakis et al., 2010). The deficit in learning temporal structure could potentially be due to widespread neurodegeneration in frontal cortex, parietal cortex and basal ganglia, which are known to be involved in time estimation (Coull et al., 2011; Coull et al., 2013). Premotor and parietal cortex are particularly relevant for anticipation of cues and response preparation (Coull et al., 2011).

4.5. Movement initiation

Previous findings in humans and non-human primates suggest that beta power must be suppressed below a certain threshold for movement initiation (Heinrichs-Graham and Wilson, 2016; Khanna and Carmena, 2017). Here, we observed a slower beta power suppression and

prolonged reaction times in CBS patients relative to controls, but no difference with respect to the level of beta power suppression at movement onset. This finding suggests that the power threshold for movement initiation, relative to baseline, is similar in both groups. The timing of beta power suppression to the task, however, might be pathologically altered in CBS patients.

4.6. Clinical implications

Our results evidence pathological alterations of beta desynchronization in CBS patients, presumably caused by neurodegeneration in brain circuits involved in visuo-motor mapping and implicit learning of temporal structure. These electrophysiological alterations can be evaluated easily by presenting a tool-use video, coupled with the instruction to imitate, while recording MEG/EEG. Unlike motor imagery, this task does not require a high level of patient compliance. These properties make our approach potentially interesting for translation into diagnostic tools, that might be useful for differentiating Parkinson syndromes in the future.

4.7. Limitations and outlook

We did not find significant correlations between clinical scores and beta power desynchronization. This might be due to the relatively small sample size ($N = 13$) and the symptomatic variability in our patient cohort. Alternatively, it is conceivable that the observed alterations of brain activity might relate more to neurodegeneration per se than to clinical symptoms, which are known to have different long-term dynamics in neurodegenerative diseases (Armstrong et al., 2013; Aiba et al., 2023). Lastly, our study lacked several experimental conditions of interest, such as a motor imagery task, action observation without the need to imitate or action observation from different perspectives.

Whether and how the alterations of oscillatory activity in CBS relate to atrophy could be an interesting research question for future studies. Atrophy might affect oscillatory activity directly by compromising neural oscillators, and indirectly, by slightly increasing the distance between sensors and brain tissue.

5. Conclusion

The processing of observed actions is pathologically altered in CBS, likely reflecting a selective deficit in visuo-motor mapping. In addition, CBS patients show suboptimal timing of beta suppression to the task, presumably due to deficits in implicit learning of temporal structure.

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CRediT authorship contribution statement

Marius Krösche: Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Data curation. **Christian J. Hartmann:** Writing – review & editing, Resources, Investigation, Conceptualization. **Markus Butz:** Writing – review & editing, Validation. **Alfons Schnitzler:** Writing – review & editing, Validation, Resources, Funding acquisition, Conceptualization. **Jan Hirschmann:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Data availability

We do not have permission to share the data publicly.

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Appendix A. Supplementary data

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