Oscillatory Brain Networks in Atypical Parkinsonism

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List of Abbreviations

AD	Alzheimer's disease
APS	Atypical parkinsonian syndromes
AP	Action potential
BF	Bayes factor
CBD	Corticobasal degeneration
CBS	Corticobasal Syndrome
CoE	Center of energy
EEG	Electroencephalography
EPSP	Excitatory postsynaptic potential
ERD	Event-related desynchronization
FIR	Finite impule response
FFT	Fast Fourier transform
fMRI	Funtional magnetic resonance imaging
FOOOF	Fitting oscillations and one over f
fT	Femtotesla
HC	Healthy controls
Hz	Heartz
IPSP	Inhibitory postsynaptic potential
LCMV	Linear constrainted minimum variance
LFP	Local field potential
MEG	Magnetoencephalography
M/EEG	Magnetoencephalography or electroencephalography
MoCA	Montreal cognitive assessment
MRI	Magnetic resonance imaging
MW	Morlet wavelets
µV	microvolt
PD	Parkinson's disease
PET	Positron Emission tomography
PSP	Progressive supranuclear palsy
REM	Rapid eye movement
RMS	Root mean square
ROI	Region of interest
RT	Reaction time
SMA	Supplementary motor area
STN	Subthalamic nucelus
SQUID	Superconducting quantum interference device
TKEO	Teager kaiser energy operator
tSSS	Temporal signal space separation
TULIA	Test of upper limb apraxia
UPDRS	Unified parkinson's disease rating scale
VBM	Voxel-based morphometry

Prelude

This dissertation is based on my employment at the Institute of Clinical Neuroscience and Medical Psychology at the Heinrich Heine University Düsseldorf, from October 2019 to September 2024. During this period, two manuscripts were published in scientific journals, forming the foundation of this dissertation.

Study 1

Marius Krösche, Silja Kannenberg, Markus Butz, Christian J. Hartmann, Esther Florin, Alfons Schnitzler, Jan Hirschmann, (2023). *Slowing of Frontal β Oscillations in Atypical Parkinsonism*. In: Movement Disorders 38 (5), p. 806-817. DOI: 10.1002/mds.29378

Study 2

Marius Krösche, Christian J. Hartmann, Markus Butz, Alfons Schnitzler, Jan Hirschmann, (2025). *Altered cortical network dynamics during observing and preparing action in patients with corticobasal syndrome*. In: Neurobiology of Disease 205, 106796. DOI: 10.1016/j.nbd.2025.106796

Abstract

The corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP) are rare, atypical parkinsonian syndromes (APS), that present with motor symptoms reminiscent of idiopathic Parkinson's disease (PD). Common features of both CBS and PSP include parkinsonian symptoms such as rigidity, bradykinesia and gait disturbances. However, CBS is further characterized by apraxia and cognitive decline, while PSP is defined by abnormal eye movements and early postural instability. Accurate diagnosis in the early stages of these conditions is challenging, and treatment options are limited. The rapid neurodegenerative progression in CBS and PSP is driven by the accumulation of misfolded tau-protein in the brain. CBS is associated with extensive tau pathology and atrophy in the basal ganglia and cortical areas, whereas PSP involves widespread subcortical pathology alongside frontal lobe degeneration. This dissertation investigates the electrophysiological alterations in CBS and PSP by means of magnetoencephalography (MEG), aiming to identify disease-specific signatures at rest and during an imitation task.

The first study utilized MEG recordings of CBS and PSP patients at rest, comparing them with PD patients and healthy controls (HC). A key finding was that APS patients exhibit a shift in spectral energy toward lower frequencies, specifically a peak frequency shift within the beta range (13-30 Hz). This effect, predominantly observed in frontal areas, differentiated APS patients from PD patients and HC. Additionally, similar spectral slowing was found in APS patients in other cortical areas when compared to HC only, including central and parietal areas. Notably, the spatial distribution of these alterations corresponds to brain regions known to be structurally compromised by the disease. These findings suggest a link between electrophysiological biomarkers and underlying disease-related abnormalities, like atrophy and tau pathology.

While resting state analyses provide valuable insights, task-based studies can further elucidate disease-related dysfunction by examining symptom-relevant brain networks. CBS patients commonly struggle with action imitation. Thus, the second study employed an observe-to-imitate task to assess the recruitment of action-related brain networks. CBS patients were impaired in engaging these networks during action observation and in anticipating a Go cue for movement execution. These deficits were reflected in altered beta-band activity, with suppression dynamics differing between patients and HC. However, both groups exhibited

comparable motor network recruitment just prior to movement initiation. These results suggest that CBS patients have specific impairments in visuo-motor matching and response timing, likely stemming from disruptions in frontal and parietal areas, which are frequently affected in CBS patients.

In conclusion, APS patients exhibit distinct electrophysiological alterations both at rest and during an imitation task. The identification of disease-specific spectro-spatial resting state profiles and disruptions in action-related network recruitment provide valuable starting points for further research. Expanding our understanding of electrophysiological changes in APS may ultimately contribute to improved clinical diagnostics and a more accurate prognosis.

Zusammenfassung

Das kortikobasale Syndrom (CBS) und die progressive supranukleäre Blickparese (PSP) sind beides seltene, atypische Parkinson-Syndrome (APS), die mit einer motorischen Symptomatik ähnlich der Parkinson-Krankheit (PD) zusammenhängen. Typische Parkinson-bezogene Symptome wie etwa Rigor, Bradykinesie und Gangstörungen sind Merkmale des CBS und der PSP. Das CBS ist außerdem gekennzeichnet durch Apraxie und kognitive Beeinträchtigungen, während die PSP mit Störungen der Augenbewegungen und frühen posturalen Instabilitäten einhergeht. Eine differentielle klinische Diagnose ist besonders in den frühen Krankheitsphasen herausfordernd. Die wenigen zur Verfügung stehenden Behandlungsmöglichkeiten können den Krankheitsverlauf nicht modifizieren, und die Symptome nur beschränkt reduzieren. Im Zentrum beider Erkrankungen steht die krankheitsbedingte Akkumulation von pathologischem Tau-Protein. Bei dem CBS sind insbesondere kortikale Areale und die Basalganglien durch Taupathologie und Atrophie betroffen, während bei der PSP diese krankhaften Veränderungen besonders in subkortikalen Arealen ausgeprägt sind und kortikal vorwiegend der Frontallappen betroffen ist. Die vorliegende Dissertation beschreibt elektrophysiologische Veränderungen bei dem CBS und der PSP mittels Magnetenzephalographie (MEG) mit dem Ziel, krankheitsspezifische Profile in Ruhe und während einer Imitationsaufgabe zu identifizieren.

In der ersten Studie wurden CBS- und PSP-Patienten mittels MEG in Ruhe aufgenommen und mit PD-Patienten sowie gesunden Kontrollpersonen (HC) kontrastiert. Ein wesentliches Merkmal von APS-Patienten war die Verschiebung der spektralen Energie hin zu niedrigeren Frequenzen, insbesondere von spektralen Maxima im Beta-Band (13-30 Hz). Dieser Effekt trat im Vergleich zu PD-Patienten und HC überwiegend in frontalen Regionen auf. Im alleinigen Vergleich mit HC schloss dieser spektrale Verlangsamungseffekt zusätzlich weitere zentrale und parietale Areale mit ein. Interessanterweise umfassten diese spektralen Veränderungen Gehirnregionen, die bei APS-Patienten in der Regel strukturelle Schäden aufweisen. Diese Ergebnisse legen eine Verbindung zwischen den elektrophysiologischen Veränderungen, Atrophien und Tau-Pathologie nahe.

CBS-Patienten sind häufig nicht in der Lage Bewegungen zu imitieren. In der zweiten Studie wurde eine Imitationsaufgabe verwendet, um die Aktivierung von handlungsbezogenen neuronalen Netzwerken zu untersuchen. CBS-Patienten zeigten Beeinträchtigungen in der Aktivierung dieser Netzwerke während der Bewegungsbeobachtung, sowie in der Antizipation

eines Zielstimulus (Bewegungsaufforderung). Diese Defizite spiegelten sich in veränderter Beta-Band-Aktivität wider, insbesondere einer verminderten Beta-Unterdrückung. Im Gegensatz dazu zeigten beide Gruppen eine vergleichbare Rekrutierung der motorischen Netzwerke unmittelbar vor der Bewegungsausführung. Diese Ergebnisse legen nahe, dass bei CBS-Patienten beobachtete Bewegungen Anderer das eigene motorische System vergleichsweise wenig rekrutieren, was insbesondere auf eine eingeschränkte Übersetzung visueller Informationen in motorische Repräsentationen hindeutet. Zudem ist das Timing von Bewegungsreaktionen beeinträchtigt. Diese Ergebnisse hängen wahrscheinlich mit krankheitsbedingten Veränderungen in frontalen und parietalen Arealen zusammen, die für das CBS typisch sind.

Zusammenfassend zeigen APS-Patienten ausgeprägte elektrophysiologische Veränderungen, sowohl in Ruhe als auch im Zusammenhang mit Bewegungsimitation. Krankheitsspezifische spektral-räumliche Profile in Ruhe, sowie Störungen in der Rekrutierung handlungsrelevanter Netzwerke bilden wertvolle Ausgangspunkte für aufbauende Forschungsvorhaben. Ein vertieftes Verständnis elektrophysiologischer Veränderungen bei APS könnte langfristig zu einer verbesserten klinischen Diagnostik und einer genaueren Prognose beitragen.

1. Introduction

Atypical Parkinsonism encompasses a spectrum of highly debilitating neurological disorders, including Corticobasal Syndrome (CBS) and Progressive Supranuclear Palsy (PSP), among others. Both diseases are characterized by widespread neuropathology that affects cortical and subcortical regions, leading to progressively worsening symptoms in both diseases. CBS is typically characterized by greater cortical involvement, whereas subcortical involvement is usually more pronounced in PSP (Dickson 2012; Stamelou et al. 2021). Patients experience parkinsonian motor symptoms alongside cognitive decline (Armstrong et al. 2013; Litvan et al. 1996). Additionally, higher cortical features, such as apraxia, are associated with CBS (Armstrong et al. 2013), whereas postural instability and saccadic dysfunction is more characteristic of PSP (Litvan et al. 1996). Most existing studies investigating the brain dysfunction underlying these symptoms focused on identifying structural brain changes using magnetic resonance imaging (MRI) (Whitwell et al. 2010; Josephs et al. 2010; Whitwell et al. 2020), as well as metabolic dysfunction (Pardini et al. 2019; Ge et al. 2018) and pathological protein accumulation (Smith et al. 2017; Whitwell et al. 2020) with positron emission tomography (PET). The electrophysiological alterations that underlie these disorders, however, are not well characterized to date, contrary to the extensive body of work on Parkinson's disease (PD). This thesis seeks to address this knowledge gap by providing insights into the oscillatory neural activity associated with CBS and PSP.

Alterations of neural oscillations can be studied with techniques such as electroencephalography (EEG), magnetoencephalography (MEG), or local field potential recordings (LFP) (Buzsáki et al. 2012). These methods measure electromagnetic fields, generated by neural activity, offering direct access to neurological processes (Buzsáki et al. 2012). This thesis presents two studies leveraging MEG to investigate abnormal brain activity in CBS and PSP patients. The studies examine brain dynamics at rest and during an experimental task designed to probe action observation and action imitation. By doing so, this work aims to advance our understanding of the neurophysiological underpinnings of CBS and PSP.

1.1. Neural Activity – Foundations of Electrophysiological Signals

Neural populations exhibit rhythmic activity detectable both, through external sensors from outside the skull, and locally, with electrodes inside the brain in extracellular space. The underlying biological signal of these recordings relies on the electromagnetic properties of neural activity. In 1929, Hans Berger pioneered the detection of rhythmic neural activity with EEG, and recorded brain activity in humans at rhythms between 10 Hz and 30 Hz (Berger 1929). Later, in 1972, David Cohen invented MEG, which measures the magnetic rather than the electric fields produced by the brain (Cohen 1968). Since then, researchers applied EEG and MEG extensively to characterize oscillatory brain activity in health and disease. This section describes the neurobiological sources of MEG and EEG recordings.

1.1.1. Electromagnetic Fields of Neural Origin

Neurons are computational cellular units, receiving and transmitting signals. Neuronal signaling involves coordinated changes in membrane potential, regulated by transmembrane ion currents following their electrochemical gradients (Bean and Koester 2021). Ions enter the cell and propagate toward the soma, promoting an intracellular primary current (Baillet et al. 2001). Secondary extracellular return/volume currents close the current loop (Baillet et al. 2001). The locations of ionic influx are named sink, whereas return currents are initiated at the source. The concurrent transient difference in electric potential through separation of ions yields a neural dipole and generates electric and magnetic fields in extracellular space (Baillet et al. 2001). The spatiotemporal summation of thousands of such fields can be measured by EEG or MEG (M/EEG) (Baillet et al. 2001).

The M/EEG signal mainly reflects synchronous synaptic integration of postsynaptic potentials (Buzsáki et al. 2012). The summation of excitatory postsynaptic events of at least ~10.000 pyramidal neurons is required for the generation of electromagnetic fields that could be recorded with M/EEG (Baillet 2017). Pyramidal cells have dendritic trees that are oriented in parallel, thereby allowing for signal enhancement through superposition of their electromagnetic fields (Baillet 2017). Instead, the extracellular fields of action potentials (APs) are short-lived (< 2 ms) and unlikely to superimpose temporally (Buzsáki et al. 2012). However, most recent reports suggest that multiple transmembrane currents, including APs, contribute to the M/EEG signal (cf. Box 1.).

Box 1. Neural Communication

Basic Processes of Neural Communication

Neurons maintain a resting membrane potential, driven by ionic electrochemical gradients (Koester and Siegelbaum 2021). Neurotransmitters released at the presynaptic terminal bind to postsynaptic receptors, modulating ion channel activity and generating excitatory postsynaptic potentials (EPSPs) or inhibitory postsynaptic potentials (IPSPs) (Yuste and Siegelbaum 2021). Two neurotransmitters are omnipresent in the brain. Glutamate induces EPSPs by Na^+ influx (via AMPA/NMDA receptors) and Ca^{2+} influx (via NMDA receptors). GABA induces IPSPs via Cl^- influx ($GABA_A$ receptors) or K^+ efflux ($GABA_B$ receptors) (Yuste and Siegelbaum 2021). The integration of depolarizing EPSPs and hyperpolarizing IPSPs determines the initiation of an AP at the axon initial segment (Yuste and Siegelbaum 2021), traveling along the axon as a transient spike in positive membrane potential (Bean and Koester 2021).

Transmembrane Currents and Extracellular Fields

While M/EEG signals largely reflect postsynaptic potentials of pyramidal neurons (Baillet 2017), the intricate cellular processes underlying these signals often remain obscure. Beyond passive propagation, dendritic voltage-gated channels enable bidirectional current flow between dendrites and soma (Spruston et al. 2016). Backpropagating Na^+ APs (Yuste and Siegelbaum 2021) and Ca^{2+} APs (Gidon et al. 2020) (e.g. generated in response to an axonal AP), travel from the cell body towards the dendrites, altering synaptic processes and the integration of postsynaptic potentials. Their extracellular fields likely contribute to electrophysiological recordings (Buzsáki et al. 2012). Furthermore, recent EEG modelling work suggests substantial signal contribution of multiple cellular transmembrane currents, including action potentials and afterpotentials (Thio and Grill 2023).

1.1.2. Neuronal Oscillations

Oscillations are mathematically defined as periodic (i.e. repetitive) fluctuations, parametrized by amplitude, frequency and phase (Cohen 2014). Amplitude refers to the peak deflection of an oscillation, typically measured in the ranges of microvolts (μV) when using EEG or femtotesla (fT) when using MEG, frequency denotes the number of recurrent wave cycles per second in hertz (Hz), and phase describes the circular timing of an oscillation in radians (Cohen 2014). Time-domain signals have frequency-domain representations, which can be obtained by means of the Fourier transform. Fourier-based methods for the estimation of neuronal oscillations (cf. Box 2. & Box 3.) are ubiquitous in research on neuronal activity and have extensively contributed to neuroscientific research. A subset of these methods, including Morlet wavelets, can be adapted to improve temporal sensitivity to detect short-lived events (cf. Box 3.). Fourier-based methods for analyzing neuronal signals rely on the assumption that decomposing the signal into sinusoidal basis functions offers a meaningful representation of the underlying signal (Cole and Voytek 2017). Neuronal signals contain patterns that oppose the assumption of

periodicity and smooth sinusoids (Cole and Voytek 2017). Recent methodological developments take these considerations into account, by providing the possibility to dissect periodic and aperiodic signal components (cf. Box 4.), and more detailed waveform analysis (Donoghue et al. 2020; Cole and Voytek 2019).

Neuronal oscillations are commonly grouped into frequency bands, including the delta (0.5 to 3.5 Hz), the theta (4 to 7 Hz), the alpha (8 to 12 Hz), the beta (13 to 30 Hz) and the gamma (> 30 Hz) band (Engel and Fries 2010). Numerous studies have linked oscillatory activity in these bands with a wide range of behaviors, cognitive processes (Başar et al. 2001; Da Lopes Silva 2013) and diseases (Schnitzler and Gross 2005; Başar and Güntekin 2013). However, the linkage between frequencies and functions is complex and modulated by numerous factors. For instance, neuronal oscillations change over lifespan (Cellier et al. 2021; Gómez et al. 2013), differ between individuals (Haegens et al. 2014), scale along spatial gradients (Mahjoory et al. 2020) and oscillations within the same frequency band can have different neuronal generators and facilitate various cognitive functions/behaviors (Da Lopes Silva 2013).

Box 2. The Fourier transformation (Brunton and Kutz 2022)

Fourier transformation

In mathematics, oscillations are represented as complex-valued sinusoids. According to the Fourier theorem, any signal can be represented entirely as a linear combination of sinusoidal functions, with varying frequency, amplitude and phase. The Fourier transform is the mathematical operation that maps a time-domain signal onto its frequency representation, projecting it onto a set of orthogonal sinusoidal basis functions and yielding a complex-valued Fourier coefficient for each frequency *f*.

Discrete Fourier transform

On a computer, the discretized versions of the signal u and the sinusoidal basis function ϕ_f with frequency f are represented by N samples. The discrete Fourier transform is defined follows as:

$$DFT(u(n)) = u^T \phi_f = \sum_{n=0}^{N-1} \underbrace{u_n}_{\text{Signal}} \overbrace{\mathrm{e}^{-\mathrm{i}\cdot 2\pi\cdot f\cdot \frac{n}{N}}}^{\text{Sinusoid}}$$

Spectral power can be obtained per frequency as the amplitude (i.e. magnitude of the Fourier coefficients) squared and is provided for all frequencies in the power spectrum. Spectral power is a measure of local neural population activity.

1.1.3. Oscillatory Networks

Rhythmic neural activity is ubiquitous across various spatial scales. Many neurons discharge spontaneously, exhibiting rhythmic activity (Bean 2024). Oscillatory activity is inherent to neuronal communication between distant and within local ensembles. Neuronal assemblies oscillate in synchrony (Buzsáki and Draguhn 2004) and form transient functional networks at various spatial scales (Engel et al. 2001; Helfrich and Knight 2016), potentially through phase synchronization (Fries 2015), allowing for multiple neural computations in parallel (Buzsáki and Draguhn 2004; Helfrich and Knight 2016). A long-standing hypothesis was that slow oscillations characterize long-range interareal communication, whereas local neuronal assemblies tend to resonate in oscillations of higher frequency (Da Lopes Silva 2013). However, more recent evidence challenged this strict dichotomy. Inter-areal communication can be established at gamma frequency for example (Bastos et al. 2015; Buzsáki and Schomburg 2015). In addition, slower oscillations can arrange time windows of excitability for local neuronal ensembles (Lakatos et al. 2008), and exhibit cross-frequency interactions, where the phase of slow oscillations coordinates fast oscillatory activity (Canolty et al. 2006; Lisman and Jensen 2013).

The generation and maintenance of these brain rhythms depend on the underlying neural circuitry, balancing excitatory and inhibitory neural interactions (Da Lopes Silva 2013). Synaptic inhibition coordinates time windows of neural excitability, thereby facilitating the generation of synchronized neuronal oscillations (Wang 2010). Gamma oscillations, for example, are generated within local neuronal circuits, that commonly rely on the reciprocal connection of inhibitory interneurons and excitatory pyramidal cells in small local ensembles (Buzsáki and Wang 2012). External neuronal input can initiate the generation of sustained beta rhythms in cortical circuits of pyramidal neurons and inhibitory interneurons (Sherman et al. 2016). Hippocampal theta oscillations are likely promoted by local circuitry involving inhibitory interneurons and pyramidal neurons, depending on rhythmic activity from neurons in the medial septum (Nuñez and Buño 2021). Therefore, these examples suggest that brain oscillations might provide a direct view on the functional and pathological state of brain networks (Schnitzler and Gross 2005).

Box 3. Morlet Wavelets (Cohen 2014)

Comparison to Fourier transform

The Fourier transform assumes signals as periodic and stationary in time. As a consequence, the Fourier transform is effective in extracting the spectral content of a signal, but it does not provide information when a change in spectral content occurs in time. The signal's temporal dynamics can be analyzed with wavelet-methods. Morlet wavelets (MW) are frequently used for the analysis of neuronal time series.

Morlet Wavelets

MW are defined as the product of sinusoidal basis functions (with frequency f over time *t*) and a Gaussian window with mean *m* and standard deviation *s*. The number of cycles *n* is proportional to the width of the Gaussian window.

$$MW_f(t) = \underbrace{e^{-(t-m)^2/2s^2}}_{\text{Gaussian window}} \cdot \underbrace{e^{i2\pi ft}}_{\text{Sinusoid}} \; and \; s = \frac{n}{2\pi f}$$

Wavelet Convolution

The signal is convolved with the MWs. MW convolution acts as a time-domain filter on the signal, extracting phase and amplitude at frequency *f* and time *t*. Spectral power can be computed by squaring the amplitude. The results can be visualized in a spectrogram, illustrating the change of spectral power over time and frequency.

1.2. Recording Neuronal Oscillations

1.2.1. Magnetoencephalography

MEG measures the magnetic fields, produced by ionic currents, ubiquitous to brain activity. Neighbouring pyramidal cells form approximate current dipoles when excited, and their spatial orientation supports the summation of nearby magnetic fields (Baillet et al. 2001). Neuronal sources generating tangential currents relative to the head surface, rather than orthogonal ones, produce strong MEG signals (Baillet 2017). EEG, in contrast, is more sensitive to neuronal dipoles orthogonal to the head surface, and is more affected by inhomogeneities of volume conductivity than MEG (Baillet et al. 2001).

The magnetic fields of brain activity are very weak, and noise of non-brain origin dominates the MEG signal. Therefore, the system is shielded from environmental electromagnetic noise by a chamber including layers of mu-metal, copper and aluminum (Baillet et al. 2001). Additionally, the MEG sensor array contains pick-up coils that attenuate noise sources, the so-called gradiometers (Baillet et al. 2001). Gradiometers combine two opposing coils, measuring the spatial gradient of the magnetic field (fT per distance). This architecture is sensitive to active brain sources close to the MEG helmet and attenuates distant sources, that produce more homogenous fields (Hämäläinen et al. 1993). The coils are connected to highly sensitive sensors, the superconducting quantum interference devices (SQUID), that detect tiny changes in magnetic flux under the condition of superconductivity (Baillet et al. 2001). Superconductivity requires extremely low temperatures (approx. -269°C), which are achieved by liquid helium cooling (Hämäläinen et al. 1993).

The MEG system used for the presented studies contained 306 sensors in total, 102 magnetometers and 204 planar gradiometers. Due to beneficial noise reduction and high sensitivity for cortical sources, only gradiometer signals were used in the analyses. Further attenuation of artifacts was accomplished by temporal signal space separation (Taulu and Simola 2006) and independent component analysis (Vigário et al. 2000).

1.2.2. Parametrizing Neuronal Oscillations

Neuronal time series naturally contain non-sinusoidal features, that are well visible in the time-domain and the frequency-domain. Most power spectra of brain activity can be separated into a periodic component, representing genuine oscillatory activity as peaks in narrow-band frequency intervals, and an aperiodic component, resembling a broad-band power shift along

frequencies (Da Lopes Silva 2013; Donoghue et al. 2020). For the aperiodic component, power decreases with increasing frequency f, approximating $Power \propto \frac{1}{f^x}$, where x is an exponent determining the steepness of decay (Miller et al. 2009). Recent evidence suggests that the aperiodic component conveys physiological meaning (Buzsáki et al. 2012), reflecting the balance of postsynaptic excitation and inhibition of the underlying neuronal tissue (Gao et al. 2017).

Both periodic and aperiodic components contribute to the power-value at each frequency bin in the power spectrum. Past research commonly quantified brain oscillations by the overall power within a frequency band, not distinguishing between periodic and aperiodic components. This bears the risk of over-interpreting trivial power differences, due to different head positions in the scanner, for example. These considerations are particularly relevant for resting state recordings, lacking a baseline period.

Power spectral parametrization (cf. Box 4.) mitigates this problem by separating genuine neuronal oscillations from the aperiodic background activity (Donoghue et al. 2020). Common pitfalls of this technique include errors in aperiodic component estimation, for example, when oscillatory peaks do not fully lie within the fitting ranges (Gerster et al. 2022). Careful inspection of the results and manual adjustment of parameter settings and model flexibility often improves the model fit (cf. Box 4.) (Gerster et al. 2022).

Box 4. Fitting One Over F Algorithm (FOOOF) (Donoghue et al. 2020)

The aperiodic and periodic components

The FOOOF algorithm attempts to decompose the given power spectrum into an aperiodic and a periodic component in an iterative procedure. The periodic component, aiming to capture power peaks at different frequencies, is modeled by (multiple) Gaussian distributions with center frequency *c*, width *w*, and amplitude *a*. The aperiodic component is parametrized by the offset *b* and steepness of decay *x*. The algorithm estimates the aperiodic and periodic components in semilog$_{10}$-power space.

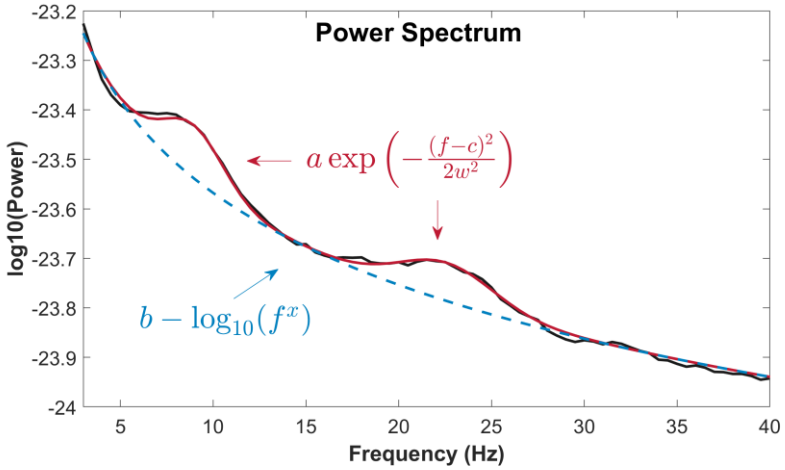

Figure 1. Parametrized Power Spectrum. Figure adapted from Krösche and colleagues (2023).

The FOOOF algorithm

The FOOOF algorithm performs three steps (see below). Estimates are computed with the least-squares method.

Step I. Initial aperiodic component estimated from power spectrum and subtracted.

Step II. Peak removal.

1. Compute SD in power over frequency.
2. If any peak exceeds the SD threshold, model the highest peak with a Gaussian distribution.
3. Subtract the modeled peak.

Repeat until all peaks have been removed.

Step III. Estimate final aperiodic component.

1.2.3. Source Reconstruction

Source reconstruction methods aim to estimate neuronal source activity from sensor activity. Importantly, sensor activity does not uniquely correspond to source activity, as different patterns of brain activity can produce the same sensor activity (Westner et al. 2022). To address this ambiguity, known as the inverse problem, source reconstruction methods rely on additional assumptions (Westner et al. 2022).

These methods begin by solving the forward problem, estimating how brain activity from a set of equivalent current dipoles projects onto the sensors. The current dipoles are arranged on a discretized grid, mimicking the brain's anatomical structure. Each current dipole is characterized by its orientation and magnitude, which determine how the magnetic field, generated by neuronal activity propagates to the sensors. The shape of the volume conductor (head and brain) is represented by the so-called head model. The head model can be a realistic shell model constructed from T1-MRI scans (Nolte 2003), or a simplified spherical model (Baillet et al. 2001). Besides anatomy, it is important to account for the head position relative to the sensors. Anatomical landmarks such as the nasion are employed to co-register the head model with the MEG system, representing both anatomical data and MEG sensors in a shared coordinate system. Using the head model, a leadfield is computed for every dipole, to predict how a magnetic field, generated by a unit current at a specific location, propagates to the sensor array (Baillet et al. 2001). The leadfield is a matrix which is inverted for source reconstruction. Additional constraints are necessary to obtain a unique inverse solution, allowing to infer neuronal activity from sensor data (van Veen et al. 1997).

Beamforming techniques are widely used in neuroscience for source reconstruction (Westner et al. 2022). These methods iterate through a set of predefined locations on a discretized grid, computing a spatial filter for each location separately (Westner et al. 2022). In both studies presented in this thesis linear constraint minimum variance (LCMV) beamforming was applied (cf. Box 5.), a beamforming method that estimates source activity in the time-domain (van Veen et al. 1997). At each location, source activity is estimated as a weighted linear combination of the sensor data (van Veen et al. 1997). The weights are provided by the spatial filter, which is computed using the sensor covariance matrix and the leadfield at that location (van Veen et al. 1997).

Box 5. Linear Constraint Minimum Variance Beamforming (van Veen et al. 1997)

LCMV Beamforming – A Balanced Computation

LCMV beamforming estimates source activity from sensor time series. LCMV beamforming aims to extract the signal from a predefined location on the discretized grid, while attenuating interference from an unknown number of other sources. To attain this objective, the method computes a spatial filter that preserves the signal (neither attenuate nor amplify i.e. unit gain) coming from a source location, while minimizing the total variance in the source data. The method leverages the leadfield matrix H and the sensor covariance matrix C_x to compute a spatial filter W at each location and uses it to estimate source activity in three-dimensions x, y, and z.

Spatial Filter Computation

Formalizing the optimization problem (a) and the solution (b):

$$\textbf{a)}\ \min_{W} \underbrace{\mathrm{tr}\left(W^{T}C_{x}W\right)}_{\text{Total Variance}} \text{ subject to } \underbrace{W^{T}H = I}_{\text{Unit Gain Constraint}} \qquad \textbf{b)}\ W = \underbrace{\left(H^{T}C_{x}^{-1}H\right)^{-1}H^{T}C_{x}^{-1}}_{\text{Spatial Filter}}$$

W*: Nx3 spatial filter matrix;* C_x*: NxN sensor covariance;* C_x^{-1}*: inverse of* C_x; H*: Nx3 leadfield matrix.*

1.3. Parkinson's Disease and Atypical Parkinsonism – Symptomology

For this thesis, I studied neural oscillations in patients with different parkinsonian syndromes. Neurological disorders in the parkinsonian disease spectrum, including PD, CBS, and PSP, present with distinct clinical profiles. Despite their unique characteristics, these diseases demonstrate numerous similarities, which render accurate diagnosis challenging, yet crucial, in clinical practice. Each disorder is characterized by specific motor and non-motor symptoms. The following section will provide an overview of the symptoms associated with PD, CBS and PSP.

Parkinsonism

"Parkinsonism" refers to a clinical syndrome characterized by four noticeable motor symptoms: bradykinesia, rigidity, tremor and postural instability (Dickson 2012). This clinical syndrome is characteristic of PD, for which postural instability manifests later in the disease course (Poewe et al. 2017). However, the underlying pathologies are heterogeneous, some presenting with Parkinsonism alongside various other motor and non-motor symptoms, but differ significantly in neuropathology, treatment options, and disease progression (Dickson 2012). Clinical detection of the underlying pathologies based on diagnostic criteria for parkinsonian syndromes remains difficult and misdiagnosis is common (Joutsa et al. 2014).

Parkinson's Disease

PD is a common neurological disorder that is marked by prominent motor and non-motor symptoms. Diagnosing PD initially requires two key criteria to be met. Bradykinesia (i.e. abnormally slowed movement with gradual reduction in speed and/or amplitude) as the main symptom and additionally at least one of the following two symptoms: rigidity (i.e. abnormally high muscle tone causing resistance to passive movement) or resting tremor (i.e. involuntary rhythmic movement of the resting extremities) (Postuma et al. 2015). Although these cardinal symptoms are central to diagnose PD, they are not exclusive to PD, so that other potential causes must be ruled out.

Furthermore, the condition also encompasses a wider range of motor and non-motor symptoms that can vary among individuals. Additional symptoms may include, but are not limited to, abnormal rapid eye movement (REM) sleep, depression and anxiety, cognitive impairments, postural instability and gait disturbances (Poewe et al. 2017). A further characteristic of PD is its staged course. Non-motor symptoms, often vegetative in nature, such as constipation,

hyposomnia and abnormal REM sleep, are already present in early stages, whereas the motor symptoms mentioned above have not yet manifested to a diagnostic extent (Poewe et al. 2017).

Corticobasal Syndrome

CBS is a neurological syndrome with corticobasal degeneration (CBD) being the most common underlying pathology (Armstrong et al. 2013). CBS often presents with akinetic-rigid Parkinsonism, alongside apraxia, cognitive decline, behavioral changes, aphasia (i.e. language formulation/comprehension dysfunction), and alien limb phenomenon (i.e. unintentional movements of a limb experienced as foreign) (Armstrong et al. 2013). Apraxia, defined as the inability to perform skilled, learned movements (Gross and Grossman 2008), affects the limbs of CBS patients (Armstrong et al. 2013). Patients often present with deficits in imitation or pantomime (Gross and Grossman 2008), though imitation is more acutely impaired (Stamenova et al. 2011). Aphasia usually affects language formulation in CBS (Armstrong et al. 2013).

CBS is rapidly progressing with an average life expectancy of 7 years after diagnosis and poorly responds to dopaminergic medication (Armstrong et al. 2013). Patients are diagnosed with probable CBS when they present with an asymmetric combination of at least two motor symptoms (limb rigidity or akinesia, among others) and two cortical features (apraxia, cortical sensory deficit, alien limb phenomena) (Armstrong et al. 2013). Possible CBS, in contrast, may present symmetrically and requires only one of the motor symptoms and one cortical feature (Armstrong et al. 2013). The pathological background of CBS is heterogenous. Beyond CBD, it can be associated with other pathologies, including PSP and Alzheimer's Disease (AD) (Ling et al. 2014; Ouchi et al. 2014; Alexander et al. 2014). In addition, CBD, the pathology, can manifest as various clinical phenotypes like PSP and behavioral variant frontotemporal dementia, exhibiting noticeable personality changes (Kouri et al. 2011).

Progressive Supranuclear Palsy

PSP, the pathology, most often manifests as Richard's syndrome (Boxer et al. 2017), the classical clinical presentation of PSP (Litvan et al. 1996). In the literature, the term "PSP" is used interchangeably to denote either the clinical phenotype (Litvan et al. 1996) or the underlying pathology (Boxer et al. 2017). Within this text the term, "PSP" is used to refer to the clinical syndrome, unless explicitly stated otherwise.

Next to a levodopa-unresponsive axial-predominant Parkinsonism, PSP is characterized by oculo-motor dysfunction (vertical supranuclear gaze palsy), early postural instability, gait

disturbances, as well as language, behavioral and cognitive dysfunction (Litvan et al. 1996; Höglinger et al. 2017). It has a mean survival duration of 5.9 to 6.9 years after diagnosis (Litvan et al. 1996). Dopaminergic medication benefits PSP patients with predominant Parkinsonism initially (Boxer et al. 2017). However, the overall responsiveness of patients with PSP is generally poor (Boxer et al. 2017).

The diagnosis of probable PSP requires oculo-motor dysfunction in combination with postural instability, akinesia or cognitive dysfunction (with predominant frontal cognitive/behavioral presentation) as an additional feature (Höglinger et al. 2017). Possible PSP requires at least one core feature like oculo-motor dysfunction or progressive gait freezing within 3 years after first PSP related symptoms began (Höglinger et al. 2017). Similar to CBS, the variable clinical phenotypes complicate accurate diagnosis (Osaki et al. 2004; Joutsa et al. 2014). PSP pathology is associated with a range of clinical phenotypes, including predominant Parkinsonism, speech and language dysfunction and CBS amongst others (Boxer et al. 2017).

1.4. Parkinson's Disease and Atypical Parkinsonism – Pathological Alterations

Patients with parkinsonian disorders show disease-related alterations in many brain regions, characterized by neuronal loss and the accumulation of misfolded proteins. Research on these alterations provided insights into the disease-specific patterns, highlighting similarities and differences across PD, CBS, and PSP. Some of these results are briefly presented in the following.

Parkinson's Disease

PD is marked by the degeneration of dopaminergic neurons in the substantia nigra pars compacta, projecting to the striatum (Lang and Lozano 1998b). Furthermore, intracellular deposition of Lewy bodies, which primarily contain fibrils of α-synuclein, are characteristic for PD (Dickson 2012). Yet, α-synuclein proteinopathy of similar extent is commonly found in neurologically unimpaired elderly individuals (Parkkinen et al. 2005) and its presence does not necessarily coincide with neurodegeneration (Dickson 2012). The pathomechanisms driving PD remain the subject of ongoing research (Riederer et al. 2023).

In addition, noradrenergic and cholinergic neurotransmitter systems are commonly affected (Bohnen et al. 2022; Benarroch 2018). Early degeneration of the locus coeruleus leads to noradrenergic denervation of widespread downstream targets, including the prefrontal cortex,

which may cause executive dysfunction in PD (Benarroch 2018). Degeneration of cholinergic neurons in the basal forebrain, in particular the nucleus basalis of Meynert, was associated with cognitive decline (Pasquini et al. 2021). However, cholinergic synaptic loss in posterior cortical areas was already found in PD patients without dementia (Horsager et al. 2022). Cholinergic deficits related to the pedunculopontine nuclei in the brainstem might be linked to postural dysfunction (Pasquini et al. 2021).

Cortical atrophy in PD patients is generally limited but increases with disease severity and is positively correlated with motor and cognitive impairments in advanced stages (Wilson et al. 2019). In conclusion, the neurodegeneration underlying PD primarily affects subcortical regions and related neurotransmitter systems in the course of the disease, with limited involvement of cortical areas (Pereira et al. 2014).

Corticobasal Syndrome and Progressive Supranuclear Palsy

While PD is characterized by α-synuclein proteinopathy, the disease mechanisms in PSP and CBS are primarily driven by tau pathology (cf. Box 6.). CBS patients exhibit widespread pathological changes in the cortex, primarily affecting frontal and parietal lobes, particularly in the pre-/postcentral regions, alongside involvement of the basal ganglia. These pathological patterns have been corroborated by tau-PET studies (Smith et al. 2017; Cho et al. 2017; Goodheart et al. 2021), metabolic-PET studies (Pardini et al. 2019), and evidence of gray matter loss in MR scans (Whitwell et al. 2010; Josephs et al. 2010). Motor areas are consistently affected in CBS patients (Goodheart et al. 2021; Pardini et al. 2019; Whitwell et al. 2010).

In contrast, patients diagnosed with PSP exhibit extensive subcortical tau pathology and atrophy, particularly in the midbrain (Jabbari et al. 2020; Stamelou et al. 2021), thalamus and basal ganglia (Whitwell et al. 2020; Stamelou et al. 2021).

Tau pathology may precede atrophy in disease progression, as in AD (La Joie et al. 2020). Widespread synaptic loss affecting the cortex, amygdala, hippocampus, and multiple subcortical regions in both PSP and CBS is associated with disease severity and cognitive decline (Holland et al. 2020). Notably, a reduction in synaptic density is already present in regions with minimal atrophy (Holland et al. 2020). These findings indicate that multiple neuropathological changes occur early in the disease, disrupting interconnected neuronal networks before atrophy becomes apparent.

In summary, cortical degeneration, particularly of frontal and parietal regions, is a hallmark of CBS, while subcortical degeneration is more prominent in PSP (Dickson 2012; Stamelou et al. 2021).

Table 1: Overview of symptoms and pathological abnormalities associated with PD, CBS and PSP. The listed symptoms and pathological abnormalities are representative, but not exhaustive.

Disease	Symptoms	Pathology/Degeneration
Parkinson's Disease (Poewe et al. 2017)	- bradykinesia, rigidity, tremor - late postural instability, gait disturbances - early non-motor symptoms (REM-sleep disturbances, constipation, hyposomnia) - depression and anxiety	- Lewy body pathology (α-synuclein) - degeneration of dopaminergic neurons (substantia nigra pars compacta) - noradrenergic deficits (early degeneration of the locus coeruleus) - cholinergic system abnormalities
Corticobasal Syndrome (Armstrong et al. 2013; Koga et al. 2022)	- akinetic-rigid Parkinsonism - apraxia - asymmetric symptoms - cognitive decline - behavioral changes - aphasia	- tau pathology - widespread cortical pathology/ degeneration (mostly frontal, motor, parietal cortices) - focal subcortical pathology (mostly basal ganglia)
Progressive Supranuclear Palsy (Höglinger et al. 2017; Stamelou et al. 2021)	- oculomotor dysfunction - early postural instability - akinesia - cognitive, language and behavioral dysfunctions	- tau pathology - extensive subcortical pathology (mostly midbrain, basal ganglia, thalamus) - frontal lobe degeneration

Box 6. Primary 4R Tauopathies

Tauopathies

Tauopathies are a group of neurodegenerative diseases marked by the accumulation of insoluble aggregates of misfolded tau within neurons and glial cells, presumably resulting in their degeneration (Höglinger et al. 2018). In its normal cellular function, tau protein, primarily found in neuronal axons, contributes to the assembly of microtubules. Microtubules are essential for organizing the cellular cytoskeleton and intracellular transport processes (Garcia and Cleveland 2001; Rösler et al. 2019). Tau protein contains either three or four (3R/4R) microtubule-binding repeats and tauopathies can be categorized into 3R tauopathies, 3R/4R tauopathies and 4R tauopathies, based on the predominant tau isoform (Rösler et al. 2019). The pathological process is marked by abnormal hyperphosphorylation of tau which disrupts its binding properties and promotes the aggregation and accumulation of larger tau complexes (Rösler et al. 2019). The pathology likely transmits intercellularly along connected neuronal networks and promotes pathophysiological processes of tau aggregation in recipient cells (Stamelou et al. 2021; Franzmeier et al. 2022). Notable tauopathies are AD, PSP and CBD, among others. AD is considered a secondary tauopathy, as the amyloid-beta pathology precedes the tau-related pathology (Jack et al. 2013). Notably, the deposition of tau, but not amyloid-beta, predicts the topography of atrophy (La Joie et al. 2020) and cognitive decline (Brier et al. 2016). PSP and CBD are primary tauopathies characterized by deposition of the 4R tau isoform (Stamelou et al. 2021). 4R tauopathies can only be distinguished with certainty based on microscopic neuropathological features in post-mortem investigation (Stamelou et al. 2021).

Disease Progression

Current models on disease progression suggest that the tau pathology in PSP and CBD originates in the basal ganglia (Leuzy et al. 2019; Kovacs et al. 2020). In early disease stages of PSP, tau deposits accumulate in neurons and glia cells within the basal ganglia and spread to nearby subcortical structures in the midbrain, thalamus and dentate nucleus (Kovacs et al. 2020). Cortical tau deposition follows, progressing from anterior-superior to posterior-inferior regions (Kovacs et al. 2020). A recent study on a large cohort of patients with Richardson's syndrome proposed that the earliest brain atrophy occurs in the medulla, midbrain and thalamus (Scotton et al. 2022). Yet, how tau pathology and atrophy relate to each other remains unclear (Franzmeier and Höglinger 2022). In CBD, tau accumulation may also begin in the basal ganglia, but tends to spread predominantly to cortical sites, particularly motor and frontal areas, with less extensive involvement of subcortical structures (Leuzy et al. 2019). Yet, the evidence for staged progression is scarce and refining staging models remains an area of ongoing research.

1.5. Parkinson's Disease and Atypical Parkinsonism – Electrophysiology

The electrophysiological abnormalities of PD have been thoroughly investigated over the last decades, highlighting the involvement of the motor system (Boon et al. 2019). Electrophysiological research on atypical Parkinsonism could be meaningfully embedded in a comparative analysis, but so far, the electrophysiology of APS is not well described. This section presents a broad overview on the electrophysiology of PD, CBS and PSP.

Parkinson's disease

PD patients exhibit abnormal electrophysiological signals, as measured with EEG, MEG and intracranial electrodes. Two key features of these abnormalities are spectral slowing, i.e. a systematic shift of spectral power toward lower frequencies, and alterations in beta oscillations in the sensorimotor system.

Spectral slowing in PD is characterized by increased power in the theta and lower alpha band, reduced power in the gamma band, and diminished beta power, predominantly in posterior regions (Stoffers et al. 2007). As the disease progresses, the slowing effect intensifies, with cognitive decline positively correlated with theta power and negatively correlated with alpha power (Olde Dubbelink et al. 2013). Yet, spectral slowing does occur in non-demented PD patients (Stoffers et al. 2007). Spectral slowing in posterior brain areas has been associated with cognitive impairments (Olde Dubbelink et al. 2014; Latreille et al. 2016).

The cortico-basal-ganglia-thalamic-circuit, central to the neuropathology of PD, is marked by aberrant beta oscillations. On the cortical level, early PD patients might show increased sensorimotor beta power at rest, compared to controls (Pollok et al. 2012), and exhibit reduced beta power in later disease stages (Heinrichs-Graham et al. 2014; Boon et al. 2019). In addition, PD is characterized by increased beta power in the subthalamic nucleus (STN), that is inversely correlated with levodopa-induced clinical improvement (Kühn et al. 2006; Ray et al. 2008). Dopaminergic medication normalizes beta power in the motor cortex (Heinrichs-Graham et al. 2014) and the STN (Heinrichs-Graham et al. 2014; Kühn et al. 2006; Ray et al. 2008). Some studies report that beta power in the motor cortex (Cao et al. 2020) and the STN (Neumann and Kühn 2017) correlate with akinetic-rigid symptom severity in the medication Off state. In addition, the STN and frontal/motor areas are functionally connected in the beta range (Litvak et al. 2011; Hirschmann et al. 2011) and the coupling is reduced by therapeutic interventions

like dopaminergic medication (Hirschmann et al. 2013) and deep brain stimulation (Oswal et al. 2016).

Corticobasal Syndrome and Progressive Supranuclear Palsy

Electrophysiological studies in patients with PSP and CBS are scarce. Previous reports point toward abnormal background activity and slowing events at visual inspection of EEG in CBS and PSP (Barcelon et al. 2019). This abnormal EEG activity localizes contralateral to the most affected bodyside in most CBS patients, and ipsilateral to the hemisphere with predominant atrophy (Tashiro et al. 2006). A study involving 6 PSP patients showed increased EEG power in lower frequencies compared to HC with a concomitant decrease in high frequency power, particularly in anterior frontal electrodes (Montplaisir et al. 1997). Additionally, Wheaton and colleagues (2008) found abnormally high interhemispheric coherency between right premotor and left parietal areas during a tool-use pantomime task in 3 CBS patients with apraxia, in contrast to a left hemisphere dominant network observed in HC. The authors proposed that the right hemisphere might compensate for left hemisphere damage.

In sum, the limited number of studies available suggest possible shifts in spectral power and compensatory neural activity during action initiation in comparison to healthy controls. However, given the small cohort sizes in studies that applied quantitative EEG analysis, the electrophysiological signatures of PSP and CBS remain underexplored.

1.6. Thesis Goals

To address the existing knowledge gap, this thesis investigated electrophysiological signatures of CBS and PSP. Study 1 focused on resting state activity, employing comprehensive power spectral analysis of MEG signals to identify spatio-spectral abnormalities characteristic of CBS and PSP. The objective was to detect alterations that distinguish APS patients from both HC and PD patients, thereby providing new insights into electrophysiological patterns potentially unique to CBS and PSP.

Study 2 was informed by the clinical observation that CBS patients frequently exhibit deficits in the imitation of skilled actions, suggesting disturbances in task-relevant neural networks. This study aimed to characterize neural activity across distinct phases of an observe-to-imitate task, namely action observation, movement preparation and movement initiation, using time frequency analysis methods. The main hypothesis was that CBS patients show altered brain activity in fronto-parietal networks, compared to healthy controls.

In summary, this thesis contributes to the understanding of CBS and PSP by applying electrophysiological methods, offering novel insights into disease-specific neural dysfunction. The original research articles detailing these studies are appended below.

2. Study 1: Slowing of Frontal β Oscillations in Atypical Parkinsonism

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Marius Krösche, Silja Kannenberg, Markus Butz, Christian J. Hartmann, Esther Florin, Alfons Schnitzler, Jan Hirschmann, (2023). *Slowing of Frontal β Oscillations in Atypical Parkinsonism*. In: Movement Disorders 38 (5), p. 806-817. DOI: 10.1002/mds.29378

Personal contribution

J.H. and A.S. received funding from the Else Kröner Fresenius Foundation (study 1 and study 2). Data acquisition was conducted by S.K. and M.B. for most PSP patients. Data acquisition for all CBS patients, a few PSP patients, a few PD patients and multiple HC was done by J.H. and me. Clinical diagnosis for all patients with atypical Parkinsonism was provided by C.J.H. Some PD patients were recorded by J.H. in a previous research project. Multiple data sets for PD patients and HC were provided by E.F., which were recorded in another research project. Data curation was done by me under supervision of J.H. Methodology, including analysis ideas and statistics, was developed in close dialogue between me and J.H. Data analysis in MATLAB and Python was conducted by me under supervision of J.H. I visualized the results under supervision of J.H. I wrote the original draft, discussing ideas with J.H. All authors except me reviewed the proposed manuscript. Answering reviewers' questions and proposals and rewriting the manuscript for publication was conducted by J.H. and me in close dialogue.

Study design 5%; Data Acquisition 33%; Data Curation 95%; Methodology 50%; Data Analysis 90%; Visualization 90%; Writing – original draft 80%; Writing – reviewing 0%; Reviewer Comments and Rewriting – 50%.

2.1. Abstract

Background: Diagnosis of atypical parkinsonian syndromes (APS) mostly relies on clinical presentation as well as structural and molecular brain imaging. Whether parkinsonian syndromes are distinguishable based on neuronal oscillations has not been investigated so far.

Objective: The aim was to identify spectral properties specific to atypical parkinsonism.

Methods: We measured resting-state magnetoencephalography in 14 patients with corticobasal syndrome (CBS), 16 patients with progressive supranuclear palsy (PSP), 33 patients with idiopathic Parkinson's disease, and 24 healthy controls. We compared spectral power as well as amplitude and frequency of power peaks between groups.

Results: Atypical parkinsonism was associated with spectral slowing, distinguishing both corticobasal syndrome and progressive supranuclear palsy from Parkinson's disease (PD) and age-matched healthy controls. Patients with atypical parkinsonism showed a shift of β peaks (13-30 Hz) toward lower frequencies in frontal areas bilaterally. A concomitant increase in θ/α power relative to controls was observed in both APS and PD.

Conclusion: Spectral slowing occurs in atypical parkinsonism, affecting frontal β oscillations in particular. Spectral slowing with a different topography has previously been observed in other neurodegenerative disorders, such as Alzheimer's disease, suggesting that spectral slowing might be an electrophysiological marker of neurodegeneration. As such, it might support differential diagnosis of parkinsonian syndromes in the future.

Keywords: magnetencephalography; corticobasal syndrome; progressive supranuclear palsy; resting state; oscillations

2.2. Introduction

Most patients with parkinsonism suffer from idiopathic Parkinson´s disease (PD) caused by neuronal loss in the substantia nigra (Lang and Lozano 1998a, 1998b). Atypical parkinsonian syndromes (APS) such as corticobasal syndrome (CBS) or progressive supranuclear palsy (PSP) resemble PD clinically. Yet they have distinct pathologies and include a wide range of additional cognitive and motor symptoms (Burrell et al. 2014; Armstrong et al. 2013; Höglinger et al. 2017; Litvan et al. 1996). The clinical hallmarks of CBS are asymmetric presentation of parkinsonism, apraxia and cognitive decline (Armstrong et al. 2013). Patients with PSP present with vertical supranuclear gaze palsy and postural instability (Höglinger et al. 2017; Litvan et al. 1996). Compared to PD, APS show a more rapid disease progression (Poewe and Wenning 2002) and poor responsiveness to levodopa (Armstrong et al. 2013; Litvan et al. 1996).

Both CBS and PSP are tauopathies, characterized by aggregation of hyperphosphorylated tau protein in diverse brain regions, in conjunction with neuronal degeneration (Dickson et al. 2002; Kouri et al. 2011; Williams and Lees 2009). Corticobasal degeneration (CBD), the pathology underlying CBS, is related to widespread tau aggregation in cortical areas and the basal ganglia (Dickson et al. 2002; Kouri et al. 2011; Forman et al. 2002). whereas the pathology of PSP is characterized by pronounced tau aggregation in the brainstem, with less cortical involvement (Williams and Lees 2009; Dickson et al. 2007; Dickson et al. 2010).

The relationship between pathology and symptomology is ambiguous for both CBS and PSP. Their clinical presentations are heterogeneous and overlapping (Armstrong et al. 2013; Höglinger et al. 2017; Williams and Lees 2009). Although diagnostic accuracy improves with disease progression and manifestation of symptoms, misdiagnosis is common (Armstrong et al. 2013; Osaki et al. 2004; Joutsa et al. 2014; Alexander et al. 2014). Because clinical examination alone is often not sufficient for an early and reliable differential diagnosis, it is of clinical relevance to identify new biomarkers. Biomarkers might emerge from several sources, including imaging (Whitwell et al. 2010; Albrecht et al. 2017; Matsuda et al. 2020; Josephs et al. 2008; Dutt et al. 2016; Brenneis et al. 2004) and electrophysiology. The electrophysiology of APS, however, is not well investigated.

Brain oscillations are electrophysiological signatures of synchronized mass communication between neurons at various scales, for example, local neuronal circuitry (Kopell et al. 2000; Börgers et al. 2005; McCarthy et al. 2011; Sherman et al. 2016) or larger thalamocortical (Steriade et al. 1993) and cortico-basal-ganglia (Oswal et al. 2021) loops. This oscillatory

activity can be detected using magnetoencephalography (MEG), which captures the coordinated postsynaptic activity of neuronal populations in real time (Baillet 2017). Although initial studies point to disease-specific electrophysiological alterations, (Tashiro et al. 2006; Barcelon et al. 2019; Montplaisir et al. 1997) it is currently not clear if and how oscillations are altered in APS in comparison to healthy subjects and PD patients.

2.3. Patients and Methods

2.3.1. Participants

We analyzed resting-state MEG measurements of 16 CBS patients, 16 PSP patients, 24 HCs and 33 nondemented PD patients of akinetic-rigid or intermediate subtype. No patient exhibited constant resting tremor. Two CBS patients were excluded from analysis due to excessive noise. Of the remaining 30 APS patients, 4 were classified as possible CBS, 10 as probable CBS, 1 as possible PSP and 15 as probable PSP (Table 2.1 & Appendix 6.1: Tab. S6.1.1), based on current diagnostic criteria for CBS (Armstrong et al. 2013) and PSP (Höglinger et al. 2017; Litvan et al. 1996).

Table 2.1: Summary data of the study cohorts. CBS: Corticobasal Syndrome, PSP: Progressive Supranuclear Palsy, PD: Parkinson´s disease; HC: Healthy controls; std: Standard deviation. Symptom score group metrics of PSP are not reported due to the small sample size (see Appendix 6.1: Tab. S6.1.1).

Group	N	Mean age (years)	Min-Max age (years)	Gender (f/m)	Diagnosis (poss./prob.)	Mean UPDRS-III (sum)	Mean MoCa (normalized)
CBS	14	65.1	52 – 79	9 / 5	4 / 10	45.86 (22.3)	0.61 (0.23)
PSP	16	70.2	64 – 78	7 / 9	1 / 15	n.a.	n.a.
PD	33	63.1	47 – 74	7 / 26	-	35.84 (11.19)	0.85 (0.08)
HC	24	65.5	56 – 78	13 / 11	-	-	

PD patients withdrew from dopaminergic medication over night before participation. Parkinsonism was quantified by the Unified Parkinson's Disease Rating Scale, Part III (UPDRS-III) (Goetz et al. 2008), cognitive abilities by the Montreal Cognitive Assessment (MoCA) (Nasreddine et al. 2005), and apraxia by Goldenberg's Apraxia Test (Goldenberg 1996), and the Test of Upper Limb Apraxia (Vanbellingen et al. 2010). UPDRS-III scores were available for CBS, PD (except 2) and three PSP patients (Appendix 6.1: Tab. S6.1.1). MoCA scores were obtainable for CBS patients (except CBS11), 5 PSP patients (Appendix 6.1: Tab. S6.1.1) and 25 PD patients. In a few cases, physical disabilities made it infeasible to rate some

items. Thus, test scores were normalized by the number of scored items before computing correlations.

The groups significantly differed in age (one-way analysis of variance: $F(3,83) = 4.15$, $p = 0.009$). Post hoc, two-sided t tests revealed that the PSP group was older than the CBS ($t(28) = -2.093$, $p = 0.046$), HC ($t(38) = 2.581$, $p = 0.014$) and the PD subjects($t(47) = 3.926$,$p = 0.0003$). UPDRS-III scores differed non-significantly between APS and PD (two-sided t-test: $t(46) = 1.803$, $p = 0.078$). Excluding APS patients above 70 years and 4 CBS patients with the largest UPDRS scores eliminated the differences in age and motor impairment and yielded similar results (Appendix 6.1: Fig. S6.1.7.). MoCA scores did significantly differ between APS and PD (two-sided t test: $t(41) = -4.358$, $p < 0.001$). All participants provided written informed consent. The study was approved by the local ethics committee in accordance with the Declaration of Helsinki (study numbers: CBS: 2019-447-andere; PSP: 2018-155-KFogU; PD: 5608R).

2.3.2. Recordings

MEG recordings were conducted using a 306-channel whole-head MEG system (MEGIN, Espoo, Finland). Participants were recorded for 10 minutes in upright position during rest with open eyes. 9 PD patients were measured for 5 minutes. Electromyograms were recorded from both forearms.

2.3.3. Data preprocessing

MEG data were preprocessed in MATLAB R2018a using the Fieldtrip Toolbox (version 14.12.2020) (Oostenveld et al. 2011). Bad channels and time segments containing artifacts or periods with tremor were discarded from further analysis. Subsequently, gradiometer time series were down-sampled to 1000 Hz, high-pass filtered (FIR-filter) 1 Hz, and subjected to an independent component analysis (Bell and Sejnowski 1995). Components containing eye blink or heartbeat artifacts were removed.

2.3.4. Source & Parcel Reconstruction

MEG data and individual T1-weighted MRI scans (Siemens Magnetom Trio, 3T MRI scanner) were co-registered and used to construct forward models via the single shell approximation method (Nolte 2003). For 7 subjects (1 HC, 2 PD, 4 PSP) the colin27 template (Holmes et al. 1998) was used for head model construction because an individual MRI was not available. Source reconstruction was performed for 567 positions on the cortical surface via linear constrained minimum variance beamforming with a regularization parameter of 5% (van Veen et al. 1997). Each source was assigned to one of 48 cortical parcels (Appendix 6.1: Fig. S6.1.1),

as defined in the automated anatomical atlas (Tzourio-Mazoyer et al. 2002). Sources were aggregated into a single parcel time series by extracting the largest eigenvector. Finally, parcel time courses were jointly orthogonalized for signal leakage reduction (Colclough et al. 2015).

2.3.5. Data Analysis

Parcel time courses were segmented into 2 s epochs with 1 s overlap. Each segment was tapered with 7 tapers of the discrete prolate spheroidal sequence for 2 Hz spectral smoothing and forwarded to Fourier transformation. Power was averaged over segments, resulting in one power spectrum per parcel and subject. Each power spectrum was corrected for its aperiodic 1/f background estimate using the *fitting oscillations and one over F* (FOOOF) algorithm (Donoghue et al. 2020) in Python 3.9.1. This toolbox additionally allowed for the detection of spectral peaks and estimation of peak frequency and peak amplitude. To avoid possible pitfalls when using FOOOF (Gerster et al. 2021), we applied an iterative fitting procedure and visual checks (see Appendix 6.1).

2.3.6. Spectral Slowing

The term spectral slowing refers to a shift of spectral energy toward lower frequencies. We investigated spectral slowing by assessing group differences in the power spectrum's center of mass, referred to as center of energy (CoE) in the following:

$$CoE = \frac{\sum_{i=1}^{n} log10(power)_i \cdot frequency_i}{\sum_{i=1}^{n} log10(power)_i} \qquad (1)$$

Because the subtraction of the aperiodic estimate from the power spectrum can occasionally lead to negative power values, the corrected spectrum's minimum was subtracted from each power value before computing the CoE, reinstating positivity.

Spectral slowing may arise due to different phenomena: 1) a peak shift toward the low frequency range, 2) an increase in peak amplitude in the low frequency range, 3) a decrease of peak amplitude in the high frequency range. To disentangle these effects, we first identified a brain region of interest (ROI) based on group differences in CoE. Within this ROI, we investigated peak frequency and peak amplitude in detail using of linear mixed modeling. This analysis was performed once for all peaks detected in the ROI and once using only the largest peak of each parcel, to exclude small, potentially false-positive peaks.

2.3.7. Statistical Analysis

For statistical comparison of CoE values, we used cluster-based permutation testing as implemented in Fieldtrip (Maris and Oostenveld 2007). The topographical neighborhood of each parcel was determined by finding all adjacent parcels within 1 cm from the parcel border. We report two-sided statistical tests with an α-level of 5% based on 10000 permutations (multiple comparison correction: cluster-wise maximum sum of t-values). Parcels showing differences in CoE underwent post-hoc analysis of spectral peaks with Linear Mixed Modelling, as implemented in Matlab's Statistics and Machine Learning Toolbox. We defined four models to test for group differences in peak frequency and peak amplitude for low frequencies (θ and α) and higher frequencies (β), respectively. *P*-values were adjusted for these four comparisons using the Benjamini-Hochberg procedure (Benjamini and Hochberg 1995). For details on the model see the Appendix 6.1.

2.4. Results

2.4.1. CBS and PSP versus HC

We compared resting-state cortical power between CBS patients, PSP patients, and HC. Fig. 1 depicts the group-mean topographies of 1/f-corrected power in the θ (4– 7.5 Hz), α (8– 12.5 Hz), low β (13– 19.5 Hz), and high β (20- 30 Hz) bands. CBS patients and PSP patients showed higher power in the θ and α bands compared to HC. θ power was mostly increased in posterior regions, whereas α power was increased in central and frontal regions for both CBS (Fig. 2.1A) and PSP patients (Fig. 2.1B).

The power differences reversed in sign for the low and the high β range, indicating larger β power in controls, particularly in central and parietal cortex. Thus, APS patients exhibited stronger θ/α power but weaker β power than controls, suggesting a shift of spectral energy towards lower frequencies. These qualitative power differences (see Appendix 6.1: Fig. S6.1.6 for statistics) motivated usage of the CoE, capturing the spectral shift in a single number. The CoE differed from HC for both the CBS and the PSP group in numerous frontal, central and parietal areas (Fig. 2.1C, D; HC vs. CBS: $p = 0.004$, HC vs. PSP: $p = 0.001$). CBS and PSP, however, did not differ significantly (no clusters found). Therefore, both groups were merged to jointly represent APS in the following (Fig. 2.2C; HC vs. APS: $p = 0.001$). Individual CoE data and spectra can be found in Appendix 6.1: Figures S6.1.3 and S6.1.5A). The pattern for CBS patients did not change qualitatively when mirroring brain images such that the

hemisphere contralateral to the symptom-dominant bodyside was always right (Appendix 6.1: Fig. S6.1.4).

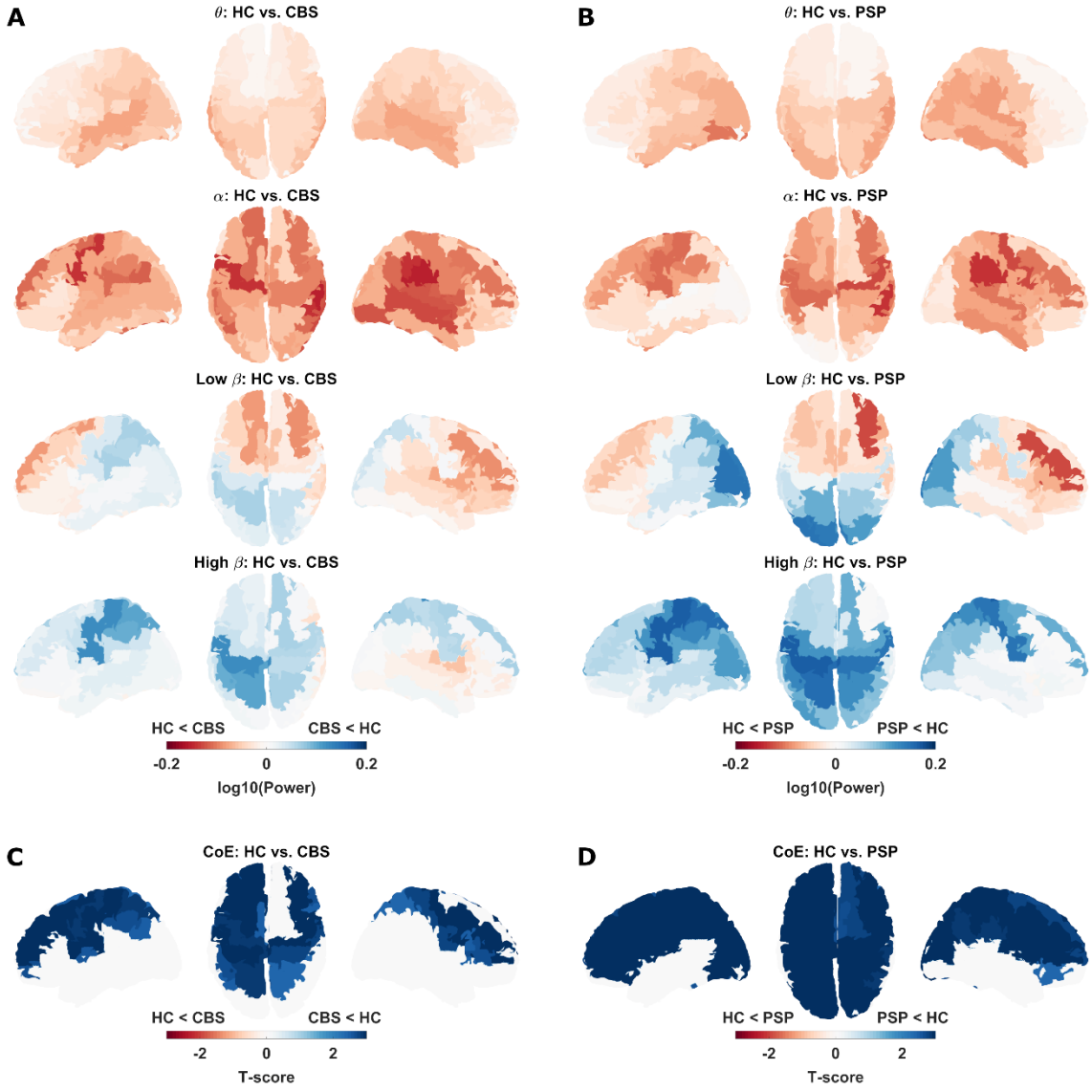

Figure 2.1. Spectral shift of energy towards lower frequencies in CBS and PSP in comparison to controls. A) Power differences between controls and CBS patients. B) Power differences between controls and PSP patients. Blue indicates that controls had more power in the respective band, whereas red indicates that CBS or PSP patients had more power. C) Statistical comparison of CoE, controls vs. CBS patients. Dark blue areas indicate regions with significant differences. D) As C) for controls vs. PSP.

2.4.2. APS versus PD

When comparing band-limited power between APS and PD, we observed a similar pattern as in the comparison to HC. APS had more α and less high β power than PD, although the difference was less strong (Fig. 2.2B). Again, the CoE was reduced in APS, but the reduction was more local, occurring in frontal areas exclusively (Fig. 2.2D; $p = 0.009$).

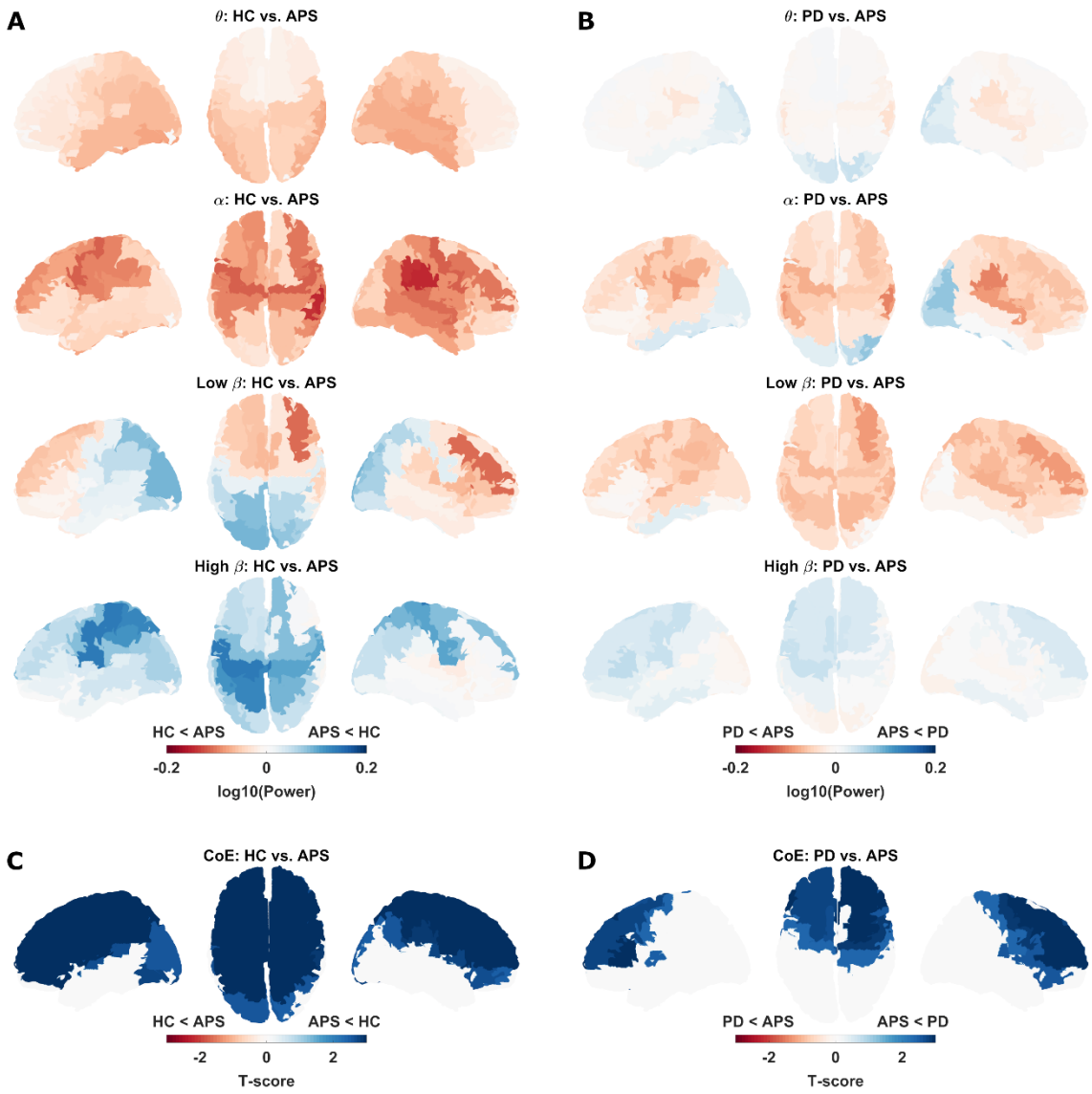

Figure 2.2. Spectral shift of energy towards lower frequencies in atypical Parkinsonism in comparison to healthy controls and patients with idiopathic Parkinson syndrome. See Fig. 1 for more explanations. A) APS vs. controls. B) APS vs. PD. C) Statistical comparison of center of energy (CoE) APS vs. controls. D) as C) for APS vs. PD.

The average CoE within the brain region with a significant difference to controls and PD patients did not correlate with motor or cognitive scores ($r_{Spearman} < |0.352|$, $p > 0.217$).

2.4.3. Spectral Peaks

The CoE analysis revealed a shift of energy toward lower frequencies in APS patients. Next, we described this shift in detail through an analysis of spectral peaks. This analysis was performed for a ROI showing significant differences in CoE in the comparisons APS vs. HC and APS vs. PD (Fig. 2.3A).

Figure 2.3C illustrates the distribution of peak frequencies in the ROI for APS patients, PD patients and HC. The distribution was bimodal for all groups, with peak frequencies clustering around 9 and 22 Hz. Thus, we performed separate statistical comparisons for the θ/α (4- 13 Hz) and the β (13- 30 Hz) bands. We present an alternative analysis based on the entire frequency range (4- 30 Hz) in Appendix 6.1: Fig. S6.1.5B.

θ/α Oscillations

Peak Frequency

There was no significant difference in θ/α peak frequency between the groups, neither when considering all peaks found in the ROI ($t_{HC}(1036) = 0.92$, $p_{HC} = 0.477$; $t_{PD}(1036) = -1.024$, $p_{PD} = 0.612$; $t_{age}(1036) = 0.227$, $p_{age} = 0.82$), nor when considering only the highest peak per ROI parcel ($t_{HC}(897) = 1.109$, $p_{HC} = 0.357$; $t_{PD}(897) = -0.857$, $p_{PD} = 0.675$; $t_{age}(897) = 0.357$, $p_{age} = 0.721$).

Peak Amplitude

We found no evidence for differences in θ/α peak amplitudes between APS patients and PD ($t(1036) = -0.555$, $p = 0.73$) or between APS patients and controls ($t(1036) = -1.913$, $p = 0.112$). Age did not influence θ/α peak amplitude ($t(1036) = -1.371$, $p = 0.683$). When considering the largest peaks per parcel, θ/α peak amplitudes showed a trend difference between APS and controls ($t_{HC}(897) = -2.01$, $p_{HC} = 0.089$; $t_{PD}(897) = -0.665$, $p_{PD} = 0.675$; $t_{age}(897) = -1.263$, $p_{age} = 0.721$). This effect was most likely due to differences in α band power (Appendix 6.1: Fig. S6.1.6). θ power differences between controls and APS as well as between controls and PD occurred in more posterior areas (Appendix 6.1: Fig. S6.1.6).

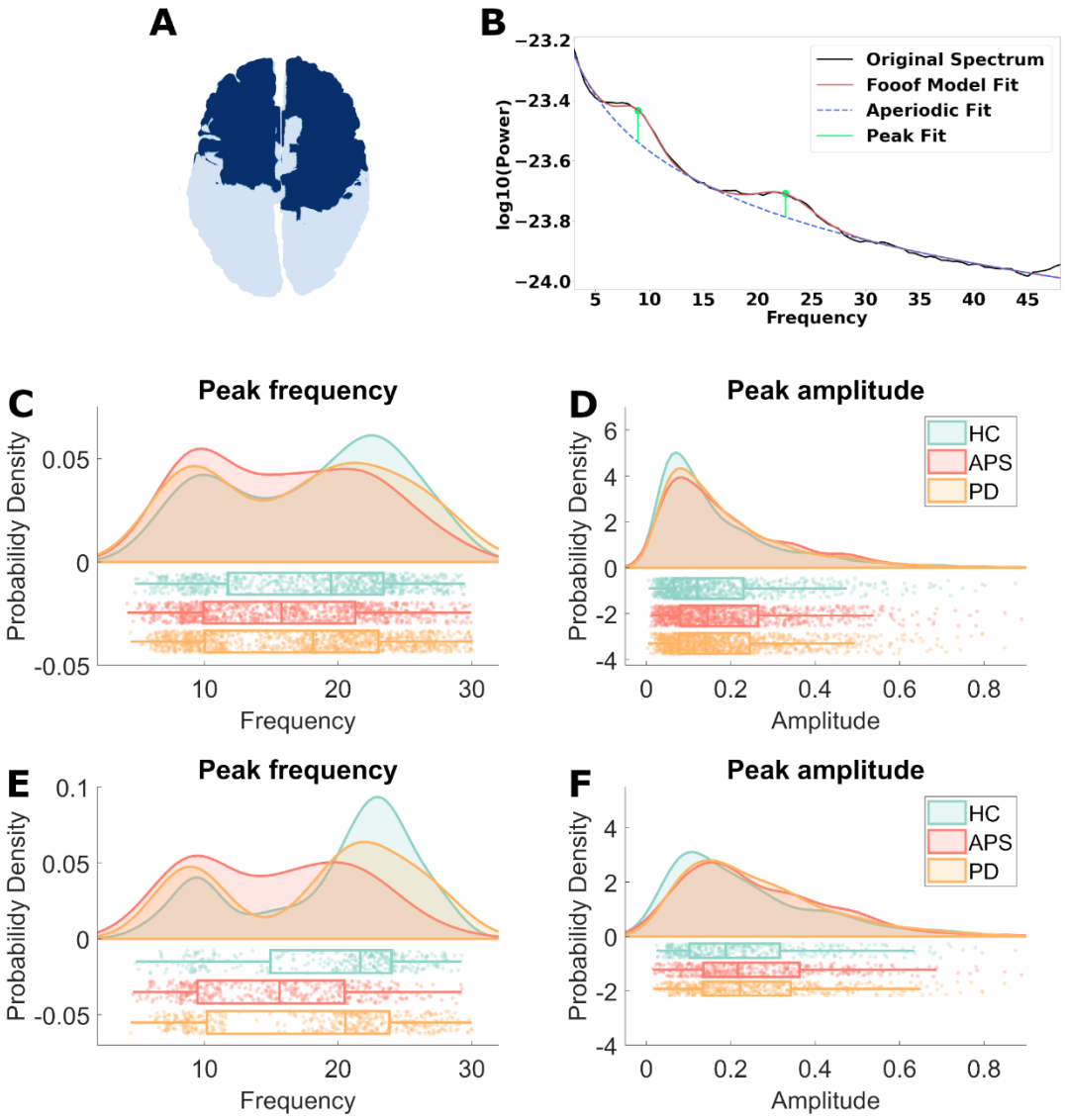

Figure 2.3. Peak frequency and peak amplitude distribution for APS, PD and HC. A) ROI for analysis of peaks. B) Example of parcel spectrum (black) and FOOOF estimate of the aperiodic background (blue dotted line) and the periodic components (red) with individual peak fits (peak 1: frequency = 8.937, amplitude = 0.108, peak 2: frequency = 22.6, amplitude = 0.077). C) Probability density of peak frequencies, illustrating how often a given peak frequency occurred in each group. The plot underneath shows the frequency of each detected peak as a dot, as well as the median peak frequency (vertical line) and the range covered by the middle 50% of the data (box) for each group. All peaks found in the ROI considered. D) Probability density of peak amplitude. All peaks found in the ROI considered. E) as C), only the largest peaks per parcel considered. F) as D), only the largest peak per parcel considered. ROI: Region of interest, HC: Healthy controls, APS: Atypical Parkinson syndromes, PD: Parkinson´s disease.

β Oscillations

Peak Frequency

β peak frequencies were lower in APS patients compared to PD patients ($t(1892) = 3.258$, $p = 0.005$) and controls ($t(1892) = 3.17$, $p = 0.006$) when considering all peaks found in the ROI (Fig. 3C). Peak frequency did not depend on age ($t(1892) = 0.506$, $p = 0.817$), or its group interactions ($t_{age:PD}(1892) = -1.803$, $p_{age:PD} = 0.253$; $t_{age:HC}(1892) = -1.125$, $p_{age:HC} = 0.347$). The reduction of β peak frequency remained significant when considering the largest β peaks instead of all β peaks ($t_{PD}(1153) = 2.959$, $p_{PD} = 0.013$; $t_{HC}(1153) = 3.504$, $p_{HC} = 0.002$).

Peak Amplitude

β amplitudes were similar between groups when considering all peaks ($t_{HC}(1892) = -0.342$, $p_{HC} = 0.732$; $t_{PD}(1892) = -0.345$, $p_{PD} = 0.73$). The main effect of age was not significant ($t(1892) = -0.655$, $p = 0.817$) and there were no interactions (all $|t(1892)\text{-values}| < 0.899$, $p\text{-values} > 0.369$). Amplitude differences remained insignificant when considering the largest β peaks ($t_{HC}(1153) = -0.178$, $p_{HC} = 0.859$; $t_{PD}(1153) = -0.014$, $p_{PD} = 0.989$). Outside the ROI, β power differences between controls and APS and controls and PD patients occurred in central, parietal, and occipital regions (Appendix 6.1: Fig. S6.1.6).

These results are evidence of a genuine slowing of frontal β oscillations in APS, in the sense of a peak shift without changes in amplitude. Because linear mixed modeling accounted for the fact that each participant contributed a different number of peaks, our findings cannot be explained by APS patients having less β peaks overall.

The Topography of Slowing

We investigated the topography of spectral slowing in APS by analyzing the anterior-posterior gradient in peak frequency. APS patients lacked the growing predominance of β over α peak frequencies when moving from the posterior to the anterior end of the brain. This gradient was visible in the PD and HC group (Fig. 2.4A, C).

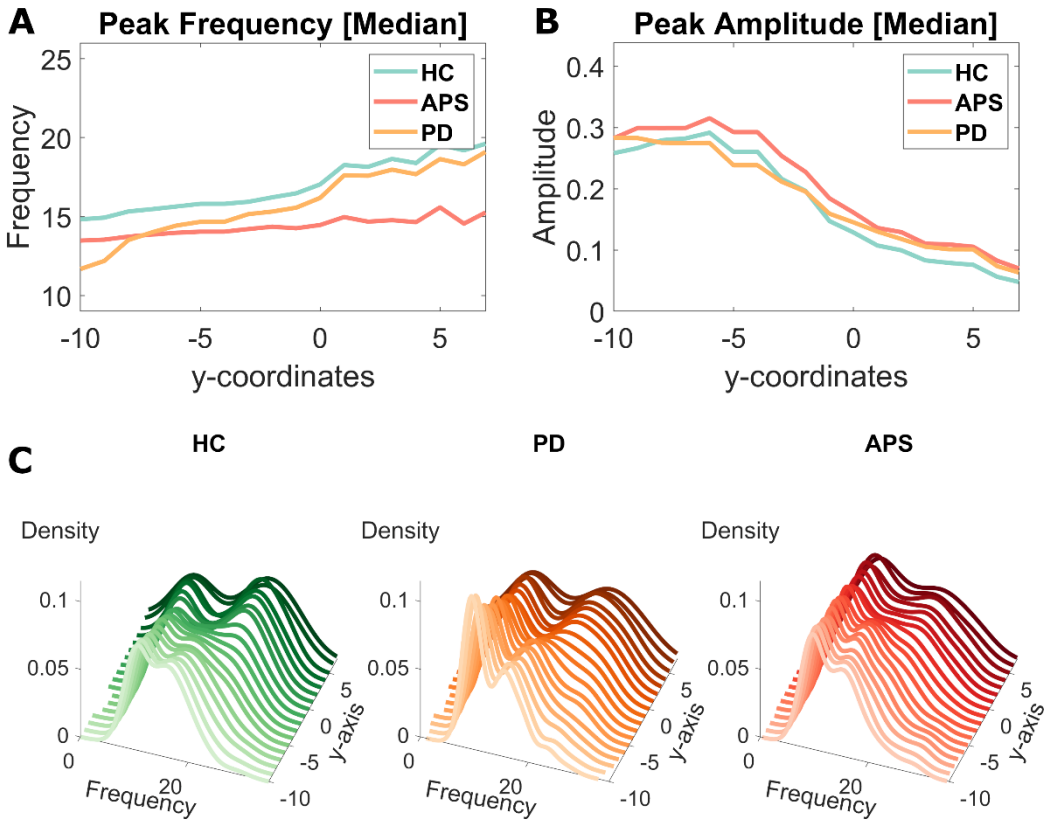

Figure 2.4. Patients with atypical Parkinson syndromes lack anterior-posterior gradient in peak frequency. A) Median peak frequency for eighteen coronal slices along the posterior to anterior axis (slice thickness: 5cm, step-size: 1 cm, y = 0 at anterior commissure). B) Median peak amplitude along the posterior to anterior axis. C) Probability density of peak frequencies, illustrating how often a given peak frequency occurred in a given slice. Note the lack of transition from α to β predominance in the APS group. HC: Healthy controls, APS: Atypical Parkinson Syndrome, PD: Parkinson´s disease.

2.5. Discussion

We show that resting-state oscillatory activity differs between APS patients, PD patients and HC. APS patients exhibit a shift of spectral energy towards lower frequencies, resulting from a slowing of frontal β oscillations independent of amplitude. Spectral slowing in APS patients was pronounced in frontal, central and parietal areas in contrast to HC, whereas frontal spectral slowing was evident in contrast to PD patients. Furthermore, oscillations in APS do not positively scale in peak frequency along the posterior to anterior axis, as they do in PD patients and HC. Thus, APS has a characteristic spatio-spectral signature.

2.5.1. Previous Studies

Slowing of neural oscillations has rarely been investigated in the context of APS. To our knowledge, only Montplaisir and colleagues (1997) reported enhanced sensor-level δ and θ power in relation to α and β power for 6 PSP patients contrasted to 6 HCs.

2.5.2. Spectral slowing in Other Diseases

The changes in power reported here are reminiscent of pathological alterations observed in other neurological diseases such as multiple sclerosis (van Schependom et al. 2021), hepatic encephalopathy (Butz et al. 2013), and AD. Especially for AD, numerous studies have reported spectral slowing (Fernández et al. 2006; Wiesman et al. 2022c), increased θ activity (Huang et al. 2000; Berendse et al. 2000; Fernández et al. 2002; Osipova et al. 2005; Dauwels et al. 2011; Jelic et al. 2000; Coben et al. 1985) and decreased α (Huang et al. 2000; Dauwels et al. 2011; Haan et al. 2008) and β activities (Berendse et al. 2000; Osipova et al. 2005; Dauwels et al. 2011; Coben et al. 1985; Haan et al. 2008). These spectral changes have been linked to disease progression (Huang et al. 2000; Jelic et al. 2000; Coben et al. 1985; Babiloni et al. 2009; Nakamura et al. 2018) and were used to differentiate AD patients from HC (Gouw et al. 2021). Because CBS and PSP, like AD, are tauopathies exhibiting spectral slowing, it is conceivable that comparable neurodegenerative processes lead to a common spectral pattern, characterized by a loss of energy in the high β band and increased power in the θ band.

Such an association between slowing and neurodegeneration might explain the differences between APS and PD observed here. PD is characterized by local midbrain degeneration (Lang and Lozano 1998a) rather than severe cortical degeneration. Although several gray matter changes are detectable in the neocortex of non-demented PD patients (Ramírez-Ruiz et al. 2005; Nishio et al. 2010; Lee et al. 2013; Uribe et al. 2018), frontocentral atrophy is not nearly as prominent as in CBS (Whitwell et al. 2010; Albrecht et al. 2017; Josephs et al. 2008; Dutt et al. 2016; Josephs et al. 2010), or PSP (Josephs et al. 2008; Brenneis et al. 2004; Paviour et al. 2006a, 2006b; Cordato et al. 2002; Gröschel et al. 2004; Stamelou et al. 2011; Whitwell et al. 2011; Schofield et al. 2011).

2.5.3. Tauopathy and Neuronal Oscillations

Several studies support a link between tauopathy, neurodegeneration and neuronal oscillations. Atrophy patterns and pathological tau burden tend to colocalize in AD (Xia et al. 2017; La Joie et al. 2020; Mak et al. 2018), CBS (Dickson et al. 2002; McMillan et al. 2016), and PSP

(Nicastro et al. 2020). Although tau burden does not necessarily correlate with atrophy in PSP patients (Schofield et al. 2011), it was found to be highly predictive of future atrophies in AD (La Joie et al. 2020).

The link between tau pathology and atrophy is relevant for the current study as previous studies suggested both tau-burden (Stomrud et al. 2010; Smailovic et al. 2018; Coomans et al. 2021) and atrophy (Nakamura et al. 2018; Fernández et al. 2003; Grunwald et al. 2007; Briels et al. 2020) to modulate spectral properties. Tau-related cerebrospinal fluid biomarkers have been found to be associated with elevated θ power in the elderly (Stomrud et al. 2010) and reduced α and β power in AD patients (Smailovic et al. 2018). Furthermore, tau accumulation was related to posterior slowing of oscillatory activity in a recent MEG study (Coomans et al. 2021) and human-tau-transgenic mice exhibit power increases in the δ and θ band in parietal areas reminiscent of spectral changes observed in AD patients (Das et al. 2018). Spectral slowing could be linked to synaptic dysfunction due to tau pathology in AD, indicating the failure of coordinated neuronal activity (Coomans et al. 2021). Oscillatory markers were also found to correlate with amyloid-β accumulation in AD (Wiesman et al. 2022c; Nakamura et al. 2018), a pathological process assumed to precede tau pathology (Jack et al. 2013; Buchhave et al. 2012), suggesting general sensitivity of oscillatory metrics to proteinopathy (Wiesman et al. 2022c).

Whether the observations linking tau, atrophy and oscillations are transferable from AD to APS is unclear. Here, we found that APS, like AD, is associated with spectral slowing. Interestingly, the topography of slowing seems to be disease-specific, with slowing predominating in areas most affected by cortical neurodegeneration. In APS, slowing occurs in frontal, rolandic and parietal areas compared to HC, matching the reported atrophy patterns (Whitwell et al. 2010; Josephs et al. 2008; Gröschel et al. 2004; Whitwell et al. 2011) and topography of tau accumulation in CBS (Forman et al. 2002; McMillan et al. 2016; Cho et al. 2017), and, with less cortical involvement, in PSP (Nicastro et al. 2020). These results suggest that oscillatory slowing could potentially serve as a marker of cortical neurodegeneration in the future, complementing structural and molecular imaging techniques.

2.5.4. Peak Frequency Gradient

In keeping with our results, a recent MEG study in young, healthy adults found β peak frequency to scale positively along the posterior-to-anterior axis (Mahjoory et al. 2020). This pattern appears to be absent in APS patients, who lacked the transition from α to β dominance upon reaching frontal cortex. Thus, the gradient might carry information relevant to diagnosis.

In contrast to Mahjoory and colleagues (2020), we did not find θ oscillations to dominate in frontal cortex. This might be due to age differences between the studies. We included elderly participants, whereas Mahjoory and colleagues (2020), recruited from a student population. θ power is known to decrease in healthy aging (Vlahou et al. 2014).

2.5.5. Common patterns in APS and PD

We found both APS and PD to differ from HC in θ, α and β band power predominantly in posterior cortical areas. Thus, an increase of low-frequency power in posterior areas appears to be a common pattern in parkinsonism. These findings align with previous studies reporting spectral slowing (Wiesman et al. 2022b), increased θ (Bosboom et al. 2006; Stoffers et al. 2007), low α (Stoffers et al. 2007), and decreased β power (Bosboom et al. 2006; Stoffers et al. 2007) in PD and further suggests that parkinsonian syndromes have both common and distinct alterations in cortical power. Notably, the topography of spectral slowing in PD patients overlaps with cortical atrophy patterns (Ramírez-Ruiz et al. 2005; Nishio et al. 2010; Lee et al. 2013; Uribe et al. 2018), emphasizing the link between spectral changes and cortical degeneration. The similarities in low oscillatory activity may emerge due to common pathological subcortical changes, for example in the locus coeruleus, that are involved in PD (Dickson 2012), PSP (Dickson 2012; Dickson 1999) and CBS (Dickson et al. 2002; Dickson 1999) and has been implicated in oscillatory slowing in rats (Berridge et al. 1993). Whereas the increase in θ power can be considered a common aspect of slowing in parkinsonism, the shift of β peak frequency in frontal areas seems to be specific to APS.

2.5.6. Distinguishing APS

While we found differences between APS and PD patients, we did not find differences between CBS and PSP. Niethammer and colleagues (2014), in contrast, have distinguished CBS from PSP with positron emission tomography. Clearly, it would be desirable to achieve this with electrophysiological techniques as well. Distinguishing atypical parkinsonian syndromes might require better subgroup homogeneity and/or considering further features of brain activity, such as connectivity. Our results set the ground for future research in this direction, highlighting the importance of the distribution of peak frequencies rather than power alone. This concept might be applicable to a wider range of MEG/EEG (electroencephalography) research.

2.5.7. Limitations

We found no correlation between spectral slowing and motor or cognitive scores and slowing persisted when groups were balanced with age and motor impairment. Although these results suggest that slowing is unrelated to motor and cognitive symptoms, we note that a lack of correlation in a small and heterogeneous sample is inconclusive. The frontal topography does point to a link with cognition, and the slowed oscillations in APS might relate to their more pronounced cognitive symptoms. We suggest readdressing this issue in a larger and more complete sample. The current one lacked clinical scores of several (mostly PSP) patients.

2.5.8. Conclusions and Clinical Impact

CBS and PSP have a characteristic spatio-spectral resting-state profile distinguishing them from PD and HC. These findings contribute to the understanding of how neurodegeneration affects neuronal oscillations. The assessment of spectral slowing, as a potential marker for neurodegeneration, might help with an earlier and more reliable initial diagnosis of APS in the future, reducing confusion with PD (Joutsa et al. 2014). Spatial patterns of spectral slowing in general might become a valuable clinical parameter. They are easy to obtain in clinical settings e.g., through resting-state EEG, and appear to differentiate between different neurological disorders and/or index cognitive impairment. Thus, they might become a helpful additional piece of information when diagnosing neurodegenerative diseases.

3. Study 2: Altered Cortical Network Dynamics during Observing and Preparing Action in Patients with Corticobasal Syndrome

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Personal contribution

J.H. and A.S. received funding from the Else Kröner Fresenius Foundation (study 1 and study 2) and the Brunhilde Moll Foundation (study 2). I acquired all datasets, supported by J.H. and M.B. Clinical diagnosis for all CBS patients was provided by C.J.H. Data curation was done by me, under supervision of J.H. Methodology, including analysis ideas and statistics, was developed in close dialogue between me and J.H. Data analysis in MATLAB and R was conducted by me, under supervision of J.H. Visualization of results was done by me under supervision of J.H. I wrote the original draft, discussing ideas with J.H. All authors except me reviewed the proposed manuscript. Answering reviewers' questions and proposals and rewriting the manuscript for publication was conducted by J.H. and me in close dialogue.

Study design 5%; Data Acquisition 80%; Data Curation 95%; Methodology 50%; Data Analysis 90%; Visualization 100%; Writing – original draft 80%; Writing – reviewing 0%; Reviewer Comments and Rewriting – 50%.

3.1. 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.

Keywords: Corticobasal Syndrome; Magnetoencephalography; Action Observation; Movement Preparation; Imitation; Beta Oscillations

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

3.2. 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 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.

3.3. Methods

3.3.1. 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.

Table 3.1: 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.

3.3.2. 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. 3.1). 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).

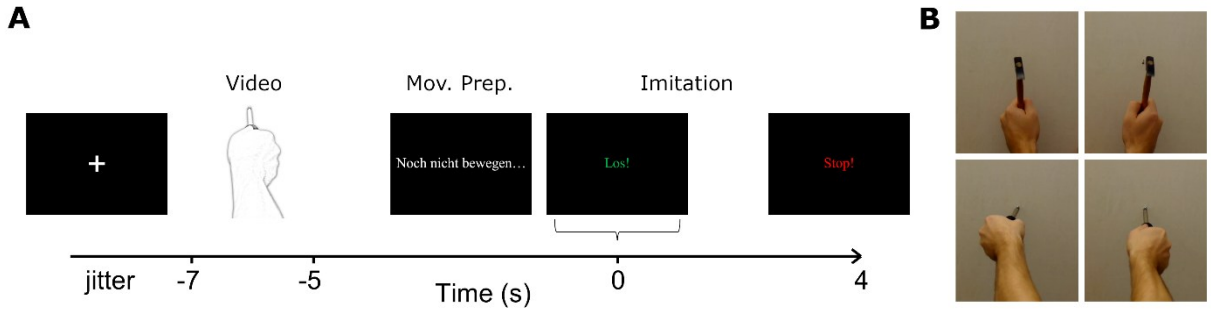

Figure 3.1. Trial design. A) Following the display of the fixation cross (1- 3 s), a 2 s tool-use video was displayed involving either a hammer or a screwdriver, operated with the left or right hand, depending on the experimental block. This was followed by the instruction to withhold movement ("Noch 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.

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.

3.3.3. 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.

3.3.4. Data Preprocessing

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 ICs removed: 2.5, range: 1–5).

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*).

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. Appendix 6.2 Tab. S6.2.1 provides more detailed information on the available trials per subject.

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.

3.3.5. 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.

3.3.6. 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.

3.3.7. 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.

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. 3.2A). Beta power was smoothed with a moving-average filter to denoise the signal (width: 160 ms) and 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.

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).

3.4. Results

3.4.1. 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. 3.2). 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. 3.2A). 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. 3.2B).

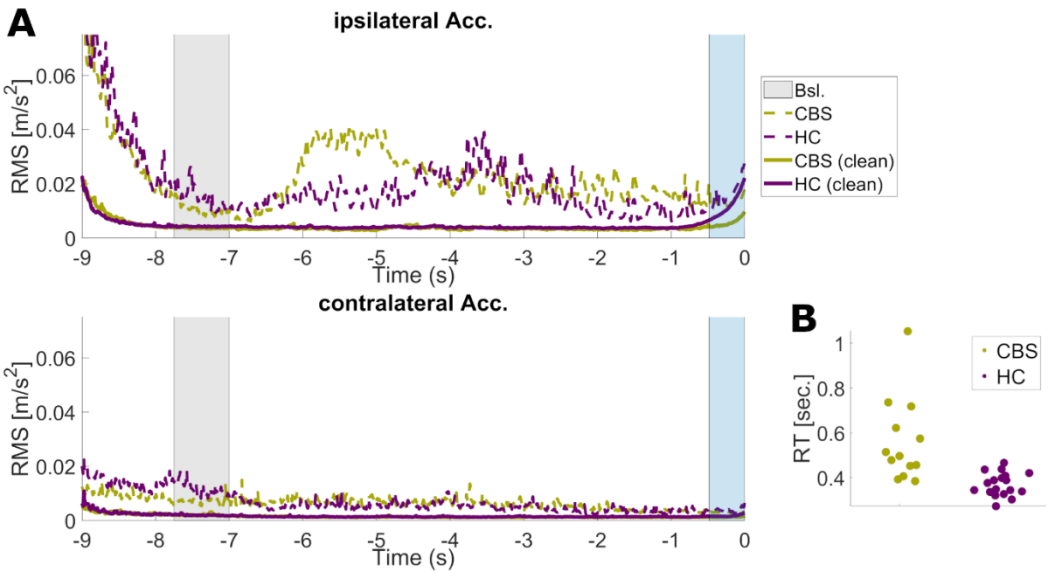

Figure 3.2. CBS patients reacted slower than healthy controls (HC). A) Root mean square (RMS) accelerometer data for the moving (ipsilateral) and the non-moving (contralateral) hand before (dashed lines) and after (solid lines) cleaning. HC presented larger RMS values than patients within the [-0.48 s to 0 s] interval (blue shading), with 0s 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.

3.4.2. 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. 3.3). 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. 3.3).

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. 3.4B; 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. 3.4C; 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.

3.4.3. 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. 3.3). 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 postcentral gyri and middle frontal gyri contralateral to the response hand (Fig. 3.4B; cluster $t_{sum} = 121.356, p = 0.039$). As for action observation, the group difference occurred the beta band specifically (Fig. 3.4C; 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. 3.2A). When excluding the last 480 ms of the trial, the statistical effect reduced to a trend (cluster $t_{sum} = 90.431, p = 0.053$).

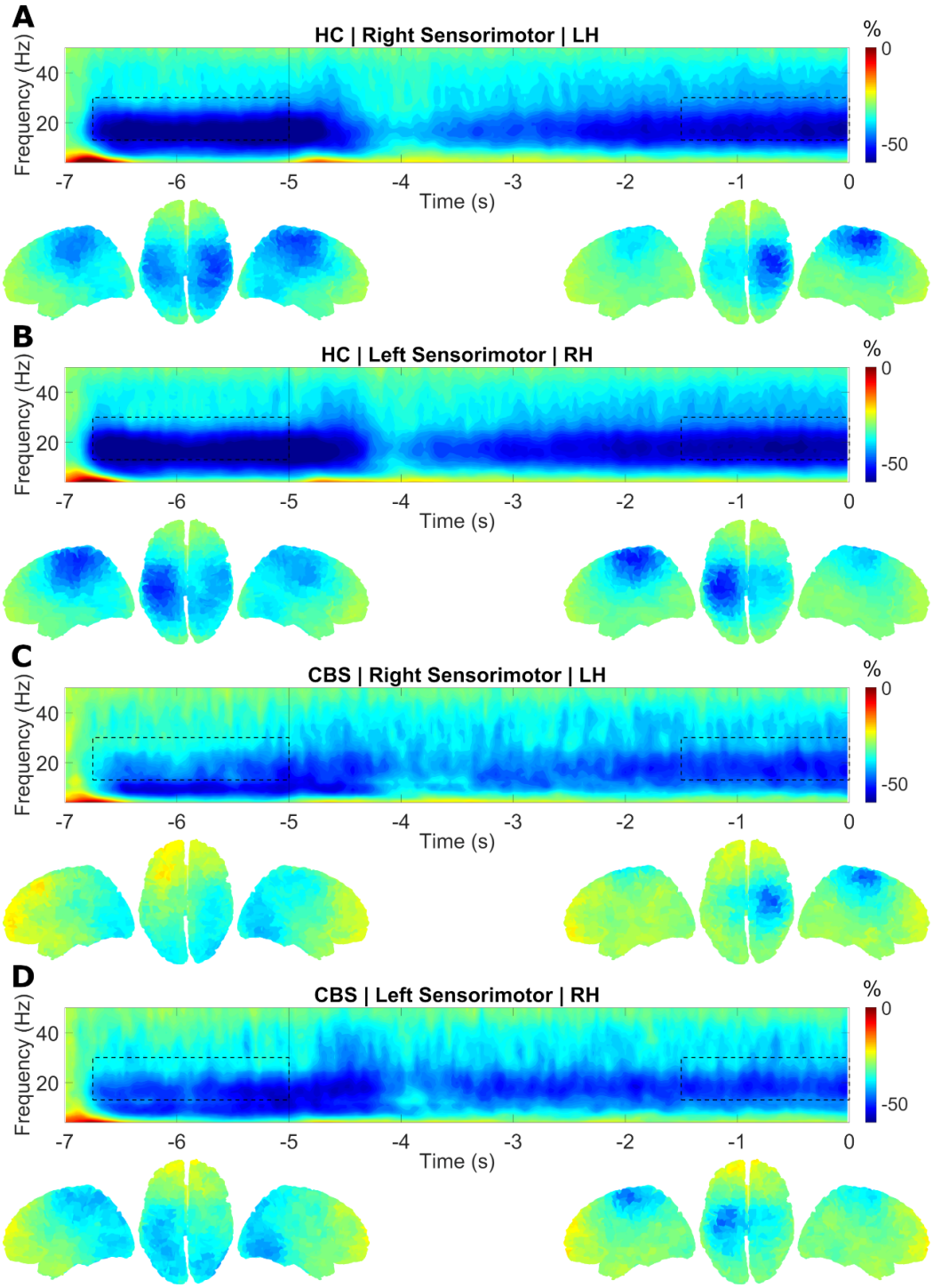

Figure 3.3. Action observation and movement preparation were associated with a decrease of beta power in sensorimotor cortex. Each panel depicts the group-average time-frequency spectrum of sensorimotor cortex contralateral to imitation bodyside. Relative power change with respect to baseline (-7.75 s to -7 s) is color-coded. The dashed boxes indicate the time-frequency selection used in the source plots below. Participants had to contribute at least 25 trials for the imitation side to be included in the illustration. Video: -7 s to -5 s. Go cue onset: 0 s. 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. HC: Healthy controls; CBS: Corticobasal Syndrome.

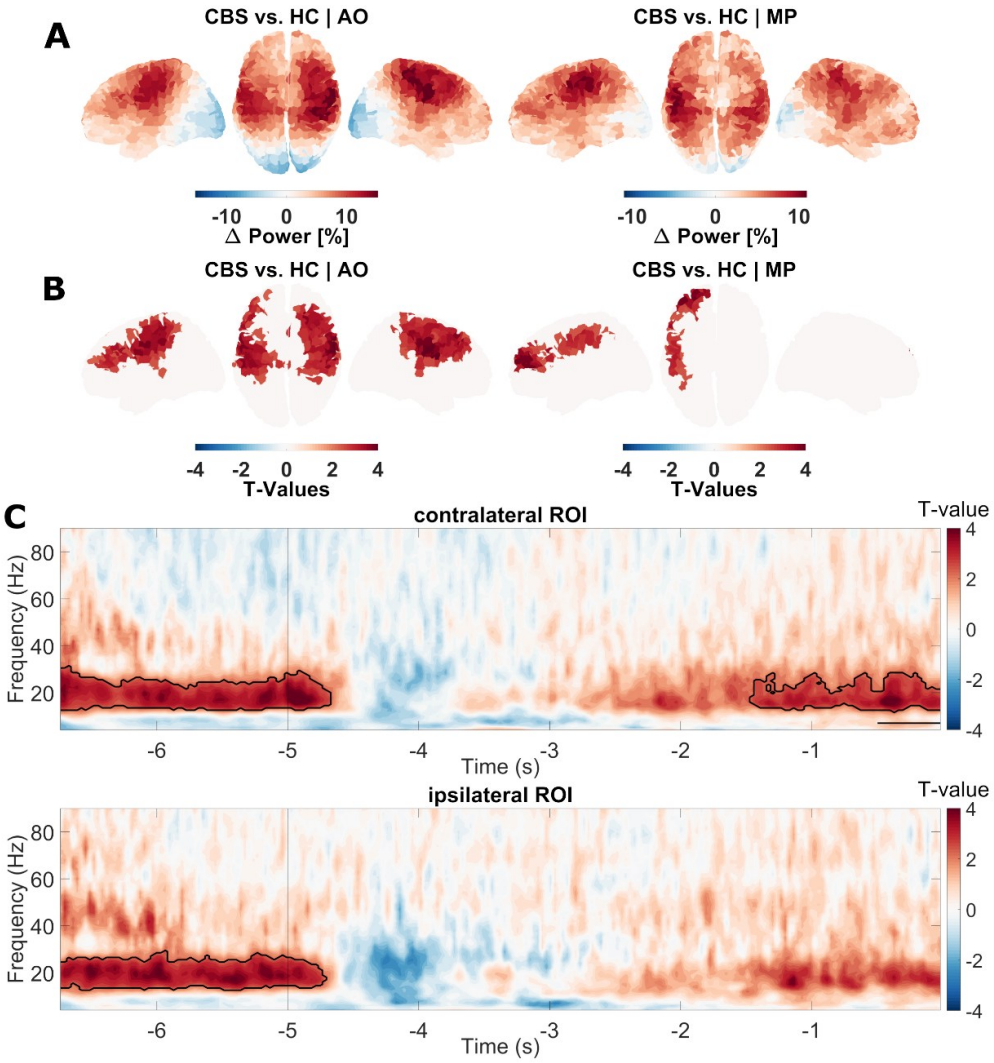

Figure 3.4. Comparison of event-related beta power desynchronization between CBS patients and healthy controls. A) Difference in group-average baseline-corrected beta-power (13-30 Hz) for action observation (-6.75 s to -5 s) and movement preparation (-1.5 s to 0 s). Warmer colors indicate weaker event-related beta desynchronization (beta ERD) in patients. B) Whole-brain statistical comparison, beta ERD in CBS patients vs. HC. Non-significant changes masked. Highlighted areas in the left panel of B) served as regions of interest (ROI). C) Statistical comparison of time-frequency maps. Significant differences indicated by solid black contour. The black horizontal line marks the epoch containing movement in HC (see Fig. 2A). AO: Action observation; MP: Movement Preparation. CBS: Corticobasal Syndrome; HC: Healthy controls.

3.4.4. 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. 3.5; cluster $t_{sum} = 8.87$, $p = 0.411$). In fact, the movement-locked ERD was remarkably similar for HC (Fig. 3.5A) and CBS (Fig. 3.5B) 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. 3.5C.

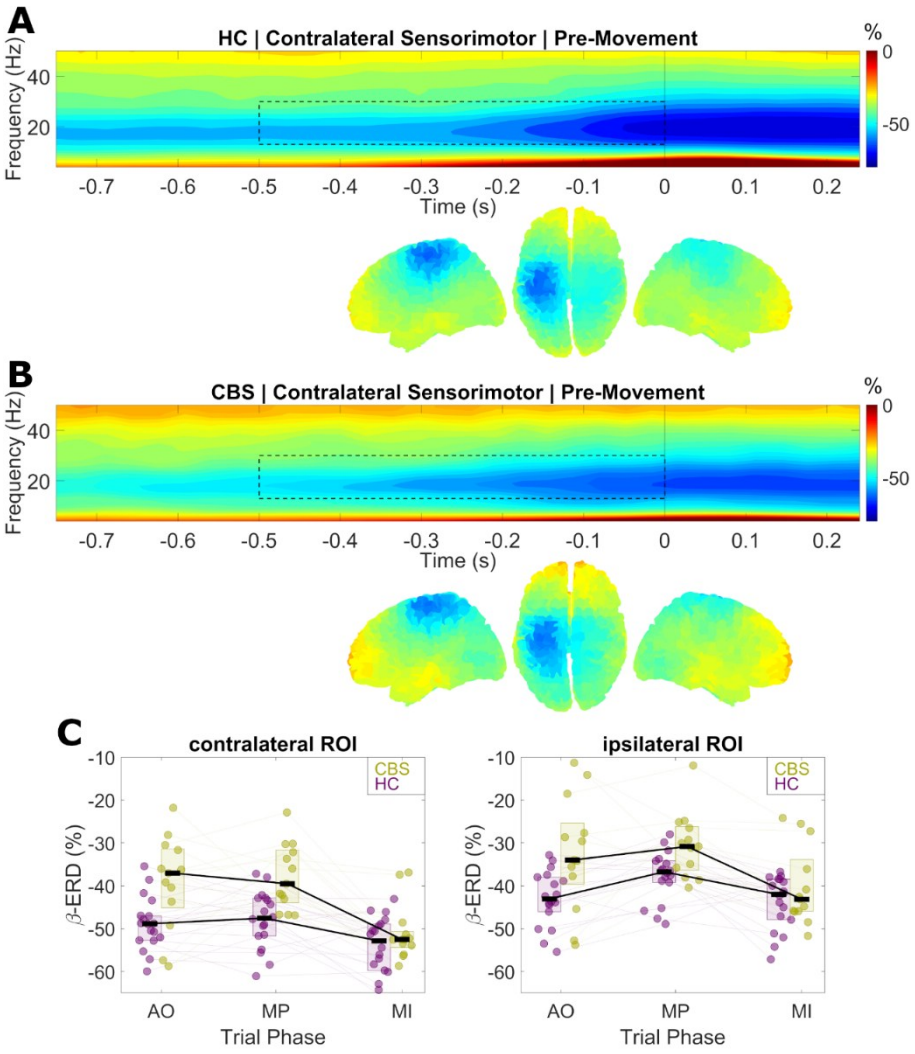

Figure 3.5. Beta power dynamics were similar for CBS patients and healthy controls immediately before movement onset. A) HC and B) CBS patients. Group-average time-frequency spectrum of sensorimotor cortex contralateral to imitation bodyside, anchored to movement onset (0 s). Relative power change with 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) Beta ERD in the region of interest per trial phase. HC: Healthy controls; CBS: Corticobasal Syndrome; ROI: Region of interest; AO: Action observation; MP: Movement preparation; MI: Movement initialization. ERD: Event-related desynchronization.

3.4.5. Go cue anticipation

The above analysis suggests that CBS patients and controls did not differ in motor cortical beta power suppression before moving (Fig. 3.5). Nevertheless, we observed group differences in beta ERD in the movement preparation phase (Fig. 3.4). 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. 3.6A; 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. 3.6B; 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.

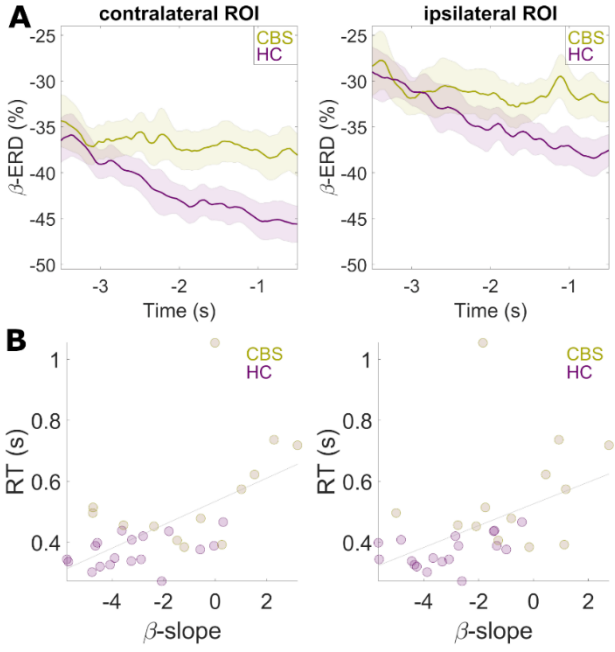

Figure 3.6. The rate of beta power suppression prior to the Go cue differed between CBS patients and healthy controls and correlated with reaction time. A. Beta power dynamics before Go cue presentation. The group means are displayed as colored lines, and the standard error is indicated by shaded areas. 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. 3.2A). CBS: Corticobasal Syndrome; HC: Healthy controls; ROI: Region of interest; RT: Reaction time.

3.4.6. 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 ($|\rho| < 0.509, p > 0.076$).

3.5. Discussion

3.5.1. Summary

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 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.

3.5.2. 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. 2014a, 2014b; 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.

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.

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 STN (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).

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).

3.5.3. 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).

3.5.4. Movement initialization

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.

3.5.5. 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.

3.5.6. 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.

3.5.7. 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.

4. General Discussion

The thesis at hand provides insights into electrophysiological alterations associated with CBS and PSP, two major syndromes within the spectrum of atypical parkinsonian syndromes. The studies focused on brain oscillations at rest and during an observe-to-imitate task.

Resting state MEG recordings revealed distinct oscillatory abnormalities in CBS and PSP, distinguishing these syndromes from HC and, collectively as APS, from PD patients (cf. study 1). A key finding was a shift in spectral power toward lower frequencies, with a specific spatio-spectral signature. Relative to HC, spectral slowing was prominent across frontal, central and parietal regions. The comparison with PD revealed more localized spectral slowing, involving frontal and central areas. These areas were characterized by a lack of high beta oscillations in APS patients.

Furthermore, this thesis provides evidence for disease-related disruptions of brain networks involved in action observation and movement preparation (cf. study 2). HC exhibited a marked pattern of beta suppression during both trial phases. Instead, CBS patients showed reduced beta suppression located primarily in frontocentral areas and an altered timing of beta suppression in reference to an upcoming target stimulus. These brain areas, commonly affected in CBS, are involved in action imitation. Noticeably, beta suppression was unchanged in comparison to HC prior to movement execution, hinting towards task-specific deficits that rely on large inter-areal networks.

Tau Pathology, Neurodegeneration and Spectral Slowing

Large parts of the frontal and parietal lobes exhibited spectral slowing in atypical Parkinson's patients, with particularly prominent changes in frontal beta activity. These findings indicate that cortical hubs of spectral slowing in CBS and PSP patients may colocalize with cortical regions that are most affected by the underlying tau pathology and neurodegeneration. Crucially, the spatial distribution of spectral slowing observed in patients with PSP and CBS partially overlaps with the topographies identified in tau-PET imaging studies (Smith et al. 2017; Goodheart et al. 2021; Nicastro et al. 2020) and patterns of brain atrophy (Whitwell et al. 2010; Nicastro et al. 2020; Brenneis et al. 2004). This multimodal pattern of spatial colocalization supports the hypothesis that electrophysiological alterations, at least in part, reflect underlying tau pathology and/or neurodegeneration.

Insights from electrophysiological studies in other tauopathies further contextualize these results. In AD, for instance, spectral slowing has been associated with both the extent of tau pathology (Coomans et al. 2021), hippocampal atrophy (Fernández et al. 2003; Nakamura et al. 2018), and the degree of cognitive impairment (Wiesman et al. 2022c). Notably, the regions exhibiting spectral slowing (Wiesman et al. 2022c), tau pathology (Kocagoncu et al. 2020; Timmers et al. 2019), or atrophy (Kocagoncu et al. 2020; Timmers et al. 2019) tend to spatially overlap in AD patients. Therefore, spectral slowing might be in part linked to local neurodegeneration in AD, in addition to distant pathological brain changes. This hypothesis aligns with findings from AD variants, such as posterior cortical atrophy, which is characterized by greater posterior tau burden (Day et al. 2017) and atrophy (Lehmann et al. 2011) and exhibits more pronounced spectral slowing compared to typical AD (Briels et al. 2020).

Furthermore, prior work suggests that electrophysiological measures may serve as sensitive markers for early stage tauopathies. Under physiological conditions, tau protein plays a critical role in various cellular processes, most notably in the stabilization of microtubules within axonal projections (Parra Bravo et al. 2024). In its pathological form, tau undergoes misfolding and aggregation, leading to cellular dysfunction (Parra Bravo et al. 2024), impacting neural activity patterns.

Accordingly, aberrant neural activity has been reported in transgenic mouse models of tauopathy, ranging from suppressed neural activity (Busche et al. 2019) to neural hyperexcitability (Maeda et al. 2016).

A growing body of evidence also links tau pathology to synaptic dysfunction. Mislocalization of abnormal tau protein into dendrites has been associated with reductions in excitatory synaptic transmission in tauopathy mouse models (Hoover et al. 2010). In AD patients, tau burden is associated with a reduction in synaptic density and is predictive of synaptic (Wang et al. 2024) and neuronal loss (La Joie et al. 2020).

Notably, tau pathology has been linked to disease progression in CBS (Palleis et al. 2024) and PSP (Kovacs et al. 2020), and similar patterns of marked synaptic degeneration, preceding overt structural atrophy, have been observed in PSP and CBS patients (Holland et al. 2020). These observations suggest that synaptic disruptions in neural circuit integrity may represent a shared hallmark across tauopathies. Given that electrophysiological signals (e.g. M/EEG) largely depend on coordinated synaptic transmission across large neural populations (Baillet 2017), they may represent these pathological changes. From this perspective, the impact of pathological processes on neural activity might translate into electrophysiological alterations and spectral slowing in particular.

Supporting this view, a recent study in an AD cohort identified alterations in alpha and beta band oscillations prior to the onset of significant brain atrophy or cognitive impairment, implicating these spectral alterations as potential indicators of early tau pathology and synaptic dysfunction (Kudo et al. 2024). Given the shared features across AD, CBS and PSP, including tau aggregation, synaptic dysfunction and regional atrophy, spectral signatures may serve as indicators of disease stages. It remains to be seen if similar results from AD research are transferable to PSP and CBS, however, as they partly differ from AD in proteinopathy.

Though tau abnormalities and neurodegeneration might alter electrophysiological signals locally, spatial correlation of electrophysiological and structural abnormalities would not necessarily imply causation. More precisely, the topography of electrophysiological abnormalities could be a consequence of local alterations in the underlying neural populations or from distant disruptions in brain networks which include the neural populations. Subcortical alterations, common to CBS (Dickson et al. 2002; Goodheart et al. 2021) and PSP (Williams and Lees 2009; Kovacs et al. 2020) in particular, could affect electrophysiological signals recorded from the cortex. Emerging evidence suggests that tau deposition may follow functionally connected brain networks. In CBS and PSP, tau deposition appears to follow such networks as indicated by fMRI (Franzmeier et al. 2022). Similarly, Schoonhoven and colleagues (2023) presented that tau might deposit along brain networks functionally connected

through synchronization in the alpha and beta bands in early stages of AD. Therefore, electrophysiological alterations recorded from the cortex may signal subcortical pathology, if these brain structures are connected.

The precise relationship between spectral slowing and region-specific neuropathology/degeneration, whether local cortical, subcortical or network-based, remains an open question. Further research is needed to clarify how tau aggregation, neurodegeneration and electrophysiological alterations interact across disease stages in atypical Parkinsonism. The findings presented in this thesis offer a comprehensive characterization of spectral abnormalities in CBS and PSP. The distinct spatio-spectral signature of atypical Parkinson's patients in comparison to HC and PD patients likely point toward specific disease courses that may carry diagnostic value. These spectral changes might change early in disease progression, reinforcing their potential as early biomarkers.

Common Spectral Alterations of Parkinsonian Disorders

Several spectral alterations identified in this work were shared across parkinsonian syndromes. Spectral slowing, in particular, emerged as a common feature not only in APS, but also in PD (Stoffers et al. 2007). In PD, spectral slowing has been linked to future cognitive decline in particular (Klassen et al. 2011; Olde Dubbelink et al. 2014; Latreille et al. 2016). In the present study (cf. study 1), CBS, PSP and PD all demonstrated increased low frequency power and decreased high frequency power in posterior cortical regions. These commonalities may reflect a common subcortical pathology, influencing cortical oscillations.

Locus coeruleus

PD is not only associated with dopaminergic degeneration in the substantia nigra, but involves a broader subcortical pathology, including degeneration of the locus coeruleus, a key source of noradrenaline (Braak et al. 2001). Interestingly, noradrenergic function might be linked to neural oscillations. Animal studies with rats showed that the activation of the locus coeruleus leads to a power shift toward higher frequencies in the frontal cortex (Berridge and Foote 1991; Liu et al. 2017). Additionally, spectral slowing recorded via occipital EEG electrodes correlates with noradrenergic dysfunction attributed to locus coeruleus degeneration in non-demented PD patients (Sommerauer et al. 2018). Similar to PD, PSP consistently involves locus coeruleus pathology (Dickson 2012). In CBS, however, the role of the noradrenergic system is less clear

(Koga et al. 2022). In autopsy proven cases of CBD, locus coeruleus is commonly affected by tau pathology, although it shows minimal neuronal loss (Dickson et al. 2002).

This pathological commonality, though differing in severity between diseases, might thus contribute to the spectral commonalities between PD, PSP and CBS observed here.

Nucleus basalis of Meynert

Degeneration of the cholinergic system could be a further source of spectral commonalities between PD, PSP and CBS. In PD, the degeneration of the nucleus basalis of Meynert has been linked to dementia (Bohnen et al. 2022), possibly preceding it (Hilker et al. 2005; Ray et al. 2018; Horsager et al. 2022). Importantly, the topography of spectral slowing in PD patients (Stoffers et al. 2007; Olde Dubbelink et al. 2014) tends to colocalize with cholinergic synaptic loss in occipital, temporal and parietal regions in non-demented PD patients (Horsager et al. 2022), linking cholinergic deficits to cortical oscillations. Cholinergic pharmacotherapy has been shown to partially restore spectral alterations by increasing alpha and beta power in posterior cortical areas and decreasing global delta power in PD patients with dementia (Bosboom et al. 2009).

The cholinergic system is likewise affected in PSP (Dickson 2012; Hirano et al. 2010). Minor pathology of the nucleus basalis of Meynert is characteristic of CBD (Dickson et al. 2002). However, cholinergic deficits have been increasingly recognized for CBS as its classical syndrome (Hirano et al. 2010). In addition, as reported for PD, the degeneration of the nucleus basalis of Meynert was found to predict cognitive decline in CBS patients in a recent study (Urso et al. 2024).

Together, these studies suggest that noradrenergic and cholinergic changes, though varying in degree across PD, PSP and CBS, likely contribute to commonalities in spectral slowing.

Substantia nigra

A further point of convergence across PD (Lang and Lozano 1998a), PSP (Williams and Lees 2009) and CBS (Dickson et al. 2002) is the degeneration of the substantia nigra and the associated depletion of dopaminergic innervation of the basal ganglia. Imaging evidence supports this, showing dopamine transporter deficits in PD (La Fuente-Fernández 2012), CBS (Constantinides et al. 2023; Missir and Cornwell 2025) and PSP (Constantinides et al. 2023), indicating nigrostriatal dysfunction as a shared feature of Parkinsonism. Importantly for this study, dopaminergic dysfunction is linked to cortical beta activity. For instance, sensorimotor

beta power in PD patients increases with L-dopa administration (Heinrichs-Graham et al. 2014; Cao et al. 2020) and is inversely correlated with akinetic-rigid motor symptoms (Cao et al. 2020). These findings suggest that dopaminergic depletion may contribute to the reduction of beta power found in parkinsonian disorders (cf. study 1).

To conclude, the partial overlap of subcortical pathology in cholinergic, noradrenergic and dopaminergic systems may account for the shared pattern of spectral slowing observed in PSP, CBS and PD.

Oscillatory Abnormalities specific to Atypical Parkinsonian Syndromes

Study 1 identified alterations in beta oscillations in fronto-central regions in APS patients at rest. Specifically, shifts in beta peak frequency were identified in regions exhibiting spectral slowing.

Recent work has linked beta oscillations to brain networks involving the frontal cortex and the basal ganglia, modulated in part by the nigrostriatal system (Chikermane et al. 2024). As discussed above, this system is compromised in all parkinsonian syndromes. In APS, however, pathophysiological changes extend beyond the nigrostriatal system. PSP is characterized by extensive subcortical pathology, including the subthalamic nucleus, the globus pallidus, the striatum, and moderate cortical degeneration, mostly in the frontal lobes (Stamelou et al. 2021; Whitwell et al. 2017). CBS is associated with marked cortical pathology, mostly in frontal and parietal areas (Mahapatra et al. 2004; Smith et al. 2017; Goodheart et al. 2021), and moderate subcortical pathology in the basal ganglia, such as the globus pallidus and the striatum (Dickson et al. 2002; Dickson 2012). This large-scale neurodegeneration likely underpins the characteristic spectral slowing pattern of APS, which is distinct from and more extreme than the pattern observed in PD.

It is important to note that while spectral slowing in fronto-central regions in APS was linked to reductions in beta peak frequency, it likely reflects just one aspect of broader spectral changes. Spectral slowing encompasses alterations across a wide frequency range and likely reflect a confluence of various local and network-based pathological changes.

Beta Rhythm Abnormalities in Action

In study 2 we investigated oscillatory dynamics in patients with CBS compared to HC, using an observe-to-imitate paradigm. This task was parsed into distinct trial phases (action observation, movement preparation and movement initialization). Beta desynchronization was

reduced during action observation and movement preparation when compared to HC, predominantly localized in frontal regions (cf. study 2). However, beta desynchronization immediately preceding movement onset was preserved in CBS patients. This suggests that CBS is not marked by a general failure to desynchronize beta rhythms. Instead, the observed effects likely reflect deficits in visuo-motor mapping and learning the task's temporal structure, respectively, as explained in more detail below.

Action Observation

Internal motor simulation, as occurring in action observation and motor imagery, relies on a distributed fronto-parietal network (Hardwick et al. 2018). Substantial spatial overlap in frontal and parietal areas exists between action observation and movement execution (Hardwick et al. 2018). These networks, however, also differ in brain network activation. Motor execution involves less engagement of parietal areas and a smaller volume of hemodynamic activation (Hardwick et al. 2018). In non-human primates, a substantial proportion of neurons in the ventral premotor cortex (~33.6%) and inferior parietal lobule (~20%) function as mirror neurons (Kilner and Lemon 2013), providing a likely neural basis for the activation of these regions during both, action observation and execution.

Importantly, CBS patients show structural abnormalities in this network. Pathological changes in frontal and parietal cortices, regions implicated in action observation, are characteristic of CBS (Whitwell et al. 2010; Smith et al. 2017; Niccolini et al. 2018). Additionally, white matter alterations in CBS patients, particularly involving the superior longitudinal fasciculus (Uchida et al. 2023), lead to compromised connectivity between frontal and parietal regions (Nakajima et al. 2020). These structural damages are believed to be the reason why CBS patients have problems with imitation. Imitation deficits have been described as a core feature of limb apraxia in CBS, emphasizing impairments in visuo-motor mapping (Stamenova et al. 2011). Limb apraxia in CBS correlates with fiber-integrity between frontal and parietal regions (Borroni et al. 2008), parietal atrophy (Borroni et al. 2008) and posterior frontal atrophy (Huey et al. 2009). Therefore, dysfunction of this larger fronto-parietal network might underly oscillatory alterations during action observation in CBS.

The fact that beta desynchronization was reduced in CBS patients compared to controls in the action observation phase of study 2 is likely related to this impaired visuo-motor mapping. Beta oscillations have been increasingly recognized to exert anti-kinetic control in motor systems (Engel and Fries 2010). Elevated beta activity has been linked to movement slowing (Pogosyan

et al. 2009; Muralidharan and Aron 2021), akinetic-rigid motor symptoms in PD (Neumann and Kühn 2017), and motor inhibition via a frontal-cortical-basal-ganglia network (Schaum et al. 2021; Swann et al. 2012; Picazio et al. 2014). In this context, beta desynchronization likely indicates a transient disinhibition of motor networks, facilitating internal motor simulation even in the absence of overt movement (Brinkman et al. 2014; Stolk et al. 2019). Accordingly, prior work found that beta rhythms desynchronize not only during action execution (Toro et al. 1994; Caetano et al. 2007), but also during observation (Hari et al. 1998; Caetano et al. 2007; Eaves et al. 2016) and imagery (Schnitzler et al. 1997; McFarland et al. 2000; Eaves et al. 2016).

Together, these findings suggest that beta desynchronization deficits observed during action observation in CBS may reflect impaired disinhibition within a partly dysfunctional fronto-parietal circuit recruited when observing actions, leading to reduced engagement of the motor system.

Movement Preparation

The second major finding of study 2 was that CBS patients showed suboptimal timing of their pre-movement beta desynchronization with respect to the Go cue in the movement preparation phase of the task. The cue followed the video at a fixed time interval, i.e. it could be perfectly anticipated after gaining some experience with the task. Healthy controls were presumably better in learning the task's temporal structure, enabling them to react faster than CBS patients (see analysis of reaction times, study 2). Notably, the rate of beta desynchronization in the movement preparation phase correlated with reaction times, suggesting that beta band dynamics reflect learning success. The lack in timing beta desynchronization observed in CBS patients could thus be interpreted as a neural correlate of a learning deficit.

This interpretation is backed by literature. Beta rhythms are increasingly recognized as top-down mechanisms, not only in sensorimotor processing, but in cognitive processes, modulated by contextual information (Engel and Fries 2010; Spitzer and Haegens 2017). For instance, beta activity has been shown to be modulated by task-related factors such as movement uncertainty (Tzagarakis et al. 2010), and the spatial and temporal predictability of target stimuli (Heideman et al. 2018). Importantly, anticipatory beta modulation has been linked to implicit learning processes (Heideman et al. 2018).

The underlying neural substrate of temporal learning is not entirely clear. It may rely on premotor and parietal areas, the cerebellum (Coull et al. 2011) and/or basal ganglia (Breska and

Ivry 2018), all of which are involved in anticipation. Therefore, the disruption in the timing of beta desynchronization i.e., motor network disinhibition, in CBS patients, likely stems from alterations in these brain regions.

Parametrizing Power Spectra for Clinical Neuroscience – Methodological Considerations

Group differences in spectral power are central to this thesis. Throughout this work, I have applied power spectra parameterization and focused on the so-called periodic component, i.e. power peaks, standing out from the overall 1 over F, aperiodic signal component (cf. 1.2.2. Parametrizing Neural Oscillations). Yet, both, the aperiodic and the periodic component, might provide complementary information on neural processing. The aperiodic component might index the excitation/inhibition balance of neural populations (Gao et al. 2017), and the periodic component instead represents genuine rhythmic neural activity (Donoghue et al. 2020). Interestingly, the periodic component in particular may carry disease-related information. It can be rather robustly estimated even from brief data segments (< 2 min) (Wiesman et al. 2022a) and exhibits greater stability than the aperiodic component in PD patients (Da Silva Castanheira et al. 2024). Additionally, the periodic component rather than the aperiodic component carries disease-related alterations in AD patients (Kopčanová et al. 2024) and has demonstrated high classification accuracy in distinguishing PD patients from HC (Da Silva Castanheira et al. 2024). In particular, spectral slowing of the periodic component was characteristic for AD patients (Kopčanová et al. 2024), fitting well with the results presented for CBS and PSP patients. In conclusion, this work demonstrates that power spectrum parameterization is a valuable approach to identify distinct oscillatory changes in neurodegenerative diseases.

4.1. Limitations and Outlook

Across both studies, no significant correlations were observed between electrophysiological alterations and clinical symptom scores. This lack of association may reflect the limited number of patients who completed the clinical test battery. In addition, the considerable heterogeneity in clinical presentation of CBS (Aiba et al. 2023; Armstrong et al. 2013) and PSP (Höglinger et al. 2017) complicates the detection of robust correlations with clinical symptom scores. Larger patient cohorts might be needed to counter these difficulties.

Furthermore, the majority of PD patients included in this work were recruited during preoperative evaluation for deep brain stimulation. PD patients who present with marked cognitive decline are not eligible for this surgical procedure, i.e. PD and APS patients differed with respect to their cognitive abilities. The reported frontal spectral abnormalities might thus stem from pathological changes related to cognitive impairments, characteristic of APS. A valuable extension of this work could include PD patients in later stages with cognitive impairment.

In addition, the observe-to-imitate task did not include a connectivity analysis between frontal and parietal areas. A particular focus of follow-up work could be the interplay of beta rhythms in frontal areas and gamma rhythms in parietal areas. De Lange and colleagues (2008) found that during motor imagery frontal beta rhythms and parietal gamma rhythms transiently interact to coordinate desynchronization of the beta rhythm and synchronization of the gamma rhythm respectively. The interaction of beta and gamma rhythms might signal the status of the fronto-parietal network that backs internal motor simulation, including action observation.

Future research could further benefit from the integration of multimodal imaging techniques to more comprehensively characterize the neurobiological underpinnings of atypical Parkinsonism. Specifically, combining tau-PET imaging and MRI-based voxel-based morphometry with MEG derived spectral signatures offers a promising avenue for elucidating disease mechanisms from complementary perspectives. This integrative approach has already shown substantial promise in AD research, demonstrating colocalization of pathological tau accumulation with alpha band synchrony abnormalities (Ranasinghe et al. 2020). Moreover, changes in alpha and beta band activity appear to precede overt brain atrophy, suggesting that such spectral markers may change in early disease-stages (Kudo et al. 2024). These findings raise the possibility that similar patterns may extend to primary tauopathies such as CBS and PSP, reinforcing the potential utility of MEG for clinical prognosis.

4.2. Conclusion

This thesis presents novel evidence for electrophysiological alterations common to CBS and PSP patients, two atypical parkinsonian syndromes that remain significantly underrepresented in the M/EEG literature. These clinical syndromes present with specific spatio-spectral signatures, distinguishing them from PD. Furthermore, neural desynchronization related to visuo-motor mapping and implicit motor learning are altered in CBS. These electrophysiological alterations might reflect underlying disruptions of large subcortico-cortical networks involving frontal and parietal cortices.

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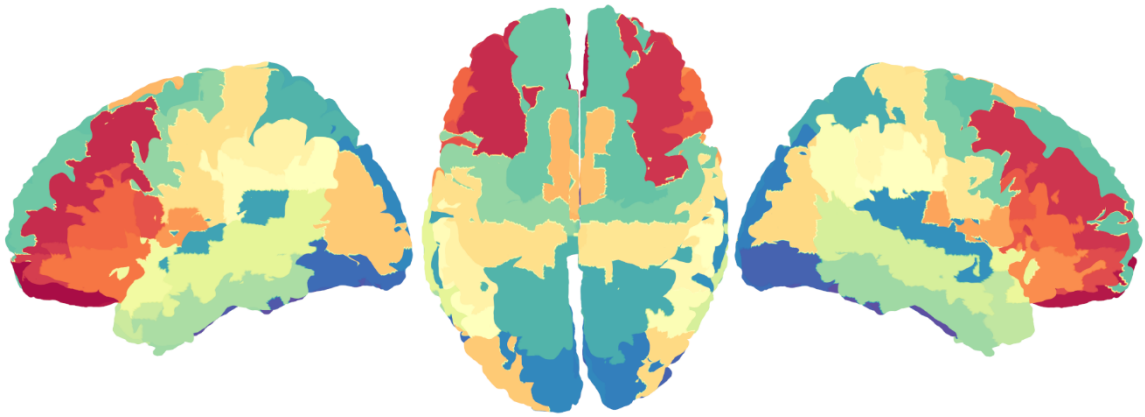
6. Appendix

6.1. Study 1: Slowing of Frontal β Oscillations in Atypical Parkinsonism - Supplementary Materials

Cortical parcellation



Supplementary Figure 6.1.1. Segmentation of cortex into 48 anatomical regions based on the AAL atlas. Rolandic operculum L/R, postcentral gyrus L/R, precentral gyrus L/R; Parietal superior cortex L/R, parietal inferior cortex L/R, supramarginal gyrus L/R, angular gyrus L/R; Superior frontal gyrus L/R, middle frontal gyrus L/R, inferior frontal gyrus pars orbitalis L/R, superior frontal gyrus pars orbitalis L/R, middle frontal gyrus pars orbitalis L/R, inferior frontal gyrus pars opercularis L/R, inferior frontal gyrus pars triangularis L/R, supplementary motor area L/R; Superior temporal gyrus L/R, superior temporal pole L/R, middle temporal gyrus L/R, middle temporal pole L/R, inferior temporal gyrus L/R; Superior occipital gyrus L/R, middle occipital gyrus L/R, inferior occipital gyrus L/R; Cerebellum L/R (not displayed).

Supplementary Table 6.1.1: Clinical information on CBS and PSP study cohort. CBS: Corticobasal Syndrome, PSP: Progressive Supranuclear Palsy; UPDRS: Unified Parkinson's disease rating scale; Goldenberg: Goldenberg's apraxia test; TULIA: Test of upper limb apraxia; MoCA: Montreal Cognitive Assessment.

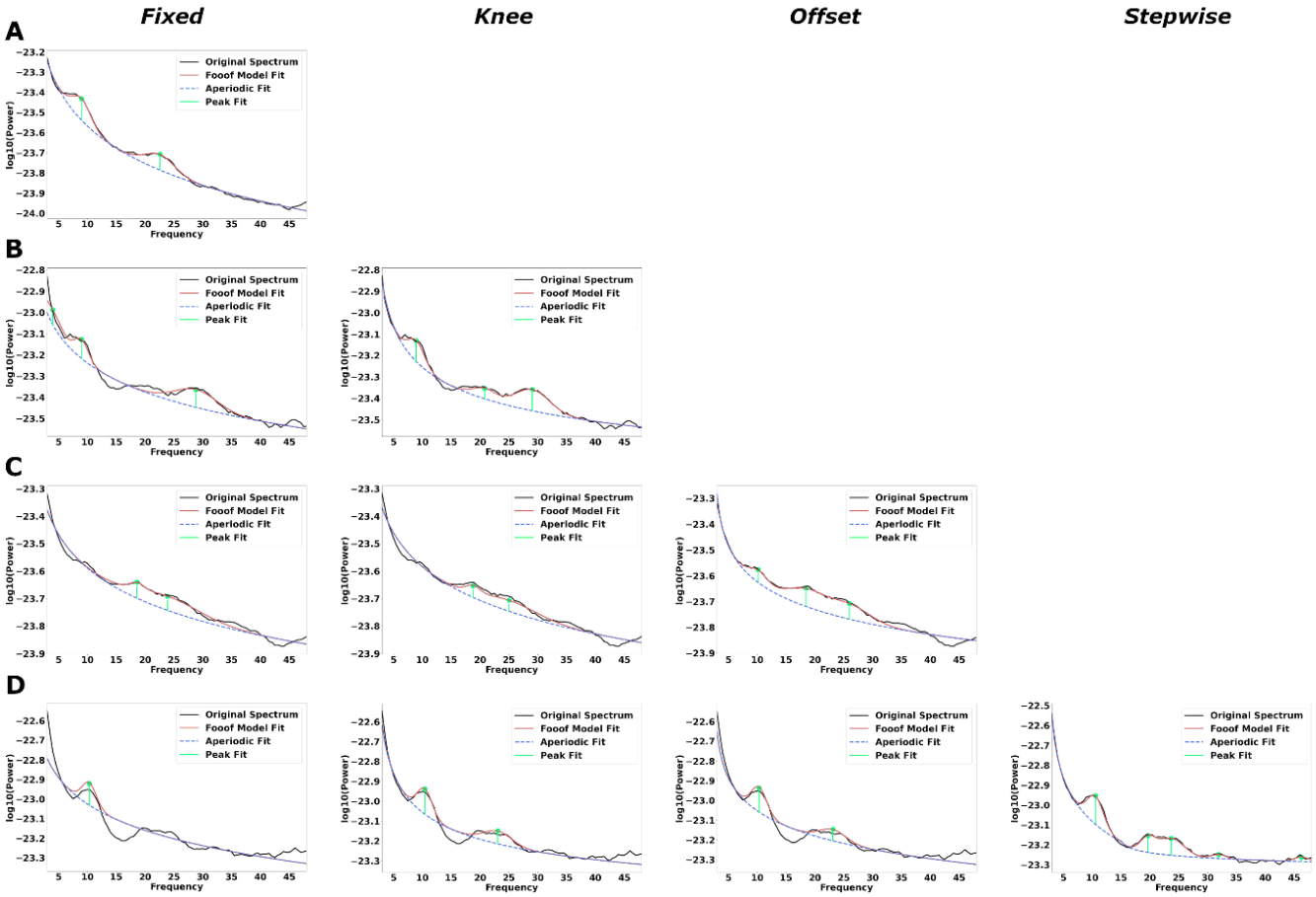
Patient	Age	Gender	Diagnosis (possible/probable)	Disease duration (years)	UPDRS III (sum)	Goldenberg (sum)	TULIA (sum)	MoCA (normalized sum)
CBS01	57	F	Possible	10	38	77	22	0.9
CBS02	61	F	Probable	3	58	33	12	0.3
CBS03	76	F	Possible	1	47	67	21	0.53
CBS04	76	F	Probable	4	60	4	2	0.68
CBS05	60	F	Probable	4	41	10	8	0.2
CBS06	61	M	Probable	1	47	78	23	0.87
CBS07	60	M	Possible	-	76	64	18	0.57
CBS08	69	F	Probable	10	83	50	17	0.44
CBS09	52	F	Possible	6	11	80	24	0.63
CBS10	65	M	Probable	5	20	52	17	0.97
CBS11	72	F	Probable	3	66	23	5	-
CBS12	52	F	Probable	6	16	58	22	0.47
CBS13	71	M	Probable	3	55	4	3	0.52
CBS14	79	M	Probable	3	24	64	17	0.8
PSP01	68	F	Probable	2	28	73	19	0.47
PSP02	64	F	Probable	3	-	-	-	-
PSP03	66	F	Probable	2	-	-	-	-
PSP04	73	M	Probable	3	-	-	-	0.8
PSP05	71	F	Probable	2	-	-	-	-
PSP06	70	M	Probable	2	-	-	-	-
PSP07	70	M	Probable	5	-	-	-	-
PSP08	72	M	Probable	6	-	-	-	-
PSP09	67	M	Probable	2	-	-	-	-
PSP10	70	M	Probable	4	-	-	-	0.73
PSP11	78	M	Probable	3	47	-	-	-
PSP12	77	F	Probable	4	33	-	-	0.8
PSP13	69	M	Probable	3	-	-	-	-
PSP14	73	F	Possible	4	-	-	-	0.87
PSP15	70	F	Probable	6	-	-	-	-
PSP16	65	M	Probable	4	-	-	-	-

Fitting aperiodic and periodic spectral components

For inter-subject comparison, we normalized power spectra by subtracting their 1/f aperiodic component computed with the toolbox *fitting oscillations & one over f* (development version 1.01.) by Donoghue et al. (2020) FOOOF also facilitated the estimation of peak frequency and peak amplitude of oscillations. The model estimate was fitted on the 3 Hz to 48 Hz interval to ensure the best possible fit on the analysis interval between 4 Hz and 30 Hz. Parameter settings were estimated in an automated procedure and adapted after visual inspection if needed to account for possible pitfalls when using FOOOF (Gerster et al. 2021).

Each power spectrum was automatically fitted in an algorithmic procedure based on four different models with different flexibility (see the analysis script on GitHub for more information). 1. *Fixed model* fitting with standard setting *'fixed'*, based on estimation of two parameters for offset and slope of the aperiodic fit. 2. *Knee model* fitting with setting *'knee'*, based on estimation of the offset, slope and a third parameter adding flexibility to the slope. 3. *Offset model* fitting the standard *fixed model* but shifting the offset between 2 Hz and 4 Hz to improve the aperiodic fit. 4. *Stepwise model* fitting of a first *fixed model* from 3 Hz to a border-value and a second *fixed model* from the border-value to 48 Hz. Examples are given below.

The algorithm chose between these four models aiming to i) minimize the discrepancy between the model offset and the original power spectrum offset (see Supplementary Fig. 6.1.2B) and ii) avoid negative values arising after subtracting the aperiodic component (see spectral trough ~15 Hz in Supplementary Fig. 6.1.2D). Following the automatic fit, all power spectra were visually inspected and corrected if necessary. Please note that we did not use parameter estimates of the 1/f aperiodic component for statistical group comparisons, as these are not comparable after fitting different models. We note that many fits would have been of insufficient quality if the same model had been applied in all cases.



Supplementary Figure 6.1.2. Example spectra for different model fits. A) Fixed model: Successful fit with two peak estimates. B) Fixed model: Unsuccessful fit. Offset estimate far from original spectrum, non-existing theta oscillation added, low-beta oscillation not detected, and aperiodic fit too high to avoid trough at ~14 Hz. Knee model: Successful fit with three peak estimates. C) Fixed model: Unsuccessful fit. Offset estimate far from original spectrum, low alpha oscillation not detected. Knee model: Unsuccessful fit. Similar to fixed model. Offset model: Successful fit. D) Fixed model: Unsuccessful fit. Offset estimate far from original spectrum, aperiodic fit too high to avoid trough at ~15 Hz, does not capture beta activity. Knee model: Unsuccessful fit. Aperiodic fit too high to avoid trough at ~15 Hz. Offset model: Unsuccessful fit. No improvement compared to knee model. Stepwise model: 1.Fixed model from 3 Hz to 15 Hz. 2. Fixed model from 15 Hz to 48 Hz. The joint model captures oscillatory activity correctly.

Linear mixed models

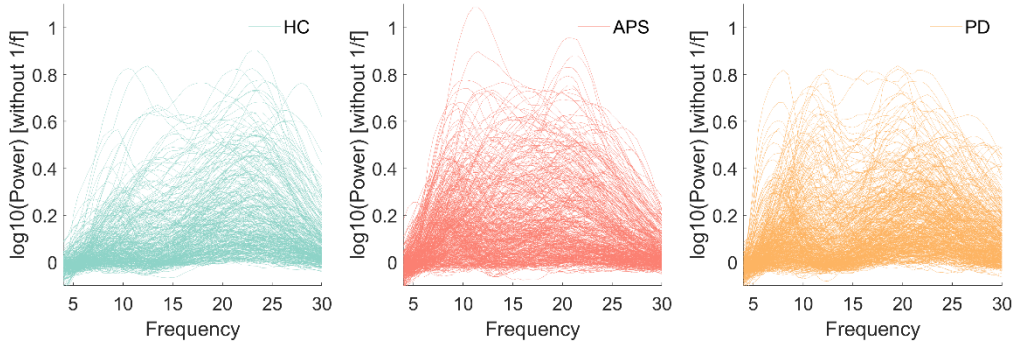
Group differences in peak frequency and peak amplitude were analyzed by means of linear mixed effects models. Age was included as a covariate together with two-way interactions. Subjects, parcels, and peak indices were defined as random effects. Continuous fixed effects were centered on their mean and APS was chosen as the reference group. Statistical results are reported in the form of *t*-values, indicating the direction of the effect, degrees of freedom, and corresponding *p*-values.

$$y_{jikn} = \mu + \alpha_i group_i + \beta_1 age + (\alpha_i\beta_1)(group_i * age) + \gamma_j subject_j + \gamma_{k(j)}(subject_j * parcel_k) + \gamma_{n(k(j))}(subject_j * parcel_k * peak_n) + \varepsilon_{jikn} \quad (2)$$

y_{jikn}: Response variable; μ: Coefficient for the fixed intercept; α_i: Coefficients for group related deviation from the fixed intercept $i \in \{1,2\}$; β_1:Coefficient for covariate age; $(\alpha_i\beta_1)$: Coefficients for interaction terms $i \in \{1,2\}$; γ_j: Coefficients of subject related random intercept $j \in \{1, \ldots, 80\}$; $\gamma_{k(j)}$: Coefficients of parcel related random intercept nested within subjects $k \in \{1, \ldots, 10\}$; $\gamma_{n(k(j))}$: Coefficients of peak related random intercept nested within parcels, which are nested within subjects $n \in \mathbb{N}$; $\varepsilon_{jikn} \sim N(0, \sigma^2)$.

Individual spectra within region of interest

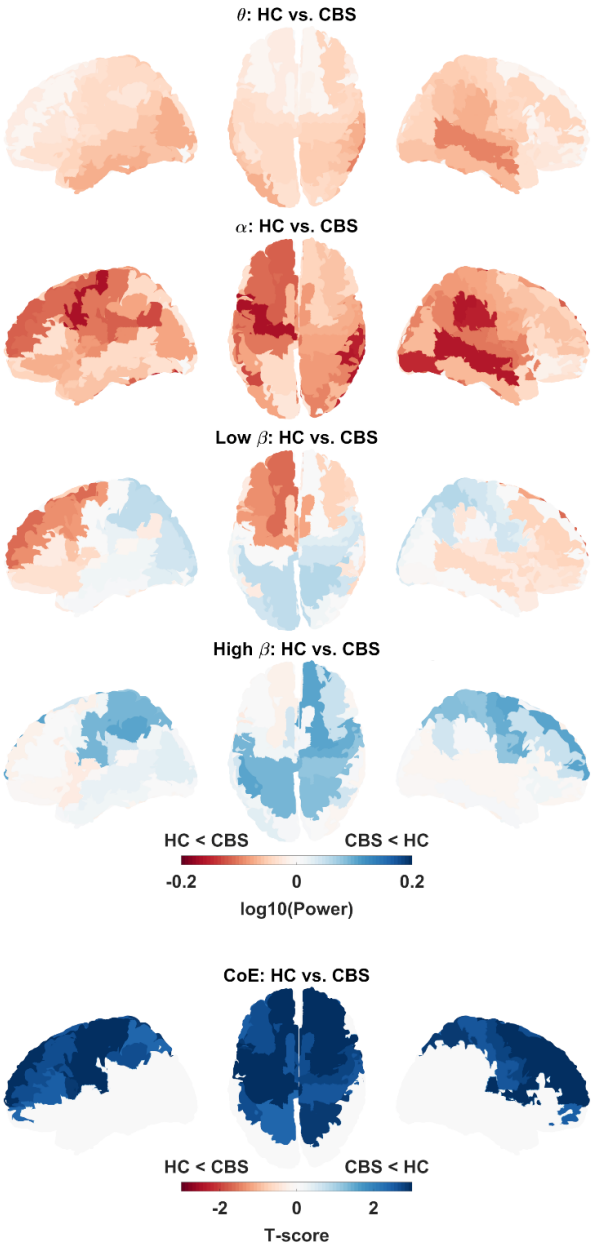
Individual spectra for all parcels and all participants are displayed separately for each group in Fig. 3. The APS and the PD cohort both showed higher power than controls in the in the theta and alpha band. Differences between APS and PD emerged in the beta band. PD, but not APS, spectra had a gap around 15 Hz. The absence of this gap reflects the beta peak shift in APS.



Supplementary Figure 6.1.3. Power spectra of all cortical parcels. HC: Healthy controls, APS: Atypical Parkinsonian syndromes, PD: Parkinson´s disease.

Accounting for symptom asymmetry

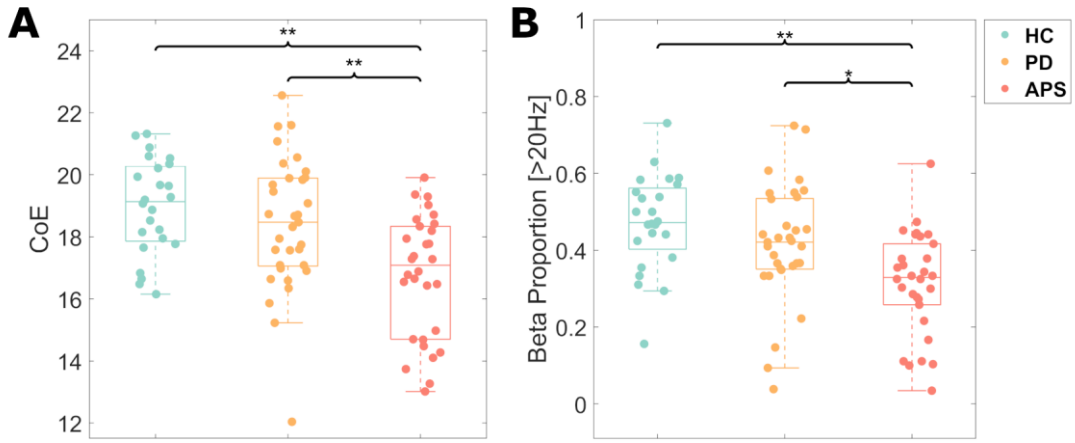
Parkinsonism, and CBS in particular, is usually lateralized, although symptoms and atrophy patterns are symmetric in some patients (Armstrong et al. 2013; Hassan et al. 2010) and lateralization was mild in our sample. In order to test the influence of asymmetry, we mirrored power topographies of the CBS group such that the hemisphere contralateral to the more affected body side always ended up on the right. This step hardly affected the results (Supplementary Fig. 6.1.4; HC vs. CBS: $p = 0.005$), suggesting at most a minor influence of lateralization.



Supplementary Figure 6.1.4. Power and CoE difference between CBS and HC after left-right mirroring according to the relative laterality scores.

Spectral slowing in individuals

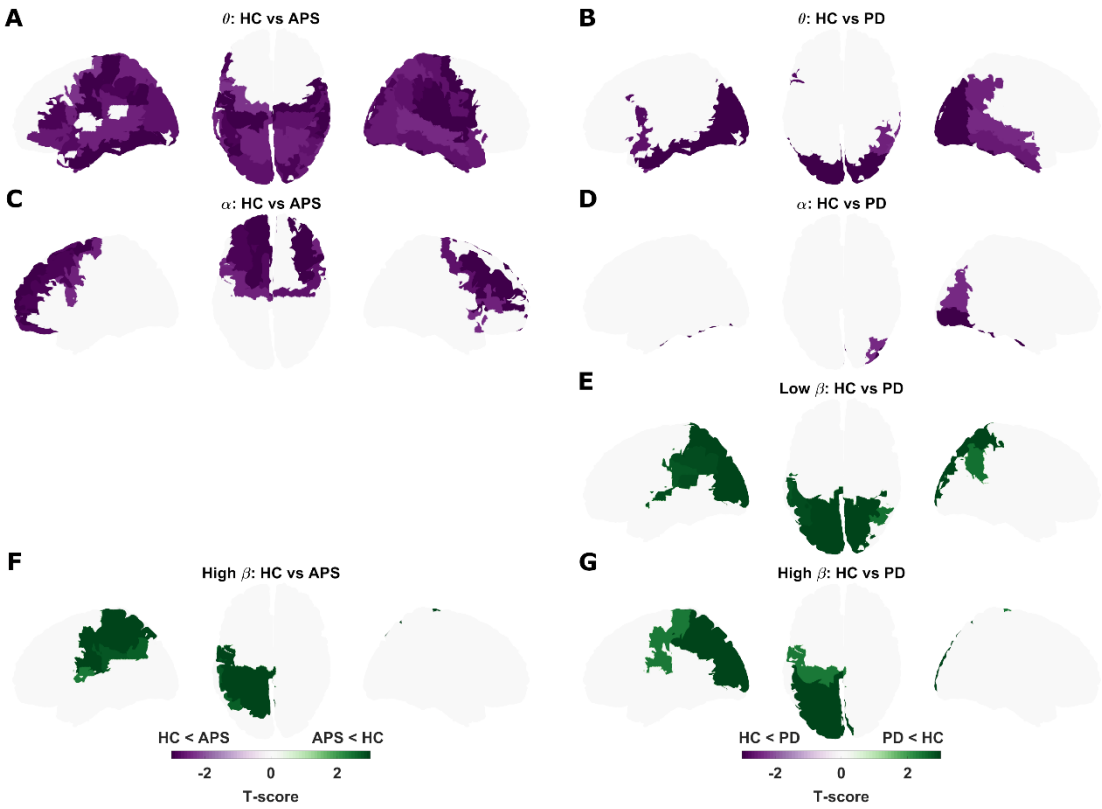
Supplementary Fig. 6.1.5A displays the ROI-average CoE for each participant. Significant group differences were found between HC and APS ($t(81) = 3.979$, $p = 0.0002$), as well as PD and APS ($t(81) = 2.83$, $p = 0.006$) as computed by linear modelling including age as a covariate. Supplementary Fig. 5B shows the individual number of high-beta peaks relative to the total number of peaks in frequency range from 4 to 30 Hz. This was diminished in APS patients compared to PD patients. A general linear model with the factor disease and the covariate age revealed a group effect. APS patients had a lower proportion of high-beta peaks than PD ($t(81) = 2.484$, $p = 0.015$) and HC ($t(81) = 4.124$, $p = 0.00008$), consistent with the results presented in the main paper. Variability in spectral slowing is larger in the patient groups (APS & PD) in comparison to HC.



Supplementary Figure 6.1.5. Individual data. A) ROI-average center of energy values for each participant. B) Proportion of high-beta peaks for each participant. HC: Healthy controls (green), PD: Idiopathic Parkinson's disease (orange), APS: Atypical parkinsonian syndrome (red). CoE region of interest mean: HC: 18.97; PD: 18.42; APS: 16.74. CoE region of interest standard deviation: HC: 1.54; PD: 2.12; APS: 1.97.

Whole-brain differences in theta, alpha and beta power & spectral slowing in PD

To understand how the difference in theta and alpha peak amplitude detected in the ROI (compare Fig. 2.3, main paper) relates to whole-brain topographies of power differences, we performed whole-brain, cluster-based permutation tests (Supplementary Fig. 6.1.6). Alpha power differences between APS and controls localized to bilateral frontal cortex, roughly consistent with the ROI used in the main paper (p = 0.007). Instead, alpha power differences between PD and controls were found in occipital regions (p = 0.02). Theta power differences between APS and controls (p = 0.001) as well as between PD and controls (p = 0.002) were observed in more posterior regions. Furthermore, beta band differences emerged in the higher beta band between APS and controls (p = 0.007), as well as PD and controls (p = 0.006), whereas lower beta band differences were only found to be significant between PD and healthy controls (p = 0.004).



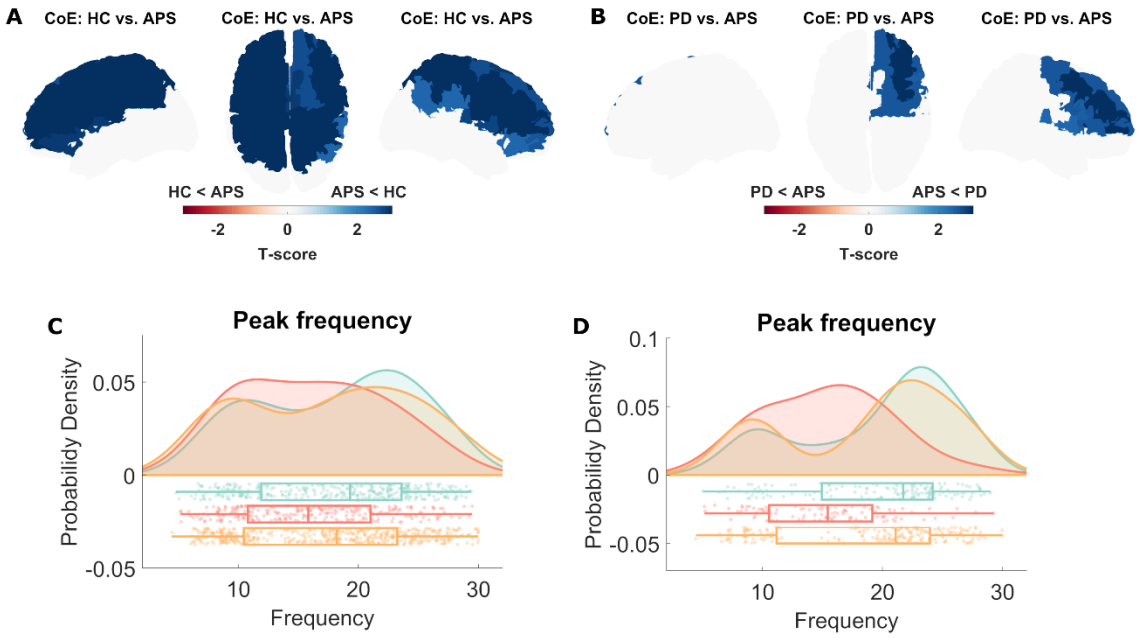
Supplementary Figure 6.1.6. Whole-brain power differences. A) Theta band power difference between HC and APS. B) Theta band power difference between HC and PD. C) Alpha band power difference between HC and APS. D) Alpha band power differences between HC and PD. E) Low beta band power difference between HC and PD. F) High beta band power difference between HC and APS. G) High beta band power differences between HC and PD.

Stratified groups: Atypical Parkinsonism vs. Parkinson's disease

To investigate the effect of age and severity of motor impairments in more detail we excluded APS patients > 70 years of age and the four CBS patients with the largest UPDRS-scores. The APS group (n = 17) did not differ from the PD group (n = 33, mean age_{PD}: 63.09, $range_{PD}$: 47 to 74; mean $UPDRS_{PD}$: 35.84 (11.19)) in age (mean age_{APS}: 63.94, $range_{APS}$: 52 to 70) or UPDRS-scores (mean $UPDRS_{APS}$: 32.38 (16.36)).

Significant CoE group differences still existed between HC and APS (p = 0.001) and PD and APS (p = 0.012). The topographies were highly similar to the original topographies, although left hemispheres changes were insignificant in the latter comparison (compare Fig. 2, main paper).

Beta peak frequencies were significantly lower in APS patients in comparison to PD patients and controls. This was the case when taking all peaks into account ($t_{PD}(734) = 3.795$, $p_{PD} < 0.001$; $t_{HC}(734) = 3.785$, $p_{HC} < 0.001$), or only the largest peaks within the beta range ($t_{PD}(424) = 4.423$, $p_{PD} < 0.001$; $t_{HC}(424) = 4.471$, $p_{HC} < 0.001$). In summary, these findings rule out confounding effects of age and motor impairment.



Supplementary Figure 6.1.7. Statistical results after exclusion of 13 APS patients due to age and severity of motor impairments. A) CoE difference between HC and APS. B) CoE difference between PD and APS. C) Distribution of all beta peaks (13-30Hz) for HC, PD patients and APS patients. D) Distribution of largest beta peaks (13-30Hz) for HC, PD patients and APS patients.

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6.2. Study 2: Altered Cortical Network Dynamics during Observing and Preparing Action in Patients with Corticobasal Syndrome - Supplementary Materials

Supplementary Table 6.2.1: Number of trials per block after cleaning.

Participant	RH01	LH01	RH02	LH02	Total
CBS01	29	32	34	27	122
CBS02	37	22	-	-	59
CBS03	27	18	-	-	45
CBS08	30	28	-	29	87
CBS10	-	28	-	-	28
CBS11	27	27	24	31	109
CBS12	10	26		26	62
CBS15	28	33	33	32	126
CBS16	27	33	34	30	124
CBS18	17	29	15	24	85
CBS19	34	29	26	0	89
CBS20	36	36	34	26	132
CBS21	27	29	-	-	56
HC11	33	31	32	32	128
HC12	34	34	30	28	126
HC13	32	31	34	35	132
HC14	27	28	29	27	111
HC15	33	23	30	32	118
HC16	39	38	31	36	144
HC17	32	31	36	37	136
HC18	30	24	26	21	101
HC24	18	15	28	26	87
HC25	26	36	32	34	128
HC26	20	26	19	27	92
HC29	20	21	28	24	93
HC30	31	35	35	31	132
HC31	32	34	26	30	122
HC32	33	30	32	31	126
HC33	40	40	39	40	159
HC34	37	37	34	39	147
HC35	39	39	40	39	157

CBS: Corticobasal Syndrome, HC: Healthy controls.

7. Acknowledgement

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Finally, I'd like to thank my wife Sarah, for her constant support and encouragement throughout these years, and my daughter Charlotte, who never fails to put a smile on my face.

8. Eidesstattliche Versicherung

Ich versichere an Eides Statt, dass die Dissertation von mir selbständig und ohne unzulässige fremde Hilfe unter Beachtung der „Grundsätze zur Sicherung guter wissenschaftlicher Praxis an der Heinrich-Heine-Universität Düsseldorf“ erstellt worden ist. Die Dissertation wurde in der vorliegenden, oder in ähnlicher Form an keiner anderen Fakultät vorgelegt. Ich habe bisher keine erfolglosen Promotionsversuche unternommen.

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Marius Krösche