Ordo ab chaos

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Timing cognition in Waves

Antonio Criscuolo

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Dissertation

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By

Antonio Criscuolo

Supervisor

Prof. Dr. Sonja A. Kotz, Maastricht University

Co-supervisor

Dr. Michael Schwartze, Maastricht University

Assessment Committee

Prof. Dr. Bernadette Jansma	Maastricht University
Dr. Anne Keitel	University of Dundee, United Kingdom
Prof. Dr. Joachim Gross	Institute for Biomagnetism and BioSignal Analysis, University of Muenster, Germany
Dr. Vincent van de Ven	Maastricht University

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Chapter 1

General Introduction

General Introduction

Take a deep breath, listen: trees swinging with the wind, jazz music playing in the background, people walking, chatting. Every sensory stimulus around us, every decision we make, every action, every heartbeat happens in time. How can multimodal sensory input at multiple timescales converge into a temporally coherent perceptual representation?

In this thesis I will discuss that our lives are governed by the passage of time, and I will consequently argue that our *sense* of time is fundamental to transition from *chaos to cosmos* (Kant, 1787).

However, what is time? We cannot see it, nor touch it and yet we do somehow perceive time. How do we do so and how do we use the *sense of time* to orient, act in, and adapt to a dynamically changing environment? Does our bodily physiological activity influence our sense of time? Then, is the sense of time *subjective*? Namely, does my perception of time differ from yours? And in turn, how does it shape our perception and action?

I will try to address these questions by focusing on specific *timing* computations: the neurophysiological mechanisms to encode, track and predict temporal regularities in the sensory environment. The journey starts with an introduction on the physical understanding of time (Chapter 1, paragraph 1) and moves to its implementation in the brain (Chapter 1, paragraph 2-3). I will discuss that as physical time allows to characterize space, motion and dynamics in natural sciences, the brain similarly employs an *internal* sense of time to understand the world. As we shall see, neural waves in extended cortico-subcortical networks **sample** the sensory environment by chunking continuous sensory streams into finite units, **encode** the precise *timing* of sensory input and keep **track** of time intervals between successive onsets relative to an *endogenous* clock that **marks** the continuous flow of time. Thus, neural waves at multiple timescales let a frequency architecture of dynamic oscillators emerge, ultimately instantiating an adaptive neural code to coordinate perception and action. I will further discuss that timing computations generate and are fostered by temporal predictions: breaking the physical asymmetry of time flow, neural waves flip the *arrow of time* and access past information to inform the future. By detecting temporal *patterns*, recurrencies, *regularities*, the brain generates predictions about future events, optimizing sensory processing, perception and action.

These concepts are experimentally tested in a series of comparative and translational studies in Chapters 2-4. In Chapter 2, I explore basic neurophysiological mechanisms to encode, track and predict temporal regularities in the general population. Complementing these observations, in Chapter 3 I take an evolutionary perspective and assess cross-species (dis-) similarities in basic *timing.* Finally, in Chapter 4 I discuss that subcortical lesions causally impact our capacity to detect, produce, and synchronize with temporal regularities in the environment.

In these chapters I dedicate particular attention to the characterization of intra- and inter-individual variabilities in basic timing, in the *preferred* time, as well as in the capacities to *detect* and *synchronize* with external time. Thus, the *sense* of time is not fixed; and physical time is not fixed either. As we shall see, physical time is bound to space, and particularly at the speed at which we travel through space. I argue that our *sense* of time may similarly fluctuate, expand and contract, and vary according to one's state: a state defined by a system of endogenous body and brain physiological oscillators fluctuating at their eigenfrequency, their mutual dynamic interactions and their adaptation and *tuning* to environmental contingencies (i.e., incoming sensory stimuli and motor state). Hence, in Chapter 5 I introduce a new conceptualization of a body-brain dynamic system proposing that body physiology (e.g., respiration and heart activity) influence brain activity and cognition. This novel framework suggests that body signals represent complementary time keeping and time generating modules influencing brain activity, perception and action.

Finally, in Chapter 6 I provide an overview of the main findings, discuss their impact on basic and applied research and motivate future research formulating novel and holistic research questions on neurocognitive functioning in health and pathology.

Before that though, let time flow at its own speed: *what is time?*

1. Time and time flow

1.1. Measuring physical time

"The second is the duration of 9192631770 periods of the radiation corresponding to the transition between the two hyperfine levels of the ground state of the caesium 133 atom." - 13th General Conference on Weights and Measures in 1967.

Our best measure of time is obtained by monitoring the resonant frequency of atoms (caesium 133), thus the label *atomic clocks*. What provides this fine measure of seconds is the frequency of electromagnetic radiation, defined by the rate of transition between different energy levels. The idea to use atoms and their periodic, precise fluctuation between energy states to measure time was inspired by James Clerk Maxwell, who first proposed measuring time via the vibrations of light waves: *"A more universal unit of time might be found by taking the periodic time of vibration of the particular kind of light whose wavelength is the unit of length."* (Treatise on Electricity and Magnetism, 1873; Achard, 2005; Ramsey, 2005). These super-precise clocks now define the International Atomic Time and are used to connect the world into a unique *sense of time*. They are further used by satellite networks to allow for terrestrial, maritime, and aerial navigation with a bare 3cm error.

However, we have not always been so precise, and we may remember seeing a pendulum clock in our grandma's house. For a long time, our *best* markers of the passage of time were pendulums, harmonic oscillators whose quasi-isochronous swinging would accumulate an error of approximately 15s per day. For almost 300 years, the world relied on the creation of Christiaan Huygens (inspired by the conceptualizations of Leonardo Da Vinci in 1494 and Galileo Galilei in 1582) for scheduling daily life, home routines, work shifts, or public transportation. Before that, there were obviously other time-keeping devices, but they would accumulate several minutes of error per day, hours of error every ~4 days, and days of error per year. The early attempts to provide an objective marker of time flow date back to ancient Egypt, the Babylonians, Greek, and Chinese, who employed sundials, water, and incense clocks. These were followed by the hourglass (or sandglass) and mechanical clocks in the 14th century, and later by the pendulum clock. However, what most of us wear daily is a quartz watch, an electronic oscillator regulated by a quartz crystal.

1.2. Is there objective time?

Quartz clocks achieve an accuracy that is at least an order of magnitude above that of mechanical clocks. However, the truth is that clocks carried by different individuals will not necessarily align: there is need for a radiofrequency pulse to re-align these clocks from time to time.

There are various reasons for watches to diverge from the 'correct' time, one being that time perhaps *is not* fixed, but there are different measures of time. There is *your* time, the one measured by the watch you carry at work; and there is someone else's time, the one measured by the watch of an airline pilot crossing Europe at high altitude and speed. What I am trying to convey is to acknowledge that physical time is inherently bound to space and, in particular, to the speed at which we travel through space. This step would allow us to move from the classical Newtonian view of absolute time to Einstein's relativity (1905) and the notion of space-time. In this perspective, there is a turn in focus: we measure space by using time. Although we cannot speak of 'absolute' time (i.e., it is not universally fixed), we acknowledge that the speed of light is fixed. This new universal constant allows measuring space by using a precise measure of time as derived from cesium clocks. Next, we can calculate how long it takes for photons to travel certain distances and define a meter to be the distance travelled by light in 0.00000000334 seconds, yet another very odd number like the one we started out with.

1.3. The arrow of time

What is also odd is that while there is a relationship between time and space, there is a clear difference between them: we can travel north and south, east and west, e.g., go from Maastricht to Salerno for a vacation; but we cannot travel into the past or future. We can access information from the past and retrieve memories, but we cannot do that in the future. While most of the laws of physics are symmetric (i.e., they do not distinguish past and future: if we reverse the motion of particles, the same laws of physics would explain their behavior), there is an asymmetry in the flow of time. In fact, a cup of water falling to pieces represents a process that cannot be reversed (it would break the 2nd law of thermodynamics). Similar observations were made long before the advent of modern physics. In fact, pre-Socratic philosophers like Heraclitus (~540 B.C.E.) and Anaxagoras (~500 B.C.E.) already debated the unidirectional flow of time, and the impossibility to reverse its course. Thus, the arrow of time distinguishes past from future, and this physical asymmetry is characterized by an increase in

entropy. To catch the concept, we can use a very simple example: living beings need to consume food to generate energy and stay alive; food (which is originally in a highly ordered state) is transformed into energy, and energy is used to generate heat, which is a disordered state. Entropy increases and the process is irreversible.

Keeping this in mind, we can measure space by using time, and we can further use it to characterize *motion*: change in space as a function of time.

1.4. Using time for motion

How exactly do we quantify and characterize space and motion?

We can use Newton's laws of mechanics: the concepts of velocity, acceleration, and energy. According to Newton, the velocity of an object (i.e., the speed at which it is travelling through space and time) will be constant if there is no force altering its state. Deviations from its original motion can be quantified by the acceleration of that body, i.e., the rate of velocity change. According to the second law of motion, the acceleration of an object is proportional to the net force acting on it, with the proportionality provided by the object's mass.

This framework allows to characterize change over time, but how much time? A minute, a second, a fraction of a second?

What we want to do is breaking time down into small units to quantify *change.* However, it took a long while from Zeno of Elea (~450 B.C.E) to Archimedes (~250 B.C.E), Galileo Galilei. and finally, to Isaac Newton and Gottfried Leibniz to come up with a solution: the continuous flow of time can be subdivided into infinitesimal quantities via *calculus*. This mathematical technique allows describing the rate of change of *something* using *derivatives*, while the total amount of change can be obtained via *integrals*. Thus, the velocity at which your boat travels from Salerno to Amalfi can be obtained by looking at the slope of the curve drawn by a graph that plots changes in position as a function of time x(t). A flat line would tell you that while time flows, there is no change in position; a steep curve, instead, would indicate fast changes in little time (Fig. 1A).

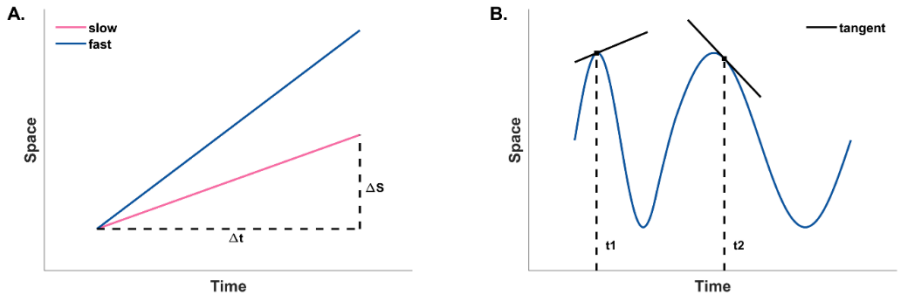

Figure 1 – Illustration on the use of derivatives to describe changes in space over time.

The slope at each (space-time) point of this graph can be obtained by drawing a tangent line at that specific (infinitesimally small) location (Fig. 1B). This systematic procedure lets us describe motion and dynamics. We can, indeed, calculate the rate of change in position (δy) over time (δx) obtaining *velocity* (v), i.e., the derivative of position with respect to time:

$$v = \frac{\delta y}{\delta x}$$

In turn, we can calculate acceleration, as the derivative of velocity with respect to time or as the second derivative of position:

$$a = \frac{\delta v}{\delta x}$$

Finally, once we have information on acceleration, we can quantify the force acting on an object:

$$F = ma$$

In this formula, the acceleration of an object is proportional to the (net) force acting on it with the constant of proportionality provided by the mass. We obtained Newton's second law of motion, the most famous equation in classical physics.

What we can also do is use the same ingredient to go a bit further: characterizing the *momentum* and kinetic *energy* of an object at any location in space and time. These fundamental properties, along with the laws for the *conservation* of momentum and energy, complete a long journey that started with Greek philosophers and Aristotle (~350 B.C.E), went on to Avicenna (~1000) and Jean Burdian (~1300), finally reaching René Descartes, Galileo Galilei, and Isaac Newton.

Motion, velocity, energy; once defined time, we discussed that we can *use* time to characterize the state of a system and its dynamic changes. In this thesis, I am particularly interested in characterizing a specific type of system: *oscillators*.

1.5. Oscillators

(*Simple harmonic*) oscillators can be exactly described by equations of motion. What makes them even more appealing is the fact that oscillators are everywhere around us: a weight hanging from a spring, the motion of an atom wiggling in a molecule, all the way up to vibrating quantum fields in particle physics and the value of the Higgs Boson field. Perhaps closer to the immediate interest of this thesis, the displacement of a pendulum clock, sounds waves, electrical currents, and neural activity can be similarly described by oscillators. These elements will be the protagonists of Chapters 1 to 4. At the end of this Chapter and in Chapter 5, I open up possibilities for more biological oscillators: I will talk about circadian, respiratory, and heart rhythms. Oscillators are ubiquitous in physics and natural sciences, so we should learn how to use them to explain physical phenomena.

As this chapter is about time, let me describe oscillators by thinking about a pendulum clock. The pendulum clock transforms energy into the motion of its pendulum (Fig. 2A). The motion is periodic; thus, the pendulum will continue to swing without changes as long as there is energy, or until it is perturbed. In the latter case, the motion of the pendulum should return to its endogenous oscillation, its *eigenfrequency*.

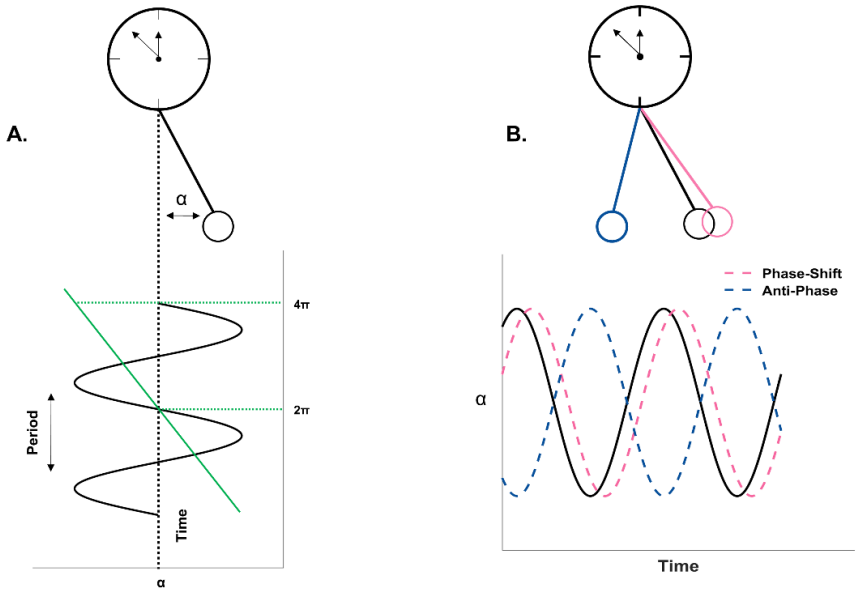

Figure 2 – The motion of a pendulum clock can be characterized by simple oscillators.

This formulation describes a *self-sustained oscillator*; an *active*, autonomous *dynamical* system (Pikovsky et al., 2002). The swinging of the pendulum traces a steady (sinusoidal) oscillation (Fig. 2A, bottom), which is characterized by the period *T*, the amount of time elapsed between two consecutive cycles of the oscillation. In turn, the period defines the *rhythm*, or the *cyclic frequency* (*f*) as follows:

$$f = \frac{1}{T}$$

Next to its frequency, the oscillator is characterized by another fundamental property, the phase. The phase determines the *state* of a period oscillator as it allows to parametrize the waveform within each cycle. The phase (green solid line in Fig. 2A) grows exponentially with the evolution of the oscillation, unambiguously marking the *where* within an oscillatory cycle (corresponding to *when* as it evolves over time) independently of the amplitude. Thus, the phase grows from 0 to 2π and its multiples (4π and beyond; green dotted lines in Fig. 2A), or can be wrapped around a unit circle and be reset at the end of each cycle (0 to 2π, and then restarting from 0). In fact, as the sine is a periodic function, two phases differing by 2π represent the same physical state. When two oscillators are in the same state they can be defined as being *phase-locked*, irrespective of their amplitudes. Similarly, two oscillators are said to be phase-locked when they are in a steady phase relationship (e.g., phase-shifted or anti-phase; Fig. 2B), although not exactly in-phase. The phase can be adjusted with the

application of small external forces: this allows (electronic) clocks to be universally *synchronized* towards atomic clocks by means of a radiofrequency pulse. Alternatively, two interacting oscillators (e.g., two metronomes on a moving platform) can mutually adjust their phase so to achieve phase-locking. This example implies that the two systems oscillate at the same frequency, as in the case of quartz clocks. However, two oscillators originally fluctuating at different frequencies can synchronize, too: this is what is called frequency *entrainment* or *locking*. The likelihood for synchronization of two systems oscillating at different periods depends on the coupling strength (i.e., the strength of interaction) and the frequency detuning (i.e., the difference in their *eigenfrequency*). The balance between coupling and frequency detuning is proportional: the higher the frequency detuning, the stronger the coupling required for entrainment. Notably, however, the (strong) coupling should not deprive either of the oscillators of their own endogenous rhythm: the self-sustained oscillator should still be able to return to its original behavior when the interaction (or perturbation) ceases. Furthermore, as discussed for phase-locking, frequency-locking can similarly be instantiated unidirectionally by imposing external forces. For instance, one may induce frequency- and/or phase-locking of neural oscillators by stimulating the sensory system with a loud metronome. Although rarely differentiated in the literature, this unidirectional synchronization is sometimes referred to as entrainment in the *broad sense* (Obleser & Kayser, 2019).

We now have the right ingredients for studying dynamic systems and simple oscillators. How can we use this framework to study how our brain processes time and the *timing* of sensory input in the environment?

We can leverage two essential observations:

1. Most of our reality displays gradients of temporal regularity: the motion of planets within galaxies, our music and speech, and complex behaviors can be characterized by *oscillators*. In this perspective, we can use the case of isochrony (e.g., in isochronous auditory sequences) to systematically investigate how we process and predict the *timing* of sensory input, and how we encode temporal regularities;
2. Secondly, we assess the coupling dynamics of oscillators: oscillations traced by an isochronous pendulum clock on a moving time-plane (Fig. 2A; an isochronous auditory sequence), and the oscillations generated by brain activity. By examining the relationship between these waves, we can formulate ideas on how we generate, encode, and predict time.

2. Time in the brain

You are in Piazza Duomo, in Amalfi (Italy), facing the beauty of the medieval cathedral of Saint Andrew, with its rich Arab-Norman, Gothic, Renaissance, Baroque decors. Myriads of tourists surround you, capturing the moment in pictures, speaking in their own languages. Next to Saint Andrew's fountain, on your right side, a musician sings 'Resta cu'mme' by Pino Daniele, and some people are singing along and filming while passing by. At the same time, you feel the warm sea breeze, the smell of fresh 'spaghetti con le vongole' (spaghetti with clams), and the subtle and refreshing smell of lemon zest from Pasticceria Pansa (ancient bakery). Your heartbeat resonates with the music, your stomach signals you are hungry, and your body temperature is rising. This vivid multisensory experience may sound pleasant, perhaps familiar if you have visited Amalfi. However, have you ever considered what was happening in your brain at that moment?

Our nervous system is bombarded by a continuous flow of information coming from both external (environment) and internal (bodily) sources. How do we coordinate multisensory input at multiple timescales and from diverse spatial sources into a unique coherent perceptual representation? How do we separate these sources into distinct streams, how do we merge streams, and how do we prioritize a stream of interest?

The philosopher Kant postulated that the *sense of time* plays a fundamental role in our perception of the world. He speculated (here paraphrased) that we employ mechanisms of temporal organization to aggregate and separate sensory information into coherent units. The sense of time, thus, precedes our sensory reality and shapes our perception, allowing to transition from *chaos to cosmos* (Grier, 2010). What is fascinating is that recent research informs the foundations of this hypothesis, in which smart grouping and segmentation functions continuously parse multivariate sensory input in time (Buzsáki, 2006; Large & Jones, 1999; Schroeder & Lakatos, 2009; Thut et al., 2012; Zoefel & VanRullen, 2016) to generate a coherent representation of the internal and external world. In this formulation, the capacities to encode the precise *timing* of sensory events around us, and to *time* our own (re-)actions become fundamental to act and adapt in a dynamically changing environment. Hence, we can imagine our own sense of time as an *internal clock* keeping track of time (e.g., elapsed time from instance *t* and instance *t*+n). Meanwhile, our clock deals with the *timing* of sensory input: it encodes the precise *when* of event A and B (t_A , t_B), and their temporal relationship (Δt between t_A , t_B). A very precise pacemaker would reliably discriminate even small Δt, allowing coherent parsing and chucking of information. Thus, if $t_A \neq t_B$ we can infer that A

and B are separated. To make it more challenging (though realistic), let us think of event A and B as sensory *streams*: let A be the lip movements of the musician singing the Pino Daniele's song and B be the speech sounds of a German tourist behind you. What we are confronted with is a continuous stream of sensory input (e.g., the speech signal can be decomposed into words, syllables, phonemes), each having their own *when* (i.e., they occur at a specific time) and each establishing a specific Δt, a temporal relationship with adjacent events (e.g., the Δt between syllables into a word), defining a *rate* (i.e., syllables occur at an average rate of 3Hz, thus there are ~3 syllables per second; Giraud & Poeppel, 2012). Encoding the *timing* of A and B has become a multi-layered temporal processing task, spanning a time-series: a continuous flow of single event onsets t_{As} and t_{Bs} with a series of Δts, finally generating a percept of the timing (or the *rhythm*) of event A (T_A with its own evolution and temporal dynamics) and event B (T_B with its own temporal dynamics). While not easy, we are generally good at this task, and can be sure that the German behind us is not singing Pino Daniele's song – the sensory streams are evolving in parallel, but $T_A \neq T_B$.

How do we implement such complex temporal processing task in the brain? How do we encode the *timing* of sensory input while keeping our own *internal* timing?

2.1. Neural waves implement time(s)

We recently introduced 'DPS', a 3-node hierarchical framework (Criscuolo et al., 2023a) to describe the essential timing functions required to act and adapt in a dynamically changing environment.

This framework leverages on a fundamental characteristic of our sensory reality: there are gradients of *temporal regularity* (Greenfield, Honing, et al., 2021). There are, indeed, periodicities within the body (e.g., heartbeat and respiration; Criscuolo, Schwartze, et al., 2022a), as well as in our variegated sensory environment (e.g., music, speech) and in complex behaviors (interpersonal interactions in the animal and the human world; Greenfield, Aihara, et al., 2021). Thus, the ability to detect, produce, and synchronize ('DPS') with temporal regularities becomes essential to navigate our environment and synchronize in social contexts.

At the core, we find *D,* which relies on the encoding of a rhythm, i.e., the neurophysiological processing of temporal regularities. Animal models have demonstrated that there are brain cells acting as 'neural chronometer', encoding the passage of time and the precise timing of

sensory events (Merchant et al., 2011; Merchant, Harrington, et al., 2013; Merchant, Pérez, et al., 2013) with a dynamic time-varying representation (Crowe et al., 2014). Thus, the sequential firing activity of these cells encodes and predicts regularly timed stimuli (Bartolo & Merchant, 2015) as well as tempo changes, further allowing to produce synchronized tapping (*P* and *S;* Gámez et al., 2018).

When looking at neuronal populations, the time-processing computations of single cells are reflected in *neural waves*: fluctuations of neural activity align with the timing of sensory events (e.g., Lakatos et al., 2008). Neural waves or neural *oscillations*, correspond to rhythmic changes in the excitability of neuronal populations (Bishop, 1932; Buzsáki & Draguhn, 2004). These fluctuations are a fundamental property of neural activity in both humans and animals (Buzsáki, 2006; Buzsáki et al., 2012, 2013), and they allow organizing single cell spiking and regional as well inter-regional spike traffic across the brain (Buzsáki, 2006; Fries, 2005; Wang, 2010) and at multiple timescales (Lakatos et al., 2005). A variety of methodological approaches exist to acquire and analyze such rich timeseries (Criscuolo & Brattico, 2023), characterize their varying properties across the brain (e.g., Keitel & Gross, 2016), and assess their role in information flow (e.g., Canolty & Knight, 2010; Fries, 2015). What is generally clear, despite the specific method in use, is that neural waves coordinate sensory input in time: events falling within the excitability window are preferentially processed, while events occurring within the inhibitory window are filtered out (Lakatos et al., 2013; Schroeder & Lakatos, 2009). The sensory environment is, thus, *sampled* in a (quasi-)rhythmic manner, and the pace of sampling is determined by the speed of one's internal clock(s) and the capacity to align neural waves to external rhythms. In this perspective, neural oscillations track sensory input at multiple timescales: going back to our speech example, words (~1Hz), syllables (~3Hz) and phonemes (~10Hz) are tracked by tempo-matching endogenous neural oscillations. However, *if* you rather decide to focus on the romantic Pino Daniele's song, your oscillations would fluctuate at different rates, thus aligning to musical rhythms and prioritizing *that* sensory stream (Lakatos et al., 2013; Schroeder & Lakatos, 2009).

The alignment of neuronal oscillations to salient periodicities in sensory streams is generally referred to as *entrainment* (Haegens & Zion Golumbic, 2018; Henry et al., 2014; Lakatos et al., 2008; Obleser & Kayser, 2019). Entrainment is a mechanism whereby an endogenous oscillator tends to *tune-in* and *-out* of external sources oscillating in proximity to their eigenfrequency. This formulation encapsulates a few assumptions: to *entrain,* neural waves should (i) be described as self-sustained (endogenous) oscillators, pre-existing, and outlasting

the external stimulation; (ii) adapt their endogenous oscillatory rate (F_A) so to match the external rate (F_B); (iii) go back to their spontaneous rate (eigenfrequency) when the stimulation ceases; (iv) be frequency-selective, thus can speed up and slow down within boundaries described by an Arnold tongue. The Arnold tongue characterizes the possibilities for frequency-tuning (frequency entrainment) and depends upon the frequency and amplitude of the external rhythm. Thus, with increasing ΔF (F_A - F_B) higher amplitudes are needed to induce entrainment. Finally, neural waves should (v) show dynamic changes while tuning-in and -out with the external stimulation frequency, thus displaying acceleration and deceleration trends over a few cycles (Lakatos et al., 2013; Spaak et al., 2012). The internal clock should be stable enough to keep internal timing, while accommodating time-varying environmental rhythms (Barnes & Jones, 2000). The presence of these dynamics is fundamental to distinguish 'real' entrainment from *resonance* and series of stimulus-locked evoked responses (Helfrich et al., 2019).

Resonance (Large & Snyder, 2009) is a physical phenomenon whereby the amplitude of an endogenous oscillator would *resonate* (i.e., it would be amplified) in presence of an external stimulus matching or in close proximity to its eigenfrequency. There is frequency-specificity and alignment of oscillations as in entrainment, but absence of *tuning* dynamics.

What is also possible is that neurons simply fire in response to each stimulus onset in a time-series, generating a sequela of entrainment-like time-locked evoked responses. For instance, neurons would respond promptly to each syllable onset within a speech sequence, ultimately revealing an entrainment-like pattern of oscillatory activity. Here, however, assumptions i-v are not met: we are not describing a self-sustained oscillator dynamically adapting its rate to the external rhythm; this is a rather buzzer-like activity. Disentangling *true* entrainment from entrainment-like phenomena is not easy (Breska & Deouell, 2017; Henry et al., 2014; Henry & Obleser, 2012; Herrmann et al., 2013; Lerousseau et al., 2021; Morillon & Baillet, 2017) yet it is fundamental to deepen our understanding of neural oscillatory dynamics and how we employ them to detect, produce, and synchronize with temporal regularities in the environment.

2.2. Flipping the arrow of time to inform the future

Are we always processing the *when* of each single sensory input around us?

The answer is ‘sort of’. We are continuously monitoring sensory streams, but we can rely on the fact that most of our sensory reality displays some gradient of *temporal regularity* (Greenfield, Honing, et al., 2021). There are periodicities within the body (e.g., heartbeat and respiration; (Criscuolo et al., 2022a) as well as in our variegated sensory environment (e.g., music, speech). I have already mentioned that speech can be decomposed into subunits occurring at a specific rate, defining phoneme, syllable, and word rates (Giraud & Poeppel, 2012). This temporal regularity, here also referred to as *rhythm*, is what enables individuals to generate predictions about the *when* of sensory events. As physics depends on *recurrent patterns* to generate laws of nature, our brain uses (temporal) patterns to infer what comes next and when. Hence, you may know when to expect the next syllables because you encoded my *speech rhythms.* The capacity to *detect* patterns and temporal regularities becomes, then, fundamental to produce and synchronize with rhythms: we can dance to music because we know *when* the next beat falls, and we can synchronize with others because their action timing is predictable. Consequently, we can argue that temporal predictions allow for proactive adaptive behavior: predictions are exploited to foster sensory processing, perception, allocation of attention and ultimately to speed-up behavior and action (Arnal, 2012; Friston, 2005; Háden et al., 2015; Koelsch et al., 2019; Nobre et al., 2012; Schröger et al., 2015).

Yet how do we achieve this?

I already introduced the concept of entrainment and discussed that neural waves dynamically align and track external rhythms in human (Criscuolo et al., 2023b) as well as in nonhuman animals (Criscuolo et al., 2023a) thereby encoding their temporal regularity. What I did not discuss yet, is that rhythmic brain activity leverages the encoded regularity to establish predictions about the *when* of next events (Lakatos et al., 2013), thereby *dynamic attending* (Mari R. Jones, 1976; Large & Jones, 1999) the sensory environment.

Such predictions are visible as anticipatory neural activity (Arnal, 2012; Fujioka et al., 2009, 2012; Large & Snyder, 2009), and ultimately allow producing and synchronizing behaviors in a predictive manner (Bartolo & Merchant, 2015; Gámez et al., 2018). The brain, thus, operates an “adaptation by anticipation” (Fraisse, 1963; p. 18) mechanism to optimize behavior and does so across sensory modalities (Arnal & Giraud, 2012; Cravo et al., 2013; Friston, 2005; Morillon et al., 2016; Nobre et al., 2012). Not only due to the inherent (quasi-)rhythmic nature of many environmental stimuli, a wide variety of neurocognitive functions ranging from speech (Giraud & Poeppel, 2012), reading (Goswami, 2011), and music (Doelling & Poeppel,

2015) processing rely on basic timing abilities. Thus, understanding the basic functional mechanisms by which neural activity encodes, tracks, predicts, and synchronize with temporal regularities in the sensory environment becomes fundamental to better understand a variety of neurocognitive functions in healthy as well as in clinical populations.

2.3. Perception fluctuates in waves: the case of accentuations

I have discussed that neural oscillations represent fluctuations in the excitability of neuronal populations. The alternation of high- and low-excitability phases instantiates a 'rhythmic mode' of sensing (Lakatos et al., 2013) and attending (Mari R. Jones, 1976; Large & Jones, 1999) the environment. Thus, neural waves implement a spectrotemporal filter (Lakatos et al., 2013), prioritizing sensory events falling in the high-excitability window.

The alternation of high- and low-salience may influence (or bias) subjective perception and behavioral performance (e.g., perceptual tasks; Iemi & Busch, 2018; Zoefel & VanRullen, 2017). For instance, when listening to a ticking clock, humans show a disposition to perceive *subjective accentuations* (or *rhythmization*; Brochard et al., 2003): although the sounds are physically identical, the human brain tends to perceive a *tic-toc* illusion. Hence, the hypothesis that while synchronizing to an isochronous auditory sequence, neural oscillatory activity would accentuate (or group) two or three equidistant tones according to a binary (on-/off-beat; or Strong-weak (S-w)) or ternary (S-w-w) pattern. In turn, sensory processing fluctuates in function of the alternating high- and low-salience temporal windows, becoming optimal for sensory events falling in the on- as compared to the off-beat positions (Abecasis et al., 2005; Baath, 2015; Brochard et al., 2003; Poudrier, 2020; Schmidt-Kassow et al., 2011).

Subjective accentuations emerge during passive listening, and may therefore represent the most basic, yet fundamental mechanism by which neural waves allow encoding and attending the sensory environment beyond simple isochrony processing. However, although being one of the earliest rhythm- and timing- processing phenomena to be experimentally investigated (Bolton, 1894), subjective rhythmization has yet to be fully understood.

What seems to be clear is that individuals tend to accentuate mostly in patterns of two and three, while groups of four are possible but less likely (Abecasis et al., 2005; Baath, 2015; Brochard et al., 2003; Schaefer et al., 2011; Woodrow, 1909). The switch from a single tone to accentuation processing and the width of the accentuation pattern seems to depend mostly

on the rate of auditory sequences, whereby accents over four tones are most likely in very fast auditory sequences (e.g., 5Hz), while smaller groups (accents of two) are prevalent in slower stimulation rates (Poudrier, 2020). At the same time, there are subjective preferences for accentuation patterns as well as inter-individual variabilities in the *if* individuals accentuate at all. In fact, individuals do not necessarily superimpose accentuations if not explicitly instructed to do so (Baath, 2015; Poudrier, 2020). Individual differences are typically explained in the context of music expertise (Bouwer et al., 2018; Drake et al., 2000; Geiser et al., 2010), and enculturation (Iversen et al., 2008; Polak et al., 2018), but little attention has been given to intra-individual variability and understanding what happens at the neurophysiological level. Existing EEG evidence, indeed, mostly employed event-related potential (ERP) paradigms to target subjective accentuations, thus performing trial- and group-level averages. Similarly, a parallel research line has consistently showed the possibility of capturing imaginary binary or triple beats in oscillatory brain activity via Fourier analyses (Nozaradan et al., 2011). The authors showed that this phenomenon mostly engages cortical but not subcortical brain regions (Nozaradan et al., 2018), is predominantly found over auditory and premotor cortex (Nozaradan, Mouraux, et al., 2017), and is not modulated by attention (Lenc et al., 2020). Both approaches, however, prevent the assessment of ongoing neural oscillatory activity at the single-trial and -individual level, ultimately neglecting the possibility that there may be transient and time-varying accentuation patterns in neural waves. In other words, several critical questions so far remain unanswered: (i) do individuals always accentuate, or do they do it *sometimes*?; (ii) do individuals consistently accentuate over time, or do they *switch* between accentuation patterns?; (iii) do accentuations influence other cognitive processes (e.g., deviance processing)? Finally, (iv) is accent processing unique to humans or is it present in nonhuman animals? The latter is a fundamental question, as it pertains to the putative link between basic rhythm processing and the evolution of higher order cognitive functions, such as music and speech processing in humans.

These questions are addressed in Chapter 2 and 3, where we introduced a new method to assess accentuation patterns at the single-trial and individual level in humans and macaque monkeys.

2.4. The role of audio-motor and cortico-subcortical interactions

Let us shortly go back to Amalfi and imagine to be immersed in that unique, variegated, multisensory landscape. I mentioned that our brain is posed with a challenging task: achieving *ordo ab chaos*. I also discussed that the existence of temporal regularities allows forming predictions about future events, thereby facilitating sensory processing. Thus, we can enjoy Pino Daniele's song because auditory processing leverages on perceived regularities in music and speech rhythms to predictively align neural oscillations to expected event onsets. While apparently simple, the mechanism of neural entrainment still requires precise temporal coordination at the millisecond scale. Which brain networks allow for such exquisite timing?

Humans' excellent timing capacities and cross-species differences in rhythm cognition (Honing, 2012, 2018) have long been associated with neuroanatomical changes along the dorsal auditory stream, and extending into premotor and basal ganglia areas throughout evolution (Balezeau et al., 2020; Rauschecker & Scott, 2009) as well as intense training (e.g., music training (Criscuolo, Pando-Naude, et al., 2022). However, recent research showed a more influential role of sensorimotor regions (e.g., primary sensory and motor areas; Balasubramaniam et al., 2021; Wiener et al., 2019) that seem to be responsible for rhythm processing and production in both humans (Chen et al., 2008; Grahn & Brett, 2007; Kotz et al., 2018; Wiener et al., 2010) and nonhuman animals (Cisek, 2019; Mendoza & Merchant, 2014; Merchant & Honing, 2014; Sohn et al., 2019). These observations further support the view that sensorimotor regions have played a significant role in the capacity of organisms to adapt to the environment, as they phylogenetically preceded the development of higher-order brain regions.

Thus, the motor system is engaged in timing and predictive timing processing (Merchant & Yarrow, 2016; Morillon et al., 2015; Schubotz, 2007) in both active and passive paradigms (Chen et al., 2008; Fujioka et al., 2012; Grahn & Rowe, 2009). Continuous and bidirectional interactions between sensory and motor regions inform perception and action in a predictive manner (Miall & Wolpert, 1996; Patel & Iversen, 2014; Prinz, 1997; West & Gibson, 1969; Wolpert & Flanagan, 2001). In fact, the motor system influences sensory (e.g., auditory) regions via active sensing, i.e., by generating a temporally coherent representation of the sensory environment and efferent copies of motor plans (Grahn & Rowe, 2013; Merchant & Yarrow, 2016; Schroeder et al., 2010; Tian & Poeppel, 2010). Top-down predictions are mediated by sensory regions via beta-band (β; 12-25Hz) activity (Arnal et al., 2015; Arnal & Giraud, 2012; Biau & Kotz, 2018; Fujioka et al., 2012, 2015; Morillon & Baillet, 2017; Park

et al., 2015), which phase-resets delta-band (δ; 1-4Hz) oscillations, aligning them to sensory streams. Thus, audio-motor interactions are mediated via β-δ cross-frequency coupling and provide the neural code responsible for temporal processing and predictive timing (Arnal et al., 2015; Morillon et al., 2019; Morillon & Baillet, 2017; Saleh et al., 2010).

The motor system discussed here is a widely distributed network extending to cingulate, premotor, posterior parietal, and supplementary motor cortex (Wittmann, 2013), and further includes the thalamus (Barczak et al., 2018) and hippocampus (Aly & Turk-Browne, 2018). However, substantial evidence suggests the basal ganglia (BG) and the cerebellum (CE) to be at the core of the cortico-subcortico-cortical network fundamental for rhythm and timing processes (Ivry & Keele, 1989; Schwartze & Kotz, 2013). In particular, the BG are involved in generating temporal predictions and in using relative timing to extract the beat (Grahn, 2009; Grahn & Brett, 2009; Schwartze et al., 2011; Teki et al., 2011). In turn, lesions in the BG impact the capacity to encode salient periodicities in sensory streams (i.e., extracting the beat) in both complex (syncopated rhythms; Nozaradan et al., 2017) as well as simple auditory sequences (Schwartze et al., 2015). Thus, patients with BG lesions were indifferent to manipulations of the temporal regularity in auditory sequences and could not generate and employ temporal predictions to efficiently process incoming sensory streams (Schwartze et al., 2015). In synchronization-continuation tapping tasks, BG lesion patients showed intact capacity to synchronize their tapping to the external rhythm (Schwartze, Keller, et al., 2011b) but at the same time showed largely heterogeneous tapping behaviors. These revealed difficulties in coordinating and adjusting their tapping to tempo changes (Schwartze, Keller, et al., 2011b). Lesions in the CE, instead, did not disrupt the capacity to generate predictions when confronted with temporal regularities (Schwartze & Kotz, 2021). However, the lesions altered the encoding of event onsets within an auditory stream (Nozaradan, Schwartze, et al., 2017), resulting in delayed and variable early event-related responses in the EEG (Kotz et al., 2014; Schwartze & Kotz, 2021). These observations suggest the CE to encode the precise timing (the *when* of *this* event onset) of sensory stimuli in the subsecond range (Ivry et al., 1988; Ivry & Keele, 1989; Ivry & Schlerf, 2008), ultimately allowing to estimate the duration of time intervals (Grube, Cooper, et al., 2010a; Grube, Lee, et al., 2010; Knolle et al., 2012, 2013; Teki, Grube, Kumar, et al., 2011; Teki, Grube, & Griffiths, 2011). The altered capacity to precisely encode event onsets and single time intervals (Grube, Cooper, et al., 2010b) further affects the production and synchronization to rhythms (Ivry et al., 1988; Ivry & Keele, 1989) with CE lesion patients displaying larger heterogeneity in self-paced tapping, and

reduced capacities to synchronize their tapping to temporally regular sequences as well as to tempo changes (Schwartze et al., 2016a).

Most of these research lines, however, adopted either behavioral or event-related EEG paradigms, ultimately providing an incomplete view of what happens in in the patients' brains when confronted with temporal regularities. Do neural waves in BG and CE lesion patients encode, track, and predict auditory rhythms? Chapter 4 addresses this question by systematically assessing neural oscillatory activity, its coupling to external auditory rhythms, and further complements neural data with a behavioral task.

3. Time in and out of the brain

So far, I discussed the idea of an internal clock generating endogenous time and processing external timing. Next, I speculated that neural oscillations, and specifically β-δ waves, implement the adequate neural code to process and predict environmental rhythms. Lastly, I reviewed evidence, showing that an extended cortico-subcortical brain network is responsible for the above-mentioned timing processes.

However, is the brain the only organ generating endogenous time and processing the timing of external events?

Physiological body signals like respiration (Park et al., 2020; Varga & Heck, 2017), heart (Candia-Rivera, 2022; Park & Tallon-Baudry, 2014), gastrointestinal (Azzalini et al., 2019), and ocular (Pfeffer et al., 2022) rhythms, display an intrinsically (quasi-)periodic oscillatory activity that mirrors and influences rhythmic brain signals (Klimesch, 2018). In adulthood, the neurotypical resting cardiac cycle oscillates at approximately 1.25Hz per second (~75 beats per minute), breathing at 0.25Hz (~15 times per minute), and the gastric cycle at around 0.05Hz (repeats ~3 times per minute). These rhythms change with task demands (e.g., exercise, see (White et al., 2014) for a review; meditation, (Wallace & Benson, 1972)), one's health (for a meta-analysis, see (Thayer et al., 2011)), and across the lifespan (Fleming et al., 2011), but remain mostly slower than neural activity, which typically fluctuates between ~1-50Hz. On an even longer timescale, we probably find one of the most important biological periodicities: circadian rhythms. Circadian rhythms include all those physiological and behavioural processes oscillating with a period of about a day. Even in absence of

environmental time-keeping cues (e.g., variation of light intensity throughout the day) circadian rhythms remain relatively stable and show little inter-individual variability.

As previously discussed for neural waves, bodily rhythms can be described as endogenous oscillators, which can interact with other bodily rhythms by adjusting their phase but are (in principle) independent of them (Pittendrigh, 1981; Yerushalmi & Green, 2009). Consequently, bodily waves represent ideal candidates for *endogenous and adaptive clocks*. Next to the brain, we may thus have a multitude of body-brain time generators and time keeping systems. These *internal clocks* differ across individuals due to inter-individual variabilities in body physiology as well as in brain rhythms. Furthermore, these internal clocks are modulated by psychological and cognitive states, such as mood and motion. For instance, bodily physiological activity varies with motion (e.g., while running), potentially shifting the eigenfrequency and phase of our internal clocks. This observation reminds us of Einstein's view according to which physical time is bound to space and at the speed at which we travel through space. Moreover, it strengthens the hypothesis that bodily physiological activity (e.g., cardiorespiratory rhythms) implements time computations, and contributes to the *sense of time.*

What remains to be clarified, however, is the link between the body and cognition: does body physiology influence neural activity and cognition? Are body-brain physiological interactions omnipresent and stable throughout the day and the lifespan? Can altered body-brain interactions influence neurocognitive functions? And in turn, can training improve body-brain interactions?

3.1. Body-Brain Waves time cognition

Body-brain (or -mind) connections have long interested philosophers and scientists. There is evidence that Plato, Hippocrates, Descartes, and Newton, among others, have asked questions about the link between the body and the mind.

In recent years, neuroscientific research has been expanding the sole focus on neurophysiology and behavior to include several peripheral physiological signals, arguing that they should be considered as conjunct determinants of cognition. Accumulating evidence, in fact, demonstrates that neural spiking, information processing, and overt behavior can be influenced by physiological body signals (Critchley & Garfinkel, 2018): breathing (Heck et

al., 2016; Ito et al., 2014; Kluger, Balestrieri, et al., 2021), gastrointestinal (Azzalini et al., 2019; Mayer, 2011), and cardiac (Park et al., 2014; Park et al., 2016) signals modulate not only neural excitability and perception, but also consciousness (Park & Blanke, 2019), emotion regulation (Damasio & Carvalho, 2013), memory (Zelano et al., 2016), and action (Park et al., 2020).

To mention but a few examples, there is evidence that voluntary breathing control improves motor coordination, e.g., for speaking, singing, or laughing (McFarland, 2001; McKay et al., 2003). Hence, eye movements (Rassler & Raabe, 2003; Rittweger & Pöpel, 1998) and complex motor acts such as walking, cycling, and running synchronize with breathing (Bechbache & Duffin, 1977; Bramble & Carrier, 1983; Folinsbee et al., 1983; Hill et al., 1988; Jasinskas et al., 1980; Kohn et al., 2016; Rassler & Kohl, 1997), as do rowing (Mahler et al., 1991) and finger tapping (Wilke et al., 1975). These findings support a putative top-down mechanism of "motor-respiration control in action preparation" (Decety et al., 1993; Park et al., 2020). Namely, any form of action planning entails anticipatory control of breathing. At the same time, evidence suggests that motor coordination further relates to the cardiac cycle (Palser et al., 2021) as motor excitability (i.e., the sensorimotor oscillatory activity associated with motion preparation) seems to be maximal during systole (Al, Stephani, et al., 2021).

Moving to perception, tactile (Grund et al., 2022), visual signal detection (Flexman et al., 1974), visuo-spatial (Perl et al., 2019), and memory performance (Nakamura et al., 2018; Zelano et al., 2016) are modulated relative to the respiratory cycle. Similarly, to what I discussed for brain waves, there is an endogenous tendency to adaptively align respiration to sensory inputs (Johannknecht & Kayser, 2022; Perl et al., 2019) to synchronize predicted stimulus onsets to late inspiration or early expiration phases (Grund et al., 2022). This effect resembles *respiratory entrainment* to a rhythm (Allen et al., 2022), i.e., the natural breathing rate endogenously synchronizes to external inputs. Attention to breathing further reinforces alignment (Bramble & Carrier, 1983; Haas et al., 1986; Kohl et al., 1981), ultimately providing a critical neurocognitive mechanism to improve sensory processing (Allen et al., 2022). In fact, the breathing phase influences neural excitability (e.g., alpha power; Kluger et al., 2021), strengthening the notion that the respiration-brain-stimulus coupling achieves processing advantage (Allen et al., 2022; Criscuolo et al., 2022a). Evidence on the heart-cycle is slightly more confusing, as visual attention (Pramme et al., 2014, 2016), visual processing (Galvez-Pol et al., 2020; Kunzendorf et al., 2019), somatosensory perception (Al, Iliopoulos, et al., 2021; Edwards et al., 2009), motor inhibition (Rae et al., 2018; Ren et al., 2022), sensorimotor

processes (Larra et al., 2020), and interoceptive awareness (Herman & Tsakiris, 2021) are better during systole compared to diastole. However, counter evidence exists showing that auditory (Schulz et al., 2020), visual (Park et al., 2014; Salomon et al., 2016), somatosensory perception (Al et al., 2020; Al, Iliopoulos, et al., 2021; Motyka et al., 2019), reaction times (Schulz et al., 2020), and learning (Waselius et al., 2018) are more optimal during diastole than systole.

Despite these discrepancies, the observations suggest that the combined assessment of body-brain physiological measures can unravel neglected sources of information (Bashan et al., 2012) and thus promise to advance our understanding of how we evaluate, perceive, and act in a dynamically changing environment (Criscuolo et al., 2022).

3.2. The Body-Brain Dynamic System

Along these lines, in a recent opinion article (Chapter 5; Criscuolo et al., 2022a) we put forward an integrative holistic framework to examine the body-brain-behavior interface: the *body-brain dynamic system* (BBDS). We discussed that body-brain waves may provide a rich architecture of time generators and time keeping mechanisms across the body, whose critical role extends across sensory modalities and cognitive functions. This novel, holistic, and individualized approach opens to a plethora of exciting new research questions in neurotypical and pathological populations. Starting from the ontogeny of these physiological signals, one could ask who provides the *tactus* to the body-brain frequency orchestra? Are there any *leitmotivs,* i.e., recurrent patterns in body-brain coupling dynamics? Who orchestrates body-brain waves and their interactions? Are there inter-individual differences in body-brain dynamics?

These research questions require a fundamental shift in the study of human brain and behavior, and further necessitate comprehensive experimental settings, monitoring multiple body-brain physiological signals in parallel. Embracing this quest, we have recently pre-registered two research lines: the first targets the link between individual body-brain rhythms and behavioral rhythms (Criscuolo et al., 2022b), while the second aims at developing a holistic bio-feedback body-brain training to modulate neurocognitive functions and emotional states (Criscuolo & Kotz, 2023). The first research line leverages the notion of *internal clock(s)* to generate research questions such as: Are individual spontaneous behavioral rhythms shaped by bodily rhythms? For instance, are your walking and speaking rates dependent on your heart rate?

Similarly, are listening preferences (e.g., speech and music rhythms) influenced by heart and breathing rhythms? This project puts individual differences at center stage, and systematically examines body-brain dynamic interactions and their influence on a multitude of behaviors such as perception and action. The second research line, aims at expanding the traditional neurofeedback setups. We argue that modulating cognition takes more than the brain only: a comprehensive body-brain assessment, and a body-brain biofeedback will improve the efficacy of existing neurofeedback training. In particular, the project will test the influence of the new biofeedback training on attention, anxiety, and wellbeing.

Chapter 2

Individual neurophysiological signatures of spontaneous rhythm processing

Individual neurophysiological signatures of spontaneous rhythm processing

A Criscuolo, M Schwartze, MJ Henry, C Obermeier, SA Kotz

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Abstract

When sensory input conveys rhythmic regularity, we can form predictions about the timing of upcoming events. Although rhythm processing capacities differ considerably between individuals, these differences are often obscured by participant- and trial-level data averaging procedures in M/EEG research. Here, we systematically assessed neurophysiological variability displayed by individuals listening to isochronous (1.54Hz) equitone sequences interspersed with unexpected (amplitude-attenuated) deviant tones. Our approach aimed at revealing time-varying adaptive neural mechanisms for sampling the acoustic environment at multiple timescales. Rhythm tracking analyses confirmed that individuals encode temporal regularities and form temporal expectations, as indicated in delta-band (1.54Hz) power and its anticipatory phase alignment to expected tone onsets. Zooming into tone- and participant-level data, we further characterized intra- and inter-individual variabilities in phase-alignment across auditory sequences. Further, individual modelling of beta-band tone-locked responses showed that a subset of auditory sequences was sampled rhythmically by superimposing binary (strong-weak; S-w), ternary (S-w-w) and mixed accentuation patterns. In these sequences, neural responses to standard and deviant tones were modulated by a binary accentuation pattern, thus pointing towards a mechanism of dynamic attending.

Altogether, the current results point toward complementary roles of delta- and beta-band activity in rhythm processing and further highlight diverse and adaptive mechanisms to track and sample the acoustic environment at multiple timescales, even in the absence of task-specific instructions.

Highlights

Neural oscillations sample the acoustic environment at multiple timescales;

Delta-band oscillations encode temporal regularities and predict tone onsets;

Beta-band oscillations parse auditory sequences by superimposing accentuation patterns;

Delta-beta oscillations provide a neural code for dynamic attending environmental rhythms.

Introduction

Due to the inherently rhythmic nature of many environmental stimuli, neurocognitive functions such as attention (Lakatos et al., 2008) sensorimotor behavior (Merker et al., 2009), speech (Giraud & Poeppel, 2012; Sonja A. Kotz & Schwartze, 2010), reading (Goswami, 2011), and music processing (Doelling & Poeppel, 2015) rely on basic timing capacities. To generate a temporally coherent representation of a rhythmic environment, we track stimulus periodicities, use smart grouping, and continuously segment and combine multiple inputs in time (Buzsáki, 2009; Schroeder & Lakatos, 2009; Thut et al., 2012a; Zoefel & VanRullen, 2016). According to the dynamic attending theory (Large & Jones, 1999) these processes can reflect how internal attending rhythms synchronize with external rhythms. This and similar theoretical views (Fraisse, 1963; p. 18) suggest that oscillatory brain activity instantiates a realistic model for "adaptation by anticipation". Accordingly, temporally regular sensory input should make future events predictable and improve the overall effectiveness of behavior. Thus, allocating attention to salient events can facilitate sensory processing, perception, and action (Friston, 2005; Arnal, 2012; Schröger et al., 2015; Koelsch et al., 2019).

However, *continuous change is a fundamental characteristic of life* (Schwartze, Rothermich, et al., 2011), and next to temporal regularities, we frequently encounter irregular rhythms or sudden environmental changes. To account for these dynamics, any realistic adaptation mechanism likely tolerates a certain degree of temporal irregularity or unpredictability while trying to achieve synchronization (Barnes & Jones, 2000). Endogenous oscillatory activity must hence not only be precise and stable over time, but also flexible enough to achieve adequate adaptive timing (e.g., speeding-up or slowing-down). Oscillatory brain activity can actively track and process (quasi-)periodic and never strictly isochronous signals such as speech that includes rhythmic variations at phoneme (25-35Hz), syllable (4-8Hz), or word (1-3Hz) rates, as well as slower fluctuations (>1Hz) reflecting linguistic boundaries (Ding et al., 2015; Giraud & Poeppel, 2012). Moreover, it can rapidly adapt to changes in the sensory environment, likely through phase resetting (Barnes & Jones, 2000; Haegens & Zion Golumbic, 2018; Mormann et al., 2005; Obleser et al., 2012; Zoefel et al., 2018).

Particularly, delta- (δ; 1-4Hz) and beta- (β; 12-25Hz) frequency oscillations have been associated with rhythm processing, temporal prediction, and attention in humans (Arnal, 2012; Biau & Kotz, 2018; Colling et al., 2017; Fujioka et al., 2012, 2015; Morillon et al., 2016; Nozaradan et al., 2015, 2017a) and in non-human primates (Bartolo & Merchant, 2015;

Merchant et al., 2015; Merchant & Bartolo, 2018; A. D. Patel & Iversen, 2014). However, prior behavioral studies on temporal processing also reported high within-subject variability (Baath, 2015; Poudrier, 2020). Thus, a critical question arises: can the systematic assessment of individual neurophysiological variability improve our understanding of how we process environmental rhythms? (Grahn & McAuley, 2009; Kononowicz & van Rijn, 2015; Nave et al., 2022; Waschke et al., 2021).

To address this question, we let participants listen to isochronous (1.54Hz) equitone sequences, comprising frequent standard and either one or two amplitude-attenuated deviant tones while EEG was recorded. The small amplitude attenuation represented a minimally distracting unpredictable deviation from the established regularity of the auditory sequence. A deviant-counting task focused participant's attention on an acoustic feature (loudness) of the stimuli, diverting attention away from the temporal properties of the auditory sequence. We first assessed the neural signatures of spontaneous temporal processing by means of rhythm tracking analyses, expecting to observe a peak of neural oscillatory power at the stimulation rate (1.54Hz, i.e., delta-band), and a consistent phase-alignment towards expected tone onsets, indicating temporal prediction.

Second, we focused on the known human disposition to superimpose accentuation patterns onto isochronous equitone sequences as exemplified by the "tick-tock" clock effect (Brochard et al., 2003). This typically results in perceived binary (strong-weak (S-w)) accentuations, while ternary (S-w-w) and other accentuations are possible (Abecasis et al., 2005; Baath, 2015; Brochard et al., 2003; Fujioka et al., 2015; Polak et al., 2018; Poudrier, 2020; Savage et al., 2015).

Informed by previous results that confirmed a role of beta oscillations in temporal predictions (Fujioka et al., 2012) and beat processing (Fujioka et al., 2015), we expected that such accentuation patterns would show in the envelope of beta-band activity. We employed a fixed stimulation frequency where we expected more binary than ternary accents (Abecasis et al., 2005; Baath, 2015; Brochard et al., 2003; Fujioka et al., 2015; Poudrier, 2020).

Third, we looked into individual differences to answer whether: (i) individuals always accentuate, (ii) individuals accentuate consistently over time, and (iii) accentuation patterns modulate cognitive processes as reflected in deviance processing (Brochard et al., 2003). To this end, we modelled single-participant and single-trial time-locked beta-band fluctuations to gain a better understanding of intra- and inter-individual neurophysiological variability

indicating individual mechanisms employed to sample, evaluate, and adapt to environmental rhythms.

Materials & Methods

Participants

Twenty native German speakers participated in the study and signed written informed consent in accordance with the guidelines of the ethics committee of the University of Leipzig and the declaration of Helsinki. Participants (9 females; 21-29 years of age, mean 26.2 years) were right-handed (mean laterality coefficient 93.8**,** Oldfield, 1971), had normal or corrected-to-normal vision, and no known hearing deficits. Participants received 8€/h for taking part in the study. Participants were not asked to indicate musical expertise and/or daily music listening.

Experimental design and procedure

The stimuli comprised 192 sequences, consisting of 13-to-16 tones (F0 = 400 Hz, duration = 50 ms, amplitude = 70dB SPL; standard STD), presented in two recording sessions. One or two deviant tones (DEV), attenuated by 4dB relative to the STD tones, were embedded in each sequence, replacing STD tones. The first DEV tone could either occur in an odd or even-numbered position (8-11th), corresponding to a hypothetical binary Strong-weak (S-w) accentuated position, while the second DEV always fell on the 12th position (w position, Fig.1). The inter-onset-interval between successive tones was 650ms, resulting in a fixed stimulation frequency of 1.54Hz and a total sequence duration of 8.45-10.4s (13 to 16 tones * 650ms). This paradigm was thus comparable to previous behavioral studies on subjective accentuation (Brochard et al., 2003; Poudrier, 2020).

Participants were seated in a dimly lit soundproof chamber facing a computer screen. Every trial started with a fixation cross (500ms), followed by the presentation of the tone sequence. The cross was continuously displayed on the screen, preventing excessive eye movements during the presentation of the tone sequences. At the end of each sequence, a response screen appeared and prompted participants to immediately press a response button to indicate whether they had heard one or two softer tones. The button assignment was counterbalanced across participants. After the response, there was an inter-trial interval of 2000ms. A session was divided into two blocks of approximately 10 minutes each, with a short pause in between (about 25 minutes total duration).

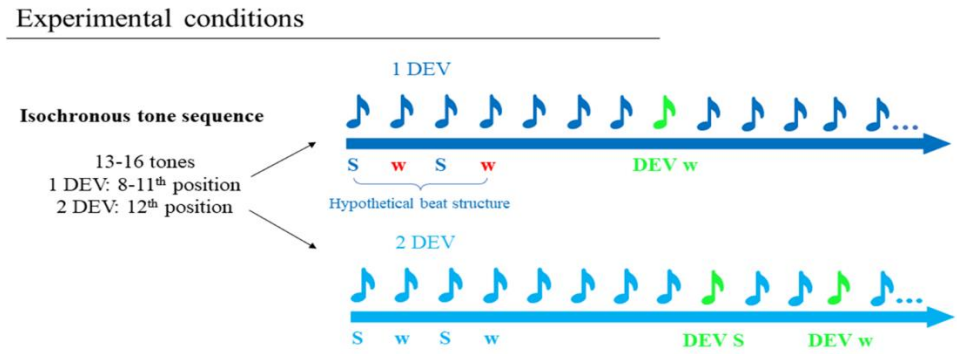


Figure 1 - Experimental conditions

Participants listened to 192 isochronous tone sequences, containing 13-to-16 tones and either one or two deviants (DEV). The first DEV could either fall on positions 8,9,10,11th, while the second DEV always fell on position 12th. A hypothetical binary accentuation pattern would designate adjacent tones as Strong-weak (S-w) duplets. In this case, the first DEV would occur with equal probability in S-w positions.

EEG recording

The EEG was recorded from 59 Ag/AgCl scalp electrodes (Electrocap International), amplified using a PORTI-32/MREFA amplifier (DC to 135 Hz), and digitized at 500 Hz. Electrode impedances were kept below 5kΩ. The left mastoid served as online reference. Additional vertical and horizontal electro-oculograms (EOGs) were recorded.

Data Analysis

Behavioral analysis

Behavioral data (i.e., response accuracy) were analyzed with a repeated-measures ANOVA with the deviant position (odd vs. even) as the independent variable and sequence order (position in the sequence, e.g., 8^{th} or 9^{th}) as a covariate.

EEG Preprocessing

Data were pre-processed using combined custom Matlab scripts/functions and the Matlab-based FieldTrip toolbox (Oostenveld et al., 2011). Data were first re-referenced to the average

of the two mastoid electrodes and then band-pass filtered with a 4th order Butterworth filter in the frequency range of 0.1-50 Hz (*ft_preprocessing*). Eye-blinks and other artifacts were identified using independent component analysis (‘*fastICA’* implemented in FieldTrip). A semi-automated pipeline was used to identify EEG components with a strong correlation (>.4; labeled as “bad” components) with the EOG time-courses to inspect the respective topographical distribution across scalp electrodes and to remove “bad” components. Data segmentation was then conducted separately for the rhythm-tracking, event-related potential (ERP), and time-frequency representation (TFR) analyses. Note that behavioral and rhythm tracking analyses are independent of the modelling and the analyses on individual accentuation patterns described later.

Rhythm tracking analyses

Rhythm-tracking analyses involved neural responses to the full equitone sequences. Following ICA, 192 (96 sequences * 2 sessions per participant) segments were created, starting from the first tone onset up to the 13th tone offset (8.45s). Fast-Fourier transform and rhythm tracking analyses, however, were performed on shorter segments starting from the 3rd up to the 13th tone offset (7.15s-long). The first two tones of the sequence were excluded from further analyses as it is known that they elicit much stronger event-related responses than tones in later positions of the sequence.

Next, we selected a fronto-central channel cluster, encompassing the sensor-level correspondents of prefrontal, pre-, para-, and post-central regions that were highlighted in previous MEG studies which employed source-localization analyses (Fujioka et al., 2012; Fujioka et al., 2015). The cluster included 16 channels: 'AFz', 'AF3', 'AF4', 'F3', 'F4', 'F5', 'F6', 'FCz', 'FC3', 'FC4', 'FC5', 'FC6', 'C1', 'C2', 'C3', 'C4'. Data from this fronto-central cluster were not averaged at this stage and were used for Fast-Fourier transform (FFT) and phase-locking analyses. While the FFT analysis mirrors the well-known ‘frequency-tagging’ approach (Nozaradan, Schwartze, et al., 2017), the employed phase analyses provide a richer description of how neural oscillations *track* external auditory rhythms. Hence, the name ‘rhythm tracking analyses’.

Fast-Fourier transform

Single-trial data from the fronto-central cluster were submitted to a FFT (“FFT data”) with an output frequency resolution of 0.14Hz (1/7.15s = .14Hz). Spectral power was calculated as

the squared absolute value of the complex Fourier output. Each trial was then normalized by the standard deviation across trials, per frequency-bin and channel. Lastly, the frequency-domain data were averaged across channels and trials. For illustration purposes only, the Fourier spectrum was restricted to 1-4Hz (Fig. 2A). The complex Fourier spectrum was also used to calculate inter-trial phase coherence (ITPC; Fig. 2A). This was calculated by dividing the Fourier coefficients by their absolute values (thus, normalizing the values to be on the unit circle), calculating the mean of these values, and finally taking the absolute value of the complex mean. Further documentation can be found on the FieldTrip website (https://www.fieldtriptoolbox.org/faq/itc/).

Phase-locking analyses

A time-resolved phase-locking analysis was performed to estimate the phase relationship between neural activity at the stimulation frequency and the sequential tone onsets.

The 8.45s-long data segments from the fronto-central cluster were bandpass-filtered with a 4th order Butterworth filter around the stimulation frequency (1.04-2.04Hz, obtaining a 1.54Hz center frequency; *ft_preprocessing*) and Hilbert-transformed to extract the analytic signal. The time-course of the real part of the analytic signal was then plotted (Fig.2B) as a function of the STD tone onset preceding (blue) and following (red) the DEV (green; note that this plot serves an illustrative purpose only). Phase-locking analyses focused on tones 3 to 13, and were performed at the sequence and channel levels by means of circular statistics (circular toolbox in Matlab; (Berens, 2009), based on the circular mean phase-angles estimated in the ~60ms (i.e., a time-window proportional to the stimulation frequency = 1/1.54Hz/10) preceding individual tone onsets. Next, the sequence- and channel-level mean vector length were calculated (MVL; (Berens, 2009) for pre-DEV STD tones and the resultant values then pooled across channels. The focus on pre-DEV tones only is motivated by the fact that the onset of a DEV tone might disrupt the predictability of the auditory sequence, and further induces a phase-reset of oscillatory activity. Next, MVLs for pre-DEV STD tones were statistically assessed against the MVL from a random distribution (random uniform distribution of phase-angles) by means of 1000 permutation tests. A p-value lower than .05 was considered statistically significant. For illustrative purposes, we also calculated participant-, channel- and sequence-level 'relative phase angles': these were expressed as the absolute phase difference between phase-angles for each channel and tone position (e.g., 3rd to 8th) and the most common phase-angle in the sequence. The most common phase-angle was

identified by means of the 'histogram' function in MATLAB, using 'probability' as parameter after rounding phase values to 1 decimal. This means, a probability value is attached to each of the phase-angles within a single-participant, -channel, and -sequence, and across a tone positions (3rd to 8th). Next, the phase value with the highest probability (i.e., the most common) was used as a reference to calculate the 'relative phase-angles'. Thus, we computed the absolute phase difference between each of the phase-angles and the most common phase value.

Examples of participant- and sequence-level relative phase-angles are plotted in Fig. 2C, and the pooling over participants, sequences, and channels is provided in Fig. 2D.

ERP and TFR data

After ICA, data were segmented into 4s-long epochs symmetrically time-locked to every tone onset. Next, we employed an automatic channel-by-channel, trial- and participant-level artifact suppression procedure (comparable to Kaneshiro et al., 2020). Artifact suppression focused on time-windows ranging from -.4 to .4s relative to each stimulus onset. Amplitude values were temporarily normalized by their standard deviation across trials and outliers (data points per epoch and channel) were defined by means of a threshold criterion (values > mean + 4*SD). The identified noisy time-windows (with 50ms symmetrical padding) were then filled with NaNs, and these missing values were replaced by means of cubic temporal interpolation (*'pchip'* option for both the built-in Matlab and FieldTrip-based interpolation functions) considering the time-course of neighboring time-windows (extending up to 100ms when possible, automatically reduced otherwise). The current approach is a novel data-driven procedure developed to minimize the data loss. It differed from (Kaneshiro et al., 2020) insofar as the channel-by-channel routine allowed the algorithm to flexibly adapt the outlier threshold estimates to the inherent noise varying over channels. Descriptive analyses revealed that the artifact suppression procedure was used for 5% of trials on average, on time-windows 100ms long, and most likely between 350-400ms after stimulus. Critically, this strategy allowed keeping all trials instead of rejecting entire epochs only partially contaminated by artifacts (i.e., as it usually happens in the typical standard artifact rejection procedure) (Kaneshiro et al., 2020).

Next, a standard whole-trial rejection procedure based on an amplitude criterion (85uV) was applied. Data were then segmented for event-related-potential (ERP) analyses ("ERP data"), including 500ms prior and following each tone onset (1s in total). Data for the time-frequency

representation analyses ("TFR data") were not further segmented at this stage. ERP data were band-pass filtered between 1-30Hz, while TFR data were low-pass filtered at 40Hz. Data were downsampled to 250Hz.

Single-trial TFR data underwent time-frequency transformation by means of a wavelet-transform (Cohen, 2014) with a frequency resolution of .25Hz. The number of fitted cycles ranged from 3 for the low frequencies (<5Hz) to 10 for high frequencies (>5Hz and up to 40Hz). The single-trial approach results in 'induced' (as compared to 'evoked') responses. TFR data were then re-segmented to reduce the total length to 2s, symmetric around tone onsets.

Mean correction of ERP and TFR data

Single-trial ERP amplitudes were mean-corrected by a global average over all epochs and computed in a time-window ranging from -0.2 to 0.3s relative to tone onset. Similarly, single-trial TFR power was normalized by computing relative percent change with reference to the global mean power across epochs (-0.2 to 0.3s relative to tone onset). This previously applied approach (Abbasi & Gross, 2020; Fujioka et al., 2012) was preferred over classical baseline correction because we aimed at analyzing power fluctuations in pre-stimulus intervals. Finally, we calculated a fronto-central channel cluster average (using the same channels as for the rhythm tracking analyses). All subsequent analyses were performed exclusively on this channel cluster.

ERP analyses

Evoked responses over trials were averaged separately for STD and DEV tones and for odd (hypothetical "Strong" position in a binary accentuation pattern; S, Fig. 3A, left) and even ("weak"; w) positions from the 3rd to the 11th tone. The first STD tones were disregarded to exclude the increased responses typically observed at the beginning of an auditory sequence. Fig. 3A shows the respective ERPs for the averaged fronto-central cluster, for STD tones in hypothetical strong and weak positions (left) and for the comparison of STD and DEV tones averaged over these positions (right). Statistical analysis was performed by means of paired-sample t-tests over a time-window ranging from 0 to 350ms relative to tone onset. An FDR-adjusted p-value lower than .05 was considered statistically significant (Benjamini & Hochberg correction).

TFR analyses

Time–frequency representations were averaged over STD trials, separately for odd and even positions (hypothetical strong and weak positions, respectively; Fig. 3B). Mean amplitudes in the low-beta band (low-β; 12-20Hz; Biau & Kotz, 2018) were then statistically compared for S-w positions by means of paired-sample t-tests over a time-window ranging from 0 to 350ms relative to tone onsets. An FDR-adjusted p-value lower than .05 was considered statistically significant (Benjamini & Hochberg correction).

Individual classification of accentuations

An individual modelling approach was adopted to identify binary and ternary accentuation patterns. Similar to earlier studies on predictive timing, (Fujioka et al., 2012; Fujioka et al., 2015), we focused on single-participant's low-β mean power peaks for STD tones in the first eight positions of the equitone sequence. Tone-level mean power peaks were calculated as follows: we first located the power peaks in time-windows centered at 100ms post-stimulus (resulting peaks from analyses in Fig. 3C) and extending 60ms (proportional to the center frequency of interest; for low-β: 1/16Hz = 60ms), prior and after each peak. Next, the resulting peak latencies were used to create a second time-window of interest centered around the individual peaks and extending 60ms before and after it. Thus, tone-level mean power peaks were calculated within these 120ms-long time-windows following the stimulus onset (from now on, β-post).

Single-tone β-post were first concatenated to mimic an 8-tone sequence (i.e., a trial). Single-participant and trial-level β-post (eight tones) were then entered into a stepwise regression model (Fig. 4A) (‘*stepwiselm*’ in Matlab) with three predictors: a binary (values: 1, -1), a ternary (1, -.5, -.5), and a constant term (ones). The stepwise regression function searches for the predictor or a combination of predictors that maximizes the fit of the model to the real data. The model thus allows the combination of multiple predictors, but no interactions between terms. Once all combinations are tested, the winning model is chosen based on the estimated adjusted eta squared. Trials for which the winning model involved the binary predictor were labeled “binary”, trials for which the winning model involved the ternary predictor were labeled “ternary”. Accordingly, we interpreted (and labeled) the combination of binary and ternary terms as “combined”. The remaining trials in which neither binary nor ternary predictors were included in the winning model, were labeled as “not classified”. Participant-level model results are provided in Suppl. Table 2 as “Preferences for accents” and expressed as the percentage of trials relative to the total number of auditory sequences (192

per participant). The subject-level goodness of fit of the model is provided in the same table. The "Preferences for accentuations" across participants are provided in Fig. 4B and expressed as the percentage of trials relative to the total number of auditory sequences (192 per participant).

Binary accents analyses

Further confirmatory analyses were performed to verify if the successfully identified "binary" trials indeed showed binary-like accentuation patterns. If so, neural responses to tones falling on odd-numbered positions should differ from those on even-numbered positions. However, there should be no differences for neural responses on the same positions: namely, tones falling on odd-numbered positions should elicit similar (i.e., non-significantly different) neural activity.

To verify if this was the case, we first vertically concatenated trials classified as "binary", and then computed a trial-based single-tone pair-wise low-beta mean peak amplitude difference (corresponding lower-triangle 2-D means are provided in Fig. 4D), i.e., amplitude differences between responses to each tone in the sequence (1-8 positions). For example, the response amplitude for the 1st position was compared to the 2nd position, then to the 3rd, and so forth. In turn, the amplitude for the 2nd position was compared to the 3rd, the 4th etc. The resulting pair-wise amplitude difference matrix had a size of N trials x N positions-1 x N positions-1. From this matrix, we statistically compared the pair-wise amplitude difference for tones in odd-positions (Fig. 4E; "odd-pos difference") and even-positions ("even-pos difference") by means of 1000 permutations of odd-even labels. An FDR-adjusted p-value lower than .05 was considered statistically significant (Benjamini & Hochberg correction). The two variables were then combined into a distribution of "binary similarity". The binary similarity combines the amplitude difference for tones in odd-numbered positions (1-3-5-7th) and the amplitude difference for tones on even-numbered positions (2-4-6-8th). Binary similarity was statistically compared to "binary dissimilarity", which was calculated as the mean difference of tones in odd versus even positions (Fig. 4E). Statistical testing was performed using 1000 permutations of odd-even labels, and an FDR-adjusted p-value lower than .05 was considered statistically significant (Benjamini & Hochberg correction).

DEV analyses as a function of binary accents

For each participant, we isolated binary trials identified with the described "individual classification of accents" procedure and explored the relation between accentuations and DEV processing to explore whether ERP responses differed according to their accents (S-w). Statistical analyses compared ERPs to DEV tones in even- (8,10th) versus odd-numbered (9,11th) positions (Fig. 4F). Notably, we considered possible "pure binary" and "phase-shifted binary" accents (or inverse binary), where the former corresponds to the typical S-w pattern in odd and even positions, and the second to the reverse w-S pattern. Indeed, individuals may start accentuating at different times along the auditory sequences, and hypothetical S-w positions may likely fall on either odd or even positions. The selection was informed by the beta coefficients associated with the identified binary trials: a positive coefficient would indicate "pure binary" (S-w), while a negative coefficient would correspond to the "inverse binary" (w-S). The distribution of "pure" and "inverse" binary is provided at the bottom left of Fig. 4B, expressed as percent of trials relative to the total number of auditory sequences (192 per participant).

Next, we re-ordered accented S-w positions according to individual binary processing (odd-numbered positions falling on S accents in "pure binary" but on w in "inverse binary"), and statistically compared their associated ERPs time-courses (Fig. 4F). Statistical testing was performed by means of paired-sample t-tests, and an FDR-adjusted p-value lower than .05 was considered as statistically significant (Benjamini & Hochberg correction).

DEV analyses in ternary and non-classified trials

We also tested whether a similar S-w effect would be observed for DEV processing in 'non-classified' trials. ERP responses for DEV tones falling on accented S (odd-numbered positions) and w (even-numbered) positions were pooled and statistically compared by means of paired-sample t-tests. An FDR-adjusted p-value lower than .05 was considered statistically significant.

Next, we focused on potential "ternary" trials. In this case, the accent can either fall on the first (S-w-w), second (w-S-w), or third (w-w-S) position. To disentangle these three accentuation patterns from the distribution of "ternary" trials, we ran a second stepwise regression model. The model featured three predictors to include the possible accentuation types: 1,-.5,-.5 (pattern 1), -.5,1,-.5 (pattern 2) and -.5,-.5,1 (pattern 3). Again, the model did not allow interaction terms and the winning model was chosen based on adjusted eta squared. The output of the model is provided in Fig. 4B (bottom right), as the percentage distribution

of three accentuation patterns across participants. Importantly, other accentuation patterns are possible as a S-w-w pattern could be represented by a stair-case amplitude change (e.g., 1, -.75, -.25) or a shuffled version (e.g., 1, -.25, -.75). Considering that binary accentuations are usually prevalent (Abecasis et al., 2005; Baath, 2015; Poudrier, 2020), possibly due to a cognitive bias structuring tonal sequences into groups of two (Polak et al., 2018; Savage et al., 2015), and that the employed stimulation rate may preferentially induce binary rather than ternary accentuations (Baath, 2015; Poudrier, 2020), even when tapping to polyrhythms (Møller et al., 2021), we did not build other models to test all possible ternary accentuations, or any other accentuation patterns. Of note is also that the employed model only used the first eight tones of the equitone sequence. This avoids the onset of DEV tones in later positions, which may disrupt ongoing accentuation, but inevitably leaves only up to two periods of a ternary accent (as compared to four repetitions of a binary accent). Consequently, even two small amplitude fluctuations with superimposed noise (inherent in EEG recordings) may drive the 'ternary' classification, but these trials may not necessarily reflect a true ternary accentuation. Accordingly, we accepted that a portion of 'ternary' trials might not be classified with the 1,-.5,-.5, -.5,1,-.5 and -.5,-.5,1 pattern.

Data and code Availability

The analysis code and the data in use here will be stored in an open repository and can be provided upon reasonable request by the corresponding author.

Results

Behavioral Data

We tested whether the counting of deviant tones (DEV) differed for deviants in odd or even positions in the equitone sequence. The respective ANOVA with deviant position (odd vs. even) and sequence order as a covariate did not reveal a significant effect of deviant position ($F(1,71) = 1.115$, $p = .295$, *eta-square* = 0.16) nor a significant effect of sequence order ($F(1,69) = .02$, $p = .97$, *eta-square* = 0). This indicates that DEV counting performance did not differ in the equitone sequence.

Rhythm tracking

Participants listened to equitone sequences presented at a stimulation rate of 1.54Hz, and we tested *whether* and *how* their neural activity would show idiosyncratic signatures of rhythm tracking. When individuals listen to these sequences, their neural activity reflects the timing of external events (Fig.2A-B). Indeed, ITPC analyses and the normalized power of the Fourier spectrum both showed a clear peak at the stimulation frequency (1.54Hz; Fig. 2A), and the time-course of delta-band neural activity showed a tendency to align to tone onsets (Fig. 2B; this plot is for illustration purposes only). To quantify the consistency of anticipatory phase alignment to the expected tone onsets, we tested the phase consistency of delta-band (1.54Hz) neural activity in a time-window preceding tones onset. Phase-locking analyses focused on the ~60ms (proportional to the stimulation frequency: 1/1.54Hz/10) prior to tone onsets. Single-participant trial-level mean vector lengths (MVL) of STD tones preceding a DEV (pre-DEV) revealed a consistent phase-relationship with STD onsets: the MVL significantly differed from a random distribution (Fig. 2D, bottom; pre-DEV in blue; Suppl. Tab. 1 for statistical results). However, we observed intra- and inter-individual differences: participants' delta-band activity did not always synchronize to tone onsets with the same phase relationship (Fig. 2C). Rather, a broad range of possible phase-lags was observed across trials, both at the level of single-participants (Fig. 2C right) as well as when pooling values across participants (Fig. 2D top-left). The distribution of single-participant phase-angles across trials accordingly did not differ from a random distribution (Suppl. Tab. 1). Phase-angles were consistent within a trial (MVL statistics in Fig. 2D bottom and Suppl. Tab. 1) but differed across trials. To further explore this variability, we computed a measure of 'relative phase'. This was calculated, at the single-participant, channel- and sequence-level as the absolute difference from each phase-angle within one sequence and the most common phase. The distribution of relative phase-angles across trials and participants shows variance which mostly ranges between 0-30 degrees (Fig. 2D, right), supporting the MVL calculation. Thus, individuals show a predictive and consistent phase-alignment of delta-band activity to expected tone onsets. However, the specific phase for this alignment is variable across trials.

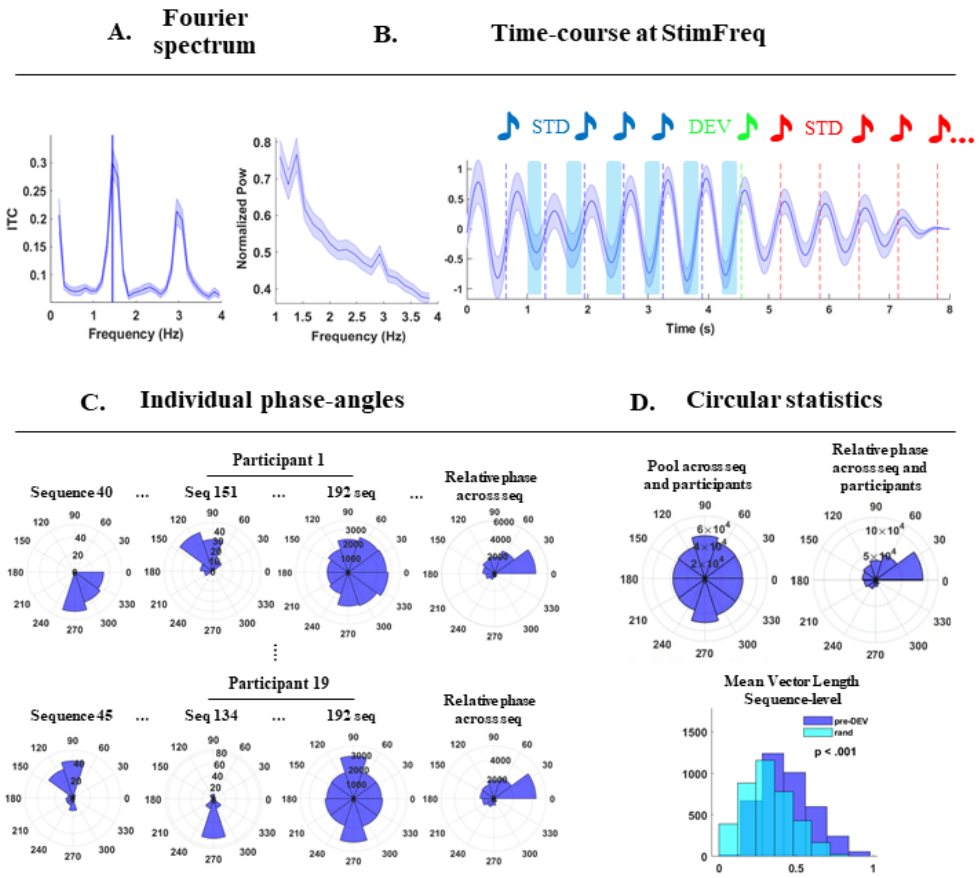


Figure 2 - Rhythm tracking analyses

A: Fourier spectrum of neural activity along the entire equitone sequence. The plots display, in order, the inter-trial phase coherence (ITC; left) and the grand-average normalized power (right) in the frequency range from 1 to 4Hz. The vertical line highlights the peak of phase coherence at the stimulation frequency (1.54Hz). B: time-course of neural activity at the stimulation frequency. Vertical bars indicate the onsets of STD tones prior- (blue) and post-DEV (red). The DEV onset is reported in green. Blue shades represent the standard errors. Light-blue rectangles indicate the focus on the pre-stimulus intervals (not scaled). C: Polar histograms for single-participant and sequence-level phase angles extracted from 60ms prior to the onsets of STD tones prior (blue) to the DEV from the fronto-central cluster of interest. Here, we report a few sequence-level phase-angles from Participant 1 (top) and Participant 19 (bottom). On the right, the polar histograms report the distribution of phase-angles across all trials (192 per participant) and the 'relative phase' across sequences. This is a measure of deviation from the most common phase-angle, at the sequence-level. D. Group-level phase-angles are randomly distributed around the polar histogram. On its right, the group-level 'relative phase'. These phase-angles indicate a variation from the most common phase-angle. At the bottom, the distribution of mean vector length (MVL) calculated at the single-participant and sequence-level and averaged across the fronto-central cluster of interest. Importantly, these MVLs are based on the raw phase-angles for pre-DEV (blue) and are statistically compared to the MVL for random distribution of phase-angles. Single-participant statistics are reported in Suppl. Tab. 1.

Analyses on Accentuations

We tested whether participants' neural activity would sample the acoustic environment by superimposing binary accentuation patterns (S-w accents in odd-numbered versus even-numbered positions) onto the equitone sequences. We analyzed event-related responses (ERP) to STD tones in S and w positions, and further inspected the time-frequency representation of time-locked responses.

ERPs to STD tones in S-w positions did not statistically differ (Fig. 3A). However, DEV tones elicited stronger N100 responses compared to STD tones (FDR-adjusted $p < .05$; Fig. 3A, right), confirming the processing of an unpredicted deviant tone.

The time-frequency representation plots of neural activity in response to STD tones mainly showed two event-locked responses (Fig. 3B): one in the theta (4-8Hz) and one in the low-beta (low-β; 12-20Hz) frequency-band. Following our hypotheses and informed by previous work (Fujioka et al., 2012; Fujioka et al., 2015), we focused on the time-course of activity in the low-β range and compared event-locked power fluctuations for STD tones on odd (S) to even (w) numbered positions along the sequence (Fig. 3C), corresponding to hypothetical S-w binary accents (blue and red, respectively). We statistically compared the time-courses of low-β activity (Fig. 3C) for STD tones in hypothetical S-w positions. The comparison did not survive FDR correction for multiple comparisons. Both FDR-adjusted *p*-values and non-adjusted *p* are provided in Fig. 3C (in black and red, respectively).

In summary, neither ERP nor TFR analyses revealed a binary accent, as STD tones elicited similar responses when they occurred in odd- and even-numbered positions in the auditory sequence. Similarly, ERPs to DEV in odd- and even-numbered positions did not statistically differ (Suppl. Fig. 1, bottom). These observations seemingly contradict original findings (Brochard et al., 2003), but might result from a different experimental setup and processing pipeline. For instance, the choice of region and time-windows of interest for statistical analyses differ from the original study.

To better characterize the phenomenon of *subjective accentuation*, we decided to zoom into inter- and intra-individual differences in *when* and *how* accentuation patterns are superimposed onto the auditory sequences. Indeed, not only may individuals start to accentuate at different points along the sequence (i.e., not necessarily at the beginning), they

may also do so differently over time (e.g., binary or ternary accents), or even not accentuate at all (Brochard et al., 2003). These alternatives were tested with a novel modelling approach.

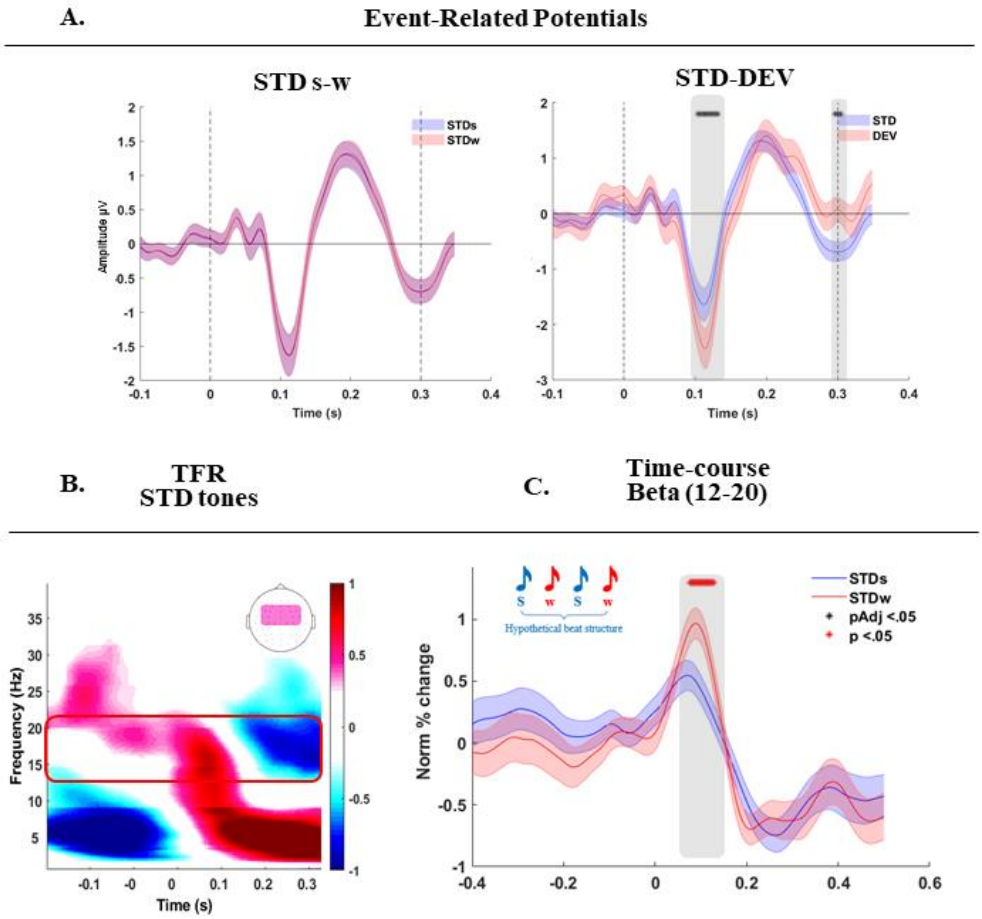


Figure 3 - Binary accents on hypothetical S-w positions.

A: On the left, ERP responses for STD tones in S (blue) w (red) positions. On the right, ERP responses for STD (blue) and DEV tones. Stars indicate significant time-windows, as assessed by means of paired-sample t-tests (FDR-adjusted p <.05). B: grand-average time-frequency spectrum time-locked to STD tones (-.2 to .35s). The frequency range spans from 1-to-40 Hz with a frequency resolution of .25Hz. The red rectangle highlights evoked responses in the low-beta (12-20Hz) frequency range, on which we performed statistical comparisons in C. The topographic plot on top displays the FC cluster average in use. C: extracted time-course of low-beta activity in hypothetical S-w positions, time-locked to STD tones onsets, in blue for odd-numbered positions (Strong) and red for even-numbered positions (weak). Shaded colors report standard errors. On top, a grey rectangle delineates the time-window in which statistical testing without multiple-comparison correction showed a difference between S and w positions. The comparison, however, did not survive FDR correction.

Modelling of individual accentuations

To address the questions of (i) whether everyone accentuates in a consistent way, (ii) whether everyone always accentuates in the first place, and (iii) whether accentuation patterns influence DEV processing (Brochard et al., 2003), we focused on trial-level data and modelled various accentuation patterns. We used a trial-based stepwise regression model to classify participant-level single-trial beta-band neural responses as best reflecting clear binary and ternary accents, or the absence of a corresponding accentuation. The choice to focus on beta-band activity was informed by previous evidence (Fujioka et al., 2012; Fujioka et al., 2015). The model predicted tone-by-tone low-β-post peak power from three predictors: binary, ternary, and constant (no accents) terms (Fig. 3A). Resulting 'preferences for accentuations' and goodness of fit are reported in Suppl. Table 2 and summarized in Fig. 4B. Note that most trials (~60%) did not clearly reflect either binary or ternary accents. In the absence of perceptual reports, it remains open whether participants did not perceive accentuations, or whether the current analyses are not sensitive enough to detect imagined accentuations at the level of neural activity.

Next, we zoomed into "binary trials", and distinguished S-w from w-S accentuation patterns based on the single-trial β-coefficients from the accent modelling (see methods). The resulting distributions are reported in Fig. 4B, bottom left. Similarly, we disentangled three possible accentuation patterns in the "ternary trials". We performed a separate stepwise regression model using S-w-w, w-S-w, and w-w-S accents as predictors (see methods). Distributions of these accents are reported in Fig. 4B, bottom right. Note that a large proportion of "ternary trials" did not further adhere to one of the ternary accentuation patterns specified as predictors. This approach allowed showing that, on a portion of trials, individuals spontaneously superimpose accentuation patterns on identical tones embedded in an isochronous equitone sequence. Importantly, the results confirm that the same participants also switched between binary, ternary, and other accentuation patterns over trials. However, in the majority of trials no consistent accentuation pattern was confirmed.

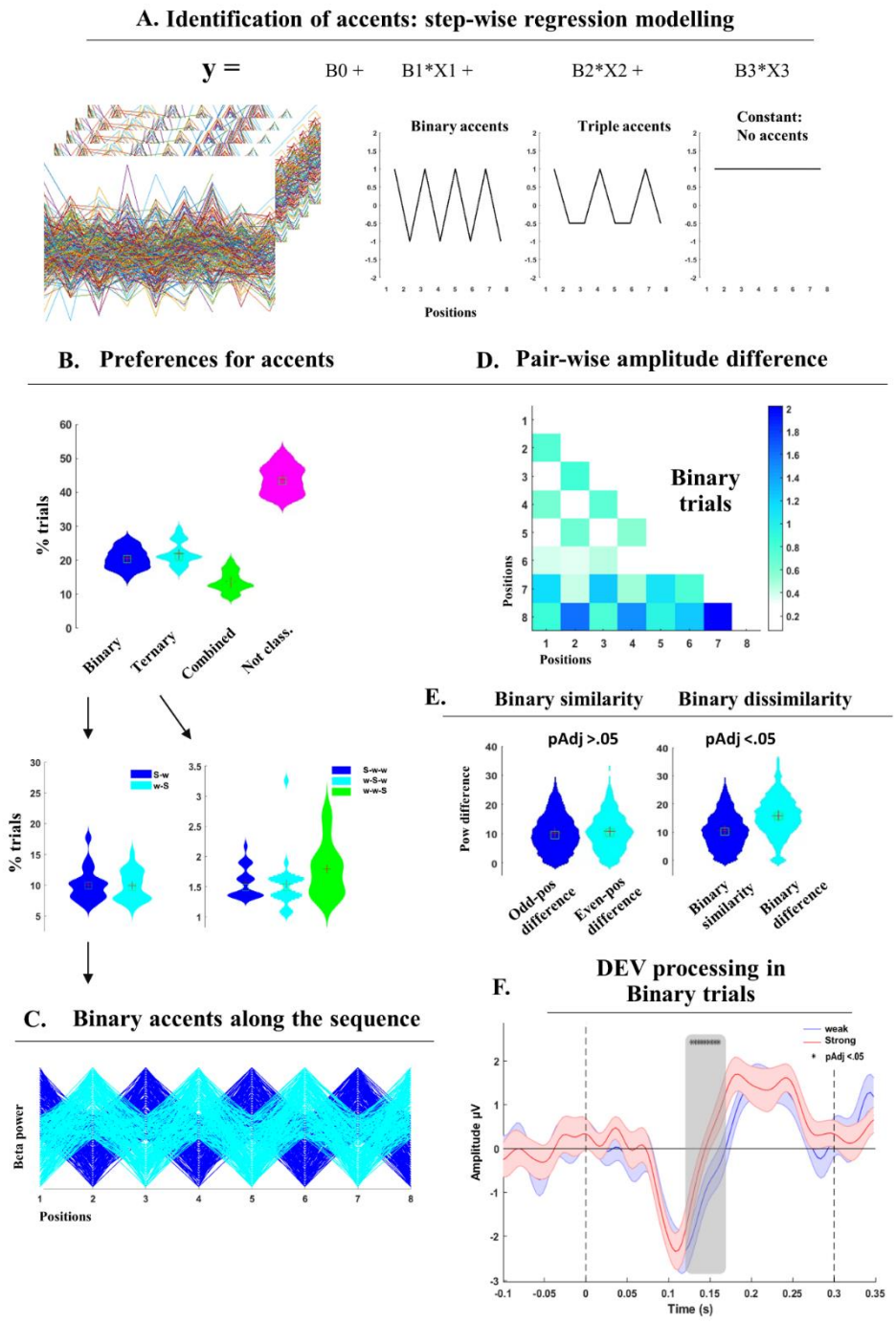


Figure 4 - Individual classification of accents and analyses on binary accents.

A: We modelled potential accentuation patterns by means of stepwise regression modelling and using low-beta post-stimulus responses as a dependent variable. The predictors were a binary (1, -1), a triple (1, -.5, -.5) and a constant term (ones). B: preferences for

accents, as reported from the modelling. In order, we plot the distribution of trials assigned to binary, ternary, combined (binary-ternary) accents, and 'not classified' (neither binary nor ternary) across participants. At the bottom, we zoom into binary trials and distinguish S-w accents from w-S accents based on trial-level Beta coefficients from the modelling. Similarly, on its right side, the distribution of ternary trials showing S-w-w, w-S-w, and w-w-S accentuation patterns. To extract these three accentuation patterns, we performed separate stepwise regression modelling as explained in the method section. C: Exemplar S-w and w-S accent fluctuations expected along 8 positions of the auditory sequence in the 'binary' trials. Blue for S-w; cyan for w-S sequences. This plot has illustration purposes only. D: grand-average pair-wise difference for low-beta peaks across the first 8 positions of the auditory sequence in binary trials. E: on the left, the distribution of amplitude differences across odd-numbered positions (in blue) and even-numbered positions (cyan). The average of these two distributions forms the 'Binary similarity'. On the right, the 'binary similarity' (blue) and the mean amplitude difference of odd- versus even-numbered position ('binary dissimilarity'; in cyan). Statistical testing was performed by means of thousand permutation testing, and an FDR-adjusted $p < .05$ was considered as statistically significant. F: ERPs to DEV tones on S-w positions in the binary trials. Statistical testing reported a significant difference in the time-window between ~120-170ms post-stimulus, as highlighted by the grey shades. ERPs to DEV tones in non-binary trials did not differ on S-w positions; see Suppl. Fig. 1.

Binary accents

Once we isolated, at the single-participant level, trials showing binary accentuation patterns, we aimed at statistically testing whether low-β responses would significantly differ in S versus w positions. Thus, we tested whether the modelling approach delivers a meaningful classification of binary accentuation.

We isolated the identified 'binary' accent trials and calculated the tone-by-tone pair-wise difference for low-β across eight positions in the acoustic sequence and preceding the DEV tone. For visualization purposes, the resulting matrix was averaged across trials and the upper symmetrical triangle was masked (Fig.4D). The original matrix (all trials) was used to calculate metrics of "Binary similarity" and "Binary dissimilarity" (Fig.4E; see 'Binary accents analyses' in the methods). The Binary similarity features the distributions of amplitude differences on odd- and even-numbered positions. For the "Binary dissimilarity" analyses we calculated the amplitude difference for tones on odd- versus even-numbered positions (corresponding to accented versus non-accented; thus labeled "Binary difference") and statistically compared it to the Binary similarity (right-side plot in Fig.4E). Statistical testing yielded a significant difference (FDR-adjusted $p < .05$). Analyses confirmed that the trials classified as 'binary' in the modelling, do indeed show a consistent binary accentuation pattern. Hence, the low-β amplitudes in STD tones in S positions significantly differ from those in w positions. To further verify the validity of the accent modelling approach, we tested whether identified 'preferences for accents' modulate DEV processing.

DEV processing based on binary accents

We investigated whether DEV processing is modulated by binary accents in 'binary' trials. Thus, we tested whether ERPs to DEV tones falling on S-w positions in the successfully identified "binary" trials would be statistically different. First, we isolated the identified binary trials and discerned 'pure binary' from 'inverse binary' trials based on the beta-coefficient resulting from the regression modelling (see methods). Next, we pooled trials belonging to the same accent (S or w) and statistically compared ERPs to DEV on S-w positions based on the identified accentuation patterns, and thus irrespectively of the sequence position (odd-numbered (9,11th positions) or even-numbered (8,10th)). Within-participant statistical comparison of the respective ERPs yielded significant difference in the time-window between 120-170ms (*p FDR adjusted <.05*; Fig. 4F).

Similarly, we tested whether the same S-w effect would be observed for those trials in which no accentuation pattern could be identified ('non-classified' trials). In these non-classified trials, DEV processing was not modulated by binary accentuation patterns (*p FDR adjusted >.05*; Suppl. Fig. 1). Similarly, DEV processing was not modulated by binary accentuations when pooling all trials (binary, ternary, and non-classified; Suppl. Fig. 1).

Lastly, exploratory analyses focused on the 'ternary' trials and modelled three possible accentuation patterns: S-w-w, w-S-w, w-w-S (Fig. 4b). However, only a small percentage of trials was assigned to these accentuation types (~2% per pattern). This likely reflects that a range of other ternary accents are possible (e.g., 1, -.75, -.25; or 1, -.25, -.75), along with their potential combinations, which were not further modelled here.

In summary, we here show that DEV processing is modulated by binary accents, but exclusively in those trials identified as 'binary' during the accent modelling. This observation supports the modelling procedure as a viable method for identification of trial- and individual-level variability in temporal processing.

Discussion

The current study aimed at exploring individual neurophysiological variability in rhythm processing. More specifically, we first examined how delta-band neural activity would track auditory rhythms. Hence, we quantified the sequence-level consistency of phase-alignment

towards expected tone onsets. Next, we tested whether neural activity in the low-beta band (12-20Hz) would reflect the superimposition of binary accentuation patterns, previously described by the "tick-tock" clock phenomenon (Brochard et al., 2003). Accentuations may reflect a neural mechanism which rhythmically and dynamically samples the environment in subunits, resembling the superimposition of a basic beat (strong–weak alternation).

When listening to equitone sequences, participants' neural activity tracked the timing of external events (Fig.2A), aligning delta-band oscillatory dynamics to expected tone onsets (Fig.2) (Buzsáki, 2009; Schroeder & Lakatos, 2009; Thut et al., 2012b; Zoefel & VanRullen, 2016). Hence, sequence-level mean vector lengths of delta-band activity preceding tone onsets displayed anticipatory coupling of brain activity to the timing of environmental stimuli. This finding further confirms theoretical views according to which the brain might generate temporal predictions to achieve successful rhythm tracking to optimize sensory processing, perception, and allocation of attention (Friston, 2005; Arnal, 2012; Schröger et al., 2015; Koelsch et al., 2019).

Notably, when pooling phase-angles across sequences either at the single-participant or group-level, we observed random phase distributions. In other words, delta-band neural activity did not always align its high-excitability phase to the expected onset of auditory tones. Rather, we observed a wide range of possible synchronization regimes, which show consistency at the sequence-level, but high variability across sequences and participants. These findings may suggest that rhythm tracking does not necessarily rely on a specific phase-alignment (high-excitability phase) with environmental stimuli to optimize stimulus processing. Rather, our data showed that neural tracking may be supported by an adaptive phase-alignment, that can vary over time and across individuals, while keeping consistency at the trial-level. However, task and attention manipulations may modulate the observed trial-level variability.

Next to rhythm tracking, we investigated the neural signatures associated with the human disposition to accentuate tones when listening to equitone sequences (Brochard et al., 2003). This spontaneous phenomenon typically induces binary (strong-weak (S-w); Brochard et al., 2003) accents, but other accentuation patterns such as ternary ones (S-w-w) are possible (Abecasis et al., 2005; Baath, 2015; Brochard et al., 2003; Fujioka et al., 2012; Fujioka et al., 2015; Poudrier, 2020). Importantly, while tones are physically identical, these superimposed accents influence observable behavior and underlying neural activity (Nozaradan et al., 2011, 2016, 2017; Schmidt-Kassow et al., 2011). However, sparse behavioral and neuroimaging

research has looked at individual differences (Jessica A. Grahn & Brett, 2007; Jessica A. Grahn & McAuley, 2009) and mainly tested task-based beat processing (e.g., Fujioka et al., 2015). Thus, the question remains whether participants naturally accentuate in the absence of specific task instructions, and if they do so in a consistent manner over time. To address these questions, we focused on participant-level neurophysiological variability and modelled single-trial beta-band activity (Fig.4A) to probe whether we could observe binary or ternary accentuation patterns. Neural activity in the beta range has been associated with rhythm (Arnal, 2012; Biau & Kotz, 2018; Fujioka et al., 2012; Fujioka et al., 2015; Morillon et al., 2016) and beat processing (Fujioka et al., 2012; Fujioka et al., 2010). The current findings confirm its prevalence in time-locked responses to STD tones (Fig.3B). Furthermore, beta-band activity showed an individuals' spontaneous disposition to superimpose accentuation patterns, even when not instructed to do so (Fig.4). Hence, we characterized inter- and within-participant differences in adopting binary and ternary accents over time (Fig. 4B and Suppl. Tab. 2). These accentuations might reflect the automatic predisposition to sample continuous auditory input streams into predictable, coherent, and finite units. This might reflect fluctuations of attentional resources over time (Bolton, 1984; Mari R. Jones, 1976; Schroeder & Lakatos, 2009) (rather than being equally distributed over time), and variations within each attentional cycle so to attribute salience to accentuated events. We tested this view by particularly focusing on binary accents (Fig. 4C-F) and showed that neural responses in the beta-band for tones falling on odd-numbered ('strong' ('S')) positions were significantly greater from those in even-numbered positions ('weak' ('w'); Fig. 4E, F) on a selection of trials. This suggests that individuals spontaneously superimpose binary accents (S-w) while listening to equitone sequences to parse and segment continuous sensory streams, potentially allocating attentional resources to salient sensory events and to optimize perception (Nobre & Van Ede, 2018; Shalev et al., 2019). However, most trials (~60%) did not reflect either binary or ternary accents (both approximately in 20% of trials, Fig. 4B). This observation may result for at least four reasons: (i) individuals do not always accentuate, when not instructed to do so; (ii) individuals do accentuate, but switch between accentuation patterns over time; (iii) the applied method or the data per se are not sensitive enough to pick up spontaneous and varied accentuations; (iv) the employed stimulation rate may be suboptimal to induce different accentuation patterns such as ternary and longer patterns (Baath, 2015; Poudrier, 2020). Indeed, prior studies on predictive timing and beta-band actvity relied on source-reconstructed neural MEG data (Fujioka et al., 2012, 2015), thus probably benefitted from a higher signal-to-noise ratio than the current study. Furthermore, although it is known cognitive bias might

induce the structuring of tonal sequences into groups of two (Polak et al., 2018; Savage et al., 2015) rather than other groupings, other studies have shown a link between stimulation rates and preferred accentuation patterns (Baath, 2015; Poudrier, 2020). Accordingly, inter-stimulus intervals between 500-900ms should preferentially induce a binary accent (and its double, i.e., accents over groups of four tones), while ternary and other accentuations are possible, although less common, at this and slower rates.

In the absence of perceptual reports, we cannot preclude these options. However, we show positive evidence that in a portion of trials participants display clear binary and ternary accentuation patterns independent of behavioral reporting or finger or foot tapping. These results support the notion that humans sample the environment in an individual, dynamic manner (Large & Jones, 1999).

We note that classifying trials based on beta fluctuations, followed by testing beta time-locked responses over sequence positions might be circular, but is confirmatory. Thus, we compared neural responses to unpredicted (deviant) tones falling on S-w positions in the classified binary trials and found a significant effect in ERP responses to DEV tones (Fig. 4F). Notably, the modulation of DEV processing was absent in those trials which did not adhere to a specific accentuation pattern (non-classified trials; Suppl. Fig. 1). These observations parallel earlier findings (Brochard et al., 2003; Jongsma et al., 2004; Schmidt-Kassow et al., 2011) and indicate that accentuations might affect how we allocate attention to the auditory environment. However, further investigations are needed to clarify this intricate link between attention deployment, attentional shifts, and temporal processing in listening contexts. Thus, future studies could further dive in the frequency-specificity of such effects and complement neural data with perceptual reports.

In summary, we characterize individual neurophysiological signatures of temporal processing, and associate them with specific delta-band phase-coupling mechanisms and with beta-band dynamics, respectively. The findings showcase the feasibility of using EEG to identify individual neurophysiological signatures of temporal processing, suggesting that common trial- and group-level averaging approaches might inevitably obscure inter-individual differences and trial-by-trial variability. In contrast, the approach adopted here allows the monitoring of neurophysiological variability underlying *flexible but consistent mechanisms* for evaluating and adapting to (un)predictable environmental stimuli. Consequently, we propose that zooming into individual variability might allow to better predict behavioral

variability in processing simple and complex environmental rhythms (e.g., speech tracking; (Kandylaki & Criscuolo, 2021)) in neurotypical and pathological populations (Schwartze et al., 2015, 2016a).

Conclusions

When listening to isochronous equitone sequences, humans' neural activity tends to spontaneously align and track the timing of auditory events. A novel trial-level modelling approach additionally confirms that individuals tend to superimpose accentuation patterns onto isochronous equitone sequences, indicating active sampling of the acoustic environment and (potentially) differential allocation of cognitive resources. We explored inter-individual and trial-level neurophysiological variability in temporal processing and auditory accentuation, and reveal flexible, time-varying neural mechanisms involved in effective evaluation and adaptation to environment rhythms. The combined findings highlight that an individualized analysis approach to neurophysiological data can indicate meaningful variation in a listening context and should be considered in a more differentiated account of the role of temporal dynamics in audition.

Declaration of interest

The authors declare no competing interest.

Supplementary materials

	Phase-angles Pre-DEV Vs Random			***Phase-angles Pre-DEV Vs post-DEV***			***MVL Pre-DEV Vs Random***		
	P vals	**Obs Diff**	**Eff Size**	**P vals**	**Obs Diff**	**Eff Size**	**P vals**	**Obs Diff**	**Eff Size**
Subj1	0.233	1.733	1.277	0.057	-2.715	-2.039	0.001	0.145	0.726
Subj2	0.689	0.719	0.520	0.906	0.073	0.056	0.001	0.121	0.654
Subj3	0.505	0.917	0.671	0.336	0.694	0.523	0.001	0.110	0.593
Subj4	0.461	-0.727	-0.539	0.755	0.160	0.121	0.001	0.156	0.834
Subj5	0.261	-1.629	-1.195	0.740	-0.176	-0.136	0.001	0.197	1.099
Subj6	0.479	0.598	0.446	0.692	0.169	0.132	0.001	0.138	0.729
Subj7	0.805	0.230	0.171	0.859	-0.089	-0.068	0.001	0.085	0.469
Subj8	0.662	-1.060	-0.758	0.069	-2.956	-2.141	0.001	0.096	0.479
Subj9	0.358	1.818	1.315	0.149	2.448	1.776	0.001	0.113	0.607
Subj10	0.606	-0.756	-0.551	0.719	-0.259	-0.196	0.001	0.109	0.616
Subj11	0.802	-0.360	-0.262	0.919	-0.100	-0.075	0.001	0.124	0.655
Subj12	0.656	0.800	0.581	0.953	0.069	0.051	0.001	0.115	0.646
Subj13	0.057	2.993	2.170	0.059	2.962	2.151	0.001	0.089	0.474
Subj14	0.094	2.838	2.048	0.146	2.633	1.900	0.001	0.141	0.721
Subj15	0.093	-2.489	-1.836	0.582	0.236	0.186	0.001	0.107	0.556
Subj16	0.123	-2.647	-1.911	0.905	0.155	0.112	0.001	0.135	0.704
Subj17	0.583	-1.229	-0.881	0.973	0.056	0.040	0.001	0.110	0.605
Subj18	0.402	1.909	1.358	0.034	-3.076	-2.205	0.001	0.135	0.718
Subj19	0.778	-0.704	-0.504	0.339	1.127	0.839	0.001	0.122	0.643
Subj20	0.314	1.407	1.033	0.475	-0.559	-0.416	0.001	0.174	0.918

Suppl. Tab. 1 - Circular statistics for phase-angles and mean vector lengths.

Statistical testing of the phase-angle differences between neural activity at the stimulation frequency (1.54Hz) for STD tones pre-DEV versus a random distribution. On the right, the statistical comparison of trial-based mean vector lengths (MVL) for STD tones pre-DEV versus a random distribution. The phase-angles are extracted, for each tone, in the pre-stimulus intervals in a time-window of 60ms (1/1.54Hz/10) and averaged with circular mean statistics. The MVL are calculated based on the trial-level phase-angle circular means. Statistical testing was performed, independently, by means of 1000 permutation tests. The table provides, in order, the p-values (rounded to 3 decimals), observed differences and effect sizes per participant.

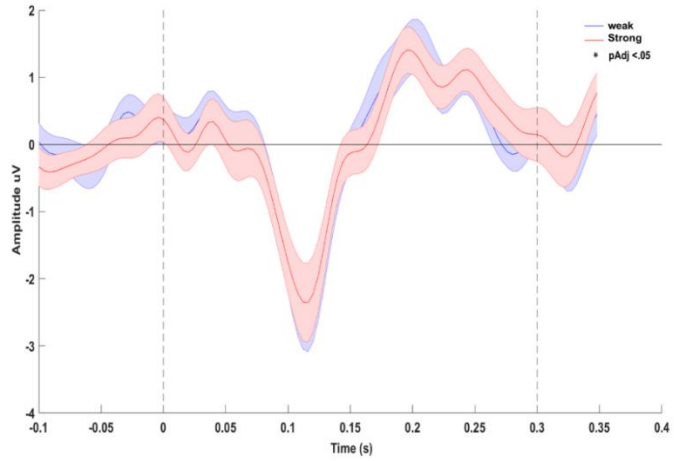
	Binary %	*Ternary %*	*Combined %*	*Other %*	**R2**
Subj1	19,3	26	9,4	45,3	0,40
Subj2	20,8	18,2	18,2	42,8	0,38
Subj3	20,3	22,9	16,1	40,7	0,39
Subj4	20,3	29,2	12,5	38	0,39
Subj5	22,4	21,4	17,7	38,5	0,41
Subj6	17,2	19,3	13	50,5	0,41
Subj7	18,2	26	12,5	43,3	0,37
Subj8	26	21,4	9,4	43,2	0,39
Subj9	17,2	20,8	14,1	47,9	0,36
Subj10	15,1	26,6	12	46,3	0,36
Subj11	22,4	17,7	13,5	46,4	0,37
Subj12	25	21,4	14,6	39	0,39
Subj13	17,7	20,8	15,6	45,9	0,39
Subj14	24	20,8	17,2	38	0,39
Subj15	17,2	20,8	19,8	42,2	0,38
Subj16	21,9	27,6	9,9	40,6	0,35
Subj17	22,9	18,8	10,9	47,4	0,34
Subj18	25	22,9	12,5	39,6	0,39
Subj19	19,8	16,7	12,5	51	0,36
Subj20	18,8	20,8	12	48,4	0,40

Suppl. Tab. 2 - Preferences for accents form the modelling.

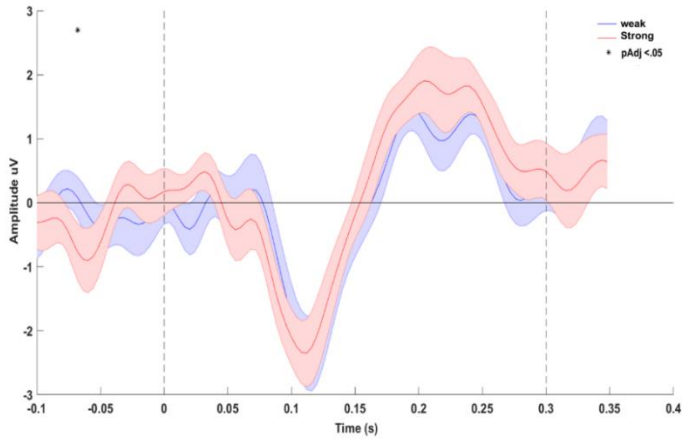
The table reports the percentages of individual preferences for (in order) binary, ternary, combined (binary + ternary) accents. The 'Other' column includes all trials which could not be classified as the above-mentioned accents. The last column on the right provides the goodness of fit (expressed as Eta-squared, 'R2') of the chosen models, averaged across trials per participant.

Supplementary Figures

DEV processing is not modulated by binary accents in non-classified trials



No sign of binary accents on DEV processing before the single-trial modelling



Suppl. Fig. 1 - DEV processing was not significantly modulated by binary accents in non-classified trials. Top: Event-related responses to DEV tones falling on even-numbered (blue) and odd-numbered (red) positions along the auditory sequence in those trials in which no accentuation pattern was observed (non-classified trials). Statistical comparison did not yield any significant difference. Bottom: the same DEV comparison before the single-trial modelling. Statistical comparison of Even-odd positions did not yield any significant difference.

Chapter 3

Macaque monkeys and humans sample temporal regularities in the acoustic environment

Macaque Monkeys and Humans Sample Temporal Regularities in the Acoustic Environment

A Criscuolo, M Schwartze, L Prado, Y Ayala, H Merchant, SA Kotz

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Abstract

Many animal species show comparable abilities to detect basic rhythms and produce rhythmic behavior. Yet, the capacities to process complex rhythms and synchronize rhythmic behavior appear to be species-specific: vocal learning animals can, but some primates might not. This discrepancy is of high interest as there is a putative link between rhythm processing and the development of sophisticated sensorimotor behavior in humans. Do our closest ancestors show comparable endogenous dispositions to sample the acoustic environment in the absence of task instructions and training?

We recorded EEG from macaque monkeys and humans while they passively listened to isochronous equitone sequences. Individual- and trial-level analyses showed that macaque monkeys' and humans' delta-band neural oscillations encoded and tracked the timing of auditory events. Further, mu- (8-15Hz) and beta-band (12-20Hz) oscillations revealed the superimposition of varied accentuation patterns on a subset of trials. These observations suggest convergence in the encoding and dynamic attending of temporal regularities in the acoustic environment, bridging a gap in the phylogenesis of rhythm cognition.

Highlights

- Macaque and human EEG show converging neural signatures of rhythm processing;
- Delta oscillations encode and track temporal regularities in the acoustic environment;
- Mu oscillations reveal superimposed accentuation patterns on isochronous sequences;
- Similar neurophysiological responses favor the phylogenesis of human rhythm cognition.

Keywords

Neural oscillations, rhythm processing, macaque monkeys, EEG, temporal regularities.

Introduction

"*The perception, if not the enjoyment, of musical cadences and of rhythm is probably common to all animals and no doubt depends on the common physiological nature of their nervous system*" – Charles Darwin.

Research in non-human animal species is considered a test case for unravelling the evolutionary origin(s) of human rhythm cognition (Honing, 2018; Kotz et al., 2018; Patel, 2014; Ravignani et al., 2019). Here, we conceptualize 'rhythm' as any pattern of events re-occurring over time. The *temporal regularity* of an acoustic event sequence (from isochronous tones to music) and complex behavior (e.g., walking and speaking) can, thus, be seen as a form of *rhythm.*

What makes us capable of *detecting* temporal regularities in the environment? And in turn, what allows us to *produce* rhythmic behaviors and *synchronize* our movements to an external rhythm? *Detection* requires the *encoding* of a rhythm, i.e., the neurophysiological processing of temporal regularity. In turn, this allows producing and synchronizing with external rhythms. However, are the capacities to *detect, produce, and synchronize* rhythms (from now on, 'DPS') innate and shared across species?

Comparative studies have shown that DPS is found in vocal learning animals (e.g., parrots; Patel et al., 2009), but only partially in others (Schachner et al., 2009). Macaque monkeys performed similarly to humans in tapping tasks (Zarco et al., 2009), showed sensitivity to temporal (ir-)regularities in auditory sequences (Selezneva et al., 2013), and chimpanzee spontaneously aligned their tapping to task-irrelevant auditory rhythms (Hattori et al., 2013). However, the macaque monkey seems unable to detect and synchronize with salient periodicities from complex rhythms such as human-made (musical) stimuli (Honing et al., 2012, 2018). Such results partially supported the notion that many species share a basic capacity for detecting temporal regularities, but some cognitive processes underlying DPS might be species-specific (Fitch, 2013; A. Patel, 2008; Patel, 2006), and further dependent upon neuroanatomical differences (Merchant & Honing, 2014; Patel & Iversen, 2014).

However, other studies, have shown that the capacity to process and synchronize behavior with rhythms also depends on voluntary control, cognitive state, attention, and motivation, beyond the actual capacity to control behavior (Wilson & Cook, 2016). When exposed to music, children do not automatically synchronize with the musical beat, but do so in a social context (in presence of adults; (Kirschner & Tomasello, 2009)). Similarly, macaque monkeys

spontaneously synchronize behavioral displays (Nagasaka et al., 2012), and bonobos tend to spontaneously synchronize rhythmic behavior with a human experimenter (Large & Gray, 2015).

Thus, a more fundamental question in comparative rhythm cognition is: do nonhuman animals have the neurophysiological predisposition to *encode* temporal regularities in the environment? Once we have addressed this question we can probe their ability for rhythmic displays, which, in isolation, do not necessarily inform about their sensory capacities to process temporal regularities (Wilson & Cook, 2016).

Accumulating evidence shows that premotor cortex cells in macaque monkeys resemble a 'neural chronometer' encoding time intervals (Merchant et al., 2011; Merchant, Harrington, et al., 2013) with a dynamic time-varying representation (Crowe et al., 2014). These cells predict regularly timed stimuli (Bartolo & Merchant, 2015) and allow predictive tapping to tempo changes (Gámez et al., 2018). Macaque monkeys' neural activity indicates the encoding and synchronization with temporal regularities in the sensory environment (Lakatos et al., 2008), and dynamic attending (Large & Jones, 1999) to sensory streams, similarly to humans (for overviews: Obleser & Kayser, 2019; Schroeder & Lakatos, 2009).

In the auditory, as well as in other sensory domains, fluctuations of neural activity instantiate a 'rhythmic mode' of sensing (Lakatos et al., 2013) and attending (Large & Jones, 1999) the environment that can bias subjective perception (Iemi & Busch, 2018; Zoefel & VanRullen, 2017). Thus, the alternation of high- and low-salience may influence how we perceive sensory input and further influences behavioral performance (e.g., perceptual tasks). For instance, humans show a disposition to perceive *subjective* accentuations (the *tic-toc illusion*) when listening to isochronous equitone sequences (Brochard et al., 2003). Even though all tones are physically identical, the human brain tends to accentuate two or three equidistant tones according to a binary (on-/off-beat; or strong-weak (S-w)) or ternary (S-w-w) pattern (Abecasis et al., 2005; Baath, 2015; Brochard et al., 2003; Poudrier, 2020; Schmidt-Kassow et al., 2011). As the phenomenon emerges during passive listening, the superimposition of accentuations may represent a spontaneous tendency to sample (or attend) the acoustic environment beyond the encoding of single event onsets or time-intervals. As such, subjective accentuation may represent an unbiased marker of endogenous rhythm processing in a quasi-naturalistic context as it does not depend on training nor task demands.

Human event-related potentials (ERPs) mirror these subjective accentuation patterns, showing amplitude differences for tones in S-w positions (Abecasis et al., 2005; Brochard et al., 2003). Neural oscillations in the alpha- and beta-band (8-20 Hz) not only coincide with but precede the onset of expected tones (Arnal, 2012; Fujioka et al., 2009, 2012; Snyder & Large, 2005), and their amplitude can be modulated by trial-level accentuation patterns (Criscuolo, Schwartze, Henry, et al., 2022). These oscillatory brain dynamics likely reflect the active generation of temporal predictions, whereby the first element in a series of two or three might be more salient (S) than others (w).

Does our closest ancestor show a comparable endogenous disposition to sample the acoustic environment in the absence of task instructions and/or training?

In the current study, we recorded EEG in two macaque monkeys who passively listened to isochronous equitone sequences. Similar to a recent study in human participants (Criscuolo, Schwartze, Henry, et al., 2022), we investigated the monkey's endogenous tendencies to (i) internalize the timing of external sound events, to (ii) track tone onsets, and to (iii) parse equitonal sequences with a superimposed binary accentuation pattern. Lastly, we directly compared human and macaque monkey EEG to (iv) test for (dis-)similarities in basic rhythm processing.

The current findings suggest that macaque monkeys have the adequate neural outfit to go beyond simple isochrony processing. The unexplored parallels between macaque and humans bridge a critical gap in the phylogenesis of rhythm cognition, potentially lending support to Darwin's notion of a shared neurophysiological predisposition for rhythm processing in non-human primates.

Materials and Methods

Experimental procedure

We tested two macaque monkeys. Monkey 1 (M1) is a 12-year-old male, Monkey 2 (M2) a 9-year-old female. Both monkeys had normal hearing and were previously trained in spatial and temporal categorization tasks (M1)(Mendoza et al., 2018) and a synchronization tapping task (M2)(Gámez et al., 2019). Both monkeys were awake (i.e., were not sedated) while EEG was recorded, sitting in a quiet room [3 (l) × 2 (d) × 2.5 (h) m] with dimmed lighting and two loudspeakers placed at a ~50cm from their ears. The animals were seated comfortably in a monkey chair, where they could freely move their head, hands, and feet. No head fixation was

used, and the EEG electrodes were attached to the monke''s scalp using tape (see EEG data acquisition below). To ease the fixation of the electrodes, the monke''s hair on the scalp and reference ear was shaved. Detailed information about human participants, EEG data collection, and analysis procedures can be found in a recent study (Criscuolo, Schwartze, Henry, et al., 2022). Briefly, we randomly selected 4 human participants from a dataset of 20 individuals (21-29 years of age, mean age 26.2 years). EEG was recorded from 59 Ag/AgCl scalp electrodes (Electrocap International), amplified using a PORTI-32/MREFA amplifier (DC to 135 Hz), and digitized at 500 Hz.

Ethics statement

Animal care and experimental procedures were approved by the National University of Mexico Institutional Animal Care and Use Committee and conformed to the principles outlined in the Guide for Care and Use of Laboratory Animals (NIH, publication number 85–23, revised 1985). The Mexican standards on research ethical protocols with non-human primates (NHP) are in the 'NORMA Oficial Mexicana NOM-062-ZOO-1999', and are in line with regulations from 13 other countries (Hartig et al., 2023).

Audiogram

The animal's hearing capacity was recorded with a scalp-recorded audiogram in partially sedated states. Sedation was induced and maintained with Ketamine (Aranada, Mexico).

Stimuli materials

For the audiogram, click sounds were produced trough TTL pulses generated with a TDT-RZ6 signal processor (Tucker-Davis Technologies, system 3, Florida, USA) at a digitization rate of 97656.24Hz. Clicks lasted 0.5ms and were delivered at a rate of 15.1Hz, in random polarities and sound intensities (from 20 to 90, steps of 10dB SPL). Twenty blocks of 4000 stimuli were presented in a single recording session to collect 1000 repetitions per click intensity. Clicks were binaurally delivered through open-field speakers (KRK 5-G3, USA) located 85cm from animal's ears. Sound intensity was calibrated using a free-field condenser microphone (426B03), a sensor signal conditioner (480C02, PCB Piezotronics, NY USA), and the TDT rPvdsEx circuits.

EEG recording

For the audiogram, continuous EEG was recorded from three Grass gold-plated electrodes (Natus Neurology, #FS-E5GH-60; Fig. 1) located at Fz, Cz, and Pz according to the 10/20 system. A reference electrode was located on the right earlobe, while the ground electrode was located at the central forehead. Scalps were shaved and cleaned with mild abrasive gel (Nuprep, Weaver and Company, USA) before the recording session to reduce scalp impedance. The signal was amplified by means of a medusa preamplifier (RA16PA, TDT systems) and digitized at 24414.06Hz with an on-line filter from 3Hz – 6000Hz. Additionally, a notch filter at 60Hz was applied to remove the line frequency.

Signal processing

Channel Cz was selected for the analyses of the audiogram, based on the known higher signal-to-noise ratio of the vertex signal. The signal was further band-pass filtered (150–3000Hz, Butterworth ^{4t}h-order filter) and epoched relative to stimulus onset (−10-66ms). EEG epochs were sorted into positive and negative polarity click presentations and sub-averages were computed for each polarity condition. An added polarity grand average was obtained and used for further analysis to avoid any transduction stimulus artifact and to minimize the cochlear and microphonic potentials. ABR waves of similar latency as those reported in anesthetized or sedated animals (Laughlin et al., 1999) were observed (Suppl. Fig. 1). A significant evoked response (2-tailed t-test, 10ms window size) was observed at 60- and 50-dB SPL for monkey 1 and 2, respectively. A previous study in fuscata macaques reported that at a level of 60dB SPL level, the monkeys were able to hear tones in a 28Hz to 37kHz range (Jackson et al., 1999), frequencies that are elicited by the click broad-band stimulus. Three ABR components were clearly identified at 90dB SPL in both monkeys. These components with positive peaks had latencies of ≈ 3, 4.6, and 8ms. The shape and latency of the first two waves agrees with previous reports (Suppl. Fig.1, (Lasky et al., 1995)). The likely neural generators of the observed waves are the cochlear nucleus, lateral lemniscus, and inferior colliculus (Lasky et al., 1995; Uno et al., 1991, 1993). The observed peak amplitudes (≈3-14μV) were larger than those reported in awake head-fixed Macaca fuscata (Uno et al., 1993) (tenths of μV) using similar level and rate parameters but close-field and monaural stimulation. Although it is known that anaesthesia or sedation might considerably diminish or even abolish evoked responses (Uno et al., 1993), the audiogram ensured that both monkeys could perceive the tones employed in the experimental paradigm as both standard (STD) tones and amplitude-

deviant (DEV) tones were above the individual hearing thresholds in both monkeys.

Experimental paradigm

Monkeys listened to 13-tone (440Hz, 85dB, 50ms duration) isochronous equitone sequences (Fig.1, right). On < 5% of the trials, amplitude-deviant tones (DEV; 66dB) could fall on the 8-9-10-11th position (Fig.1, bottom row). The inter-stimulus-interval between tones was fixed at 0.6s, corresponding to a fixed stimulus rate of (1.6667Hz). The entire trial sequence lasted 7.8s and was followed by a random inter-trial silent period between 3.5 and 5.5s. Critically, no accentuation pattern (strong-weak sounds) was imposed in the auditory sequence. M1 underwent 21 recording sessions and M2 25 sessions during which both animals listened to 100 13-tone sequences each. Out of 1300 total events, 1240 were STD tones (>95%) and 60 were DEV (4,6%). The stimulus materials in use were nearly identical for humans and monkeys (Criscuolo, Schwartze, Henry, et al., 2022).

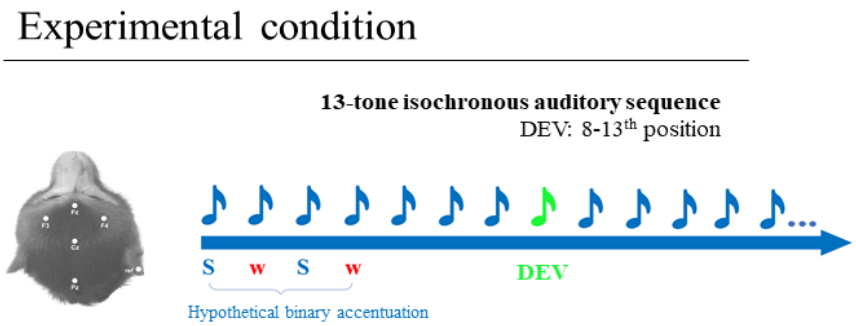


Figure 1 –- Electrode positions and stimulus sequence.

Electrode positions on the macaque monkey scalp (left) and the 13-tone isochronous equitone sequence (right). The hypothesized superimposition of binary accentuations would parse the auditory sequence in alternating“"stron”" (S) and“"wea”" (w) accents. Deviant tones (DEV) occurred from the 8th position onward. Accordingly, they could occur on S and w accentuated positions with equal probability.

EEG data acquisition

The EEG was recorded from electrodes (Grass gold-plated electrodes) attached to five scalp positions (Fz, Cz, Pz, F3, F4) according to the 10-20 system (Fig. 1). Both monkeys previously underwent surgery procedures where the head fixation posts were implanted during aseptic surgery and under gas anesthesia. Importantly, the temporal maxillary muscles of the two monkeys were retracted during the surgery, thus leaving the upper skull surface free of

muscular or eye-induced artifacts. A second surgery was performed and head holding devices were removed prior to data collection. All electrodes were attached to the scalp using Ten20 Conductive EEG paste and medical tape and were referenced to the right ear (fleshy part of the pinna). The electrodes were connected to a Tucker-Davis Technologies (TDT) head stage (#RA16LI) for low impedance electrodes. This head stage was connected to a TDT RA16PA preamplifier, which in turn was connected to a TDT RZ2 processor. RZ2 was programmed to acquire the EEG signals with a sampling rate of 610.35Hz and the bandpass filters were set at 0.01–100Hz.

Data analysis

Preprocessing

Data were pre-processed with a combination of custom Matlab scripts/functions and the Matlab-based FieldTrip toolbox (Oostenveld et al., 2011). Data were band-pass filtered with a ^{4t}h order Butterworth filter in the frequency range of 0.5-50Hz (*ft_preprocessing*). Next, data segmentation was conducted separately for 'rhythm-tracking', event-related potentials (ERP) and time-frequency representation (TFR) analyses.

Rhythm tracking analyses

Rhythm-tracking analyses were time-locked to encompass the whole equitone sequence. 100 sequences (per experimental session) were created, starting from the third tone onset and including up to the 13th tone (6.6s). Next, we computed a fronto-central channel cluster encompassing 'Fz', 'F3', 'F4', 'Cz'. Data from this front-central cluster were used for Fast-Fourier transform (FFT) and phase-locking analyses.

Fast-Fourier transform

Single-trial data from the fronto-central cluster were submitted to a FFT ("FFT data") with an output frequency resolution of 0.15Hz (1/6.6s = .15Hz). Spectral power was calculated as the squared absolute value of the complex Fourier output. Data in each frequency bin were normalized by the frequency-specific standard deviation across trials. Lastly, we averaged the frequency-domain data across channels and trials. For illustration purposes, we restricted the Fourier spectrum to 1-7Hz in Fig. 2A, top for M1 and bottom for M2.

Phase-locking analyses

A time-resolved phase-locking analysis was performed to estimate the phase relationship between neural activity at the stimulation frequency and the sequential tone onsets. Sequence-level data from the fronto-central cluster were bandpass-filtered with a ^{4t}h order Butterworth filter around the stimulation frequency (1.1-2.1Hz, considering a 1.67Hz center frequency; *ft_preprocessing*) and underwent Hilbert transform to extract the analytic signal. Next, we plotted the time-course of the real part of the analytic signal (Fig. 2B, top for M1 and bottom for M2) as a function of the onsets of STD tones preceding (blue) and following (red) the DEV (green; this plot is for illustrative purposes only). Phase-locking analyses were performed at sequence- and channel-levels by means of circular statistics (circular toolbox in Matlab; (Berens, 2009)), based on the circular mean phase-angles estimated in the 60ms (proportional to the stimulation frequency: 1/1.67Hz/10) preceding individual tone onsets. Next, the sequence- and channel-levels mean vector length (MVL; (Berens, 2009)) were calculated for pre-DEV STD tones and averaged the values across channels. MVL for pre-DEV STD tones were statistically assessed against the MVL from a random distribution (random uniform distribution of phase-angles) by means of 1000 permutation tests. A p-value lower than .05 was considered statistically significant. In Suppl. Fig. 2, we also provide session-, channel-, and sequence-level 'relative phase angles. These were expressed as the absolute phase difference between phase-angles for each tone position (e.g., third to eight) and the most common phase-angle in the sequence (the one with the highest probability, as obtained from *histogram* function in MATLAB, with 'probability' as input). The pooling over sessions and channels is displayed in Fig. 2D and 3D.

ERP and TFR data

Data were segmented into 4-s-long epochs symmetrically time-locked to every tone onset. Next, we employed a data-driven channel-by-channel and trial- and monkey-level artifact suppression procedure ((Criscuolo, Schwartze, Henry, et al., 2022); and similar to the method implemented in (Kaneshiro et al., 2020)). Artifact suppression focused on time-windows ranging from -.4 to .4s relative to each stimulus onset. Amplitude values were temporarily normalized by their standard deviation across trials and outliers (data points per epoch and channel) were defined by means of a threshold criterion (values > mean + 4*SD). The identified noisy time-windows (with 50ms symmetrical padding) then served to suppress (replace by NaNs) time-points in the non-normalized data. The missing values were replaced by means of cubic temporal interpolation (using the *'pchip'* option for both the built-in Matlab

and FieldTrip-based interpolation functions) considering the time-course of neighboring time-windows (extending up to 500ms when possible, automatically reduced otherwise). The current approach is a novel data-driven procedure developed to minimize the data loss. Thus, rather than rejecting entire epochs only partly contaminated by artifacts (i.e., standard artifact rejection procedure), we opted for an artifact suppression approach that allowed keeping all trials. Note that the channel-by-channel routine allowed the algorithm to flexibly adapt the outlier threshold estimates to the inherent noise varying over channels. Lastly, a standard whole-trial rejection procedure based on an amplitude criterion (85uV) was applied. Data selected for event-related-potential (ERP) analyses ("ERP data") were segmented including 500ms prior and following each tone onset (1s in total). Data destined to time-frequency representation analyses ("TFR data") were not further segmented at this stage. ERP data were band-pass filtered between 1-30Hz and TFR data low-pass filtered at 40Hz.

TFR data finally underwent time-frequency transformation by means of a wavelet-transform (49) with a frequency resolution of .25Hz. The number of fitted cycles ranged from 3 for the low frequencies (<5Hz) to 10 for high frequencies (>5Hz and up to 40Hz). TFR data were then re-segmented, so to reduce the total length to 2s, symmetrically distributed relative to tone onsets.

Post-processing of ERP and TFR data

Single-trial ERP amplitudes were mean-corrected by a global average over epochs and 500ms long (-0.2 to 0.3s relative to tone onset). Similarly, single-trial TFR amplitudes were normalized by computing relative percent change with reference to the global mean amplitude across epochs and 500ms long. This approach has been used elsewhere (Abbasi & Gross, 2020; Fujioka et al., 2012) and was preferred over baseline correction as we were interested in analyzing amplitude fluctuations in the pre-stimulus intervals. Then, we created a fronto-central channel cluster. All following analyses were performed exclusively on this channel cluster.

ERP analyses

We averaged evoked responses over trials separately for STD and DEV tones, and for odd (hypothetical "Strong" position in a binary accent; S, Fig. 3,4) and even ("weak"; w) serial positions from the 3rd to the 11th tone. The first standard tones were not included to avoid increased responses typically observed at the beginning of an auditory sequence. Fig. 3A and 4A show the respective ERPs for the averaged fronto-central channel, for STD tones on S-w

positions (left) and for the comparison of STD and DEV tones averaged over S-w positions (right). Statistical analysis was performed by means of paired-sample t-tests. An FDR-adjusted p-value lower than .05 was considered statistically significant (Benjamini & Hochberg correction).

TFR analyses

We averaged time–frequency representations over STD trials, separately for odd and even positions (hypothetical strong and weak positions, respectively; Fig. 3B and 4B). Next, we quantified mean peak amplitudes in the mu-band (8-15Hz) in the post-stimulus intervals (80ms (proportional to the center frequency: 1/12Hz) and compared them for S-w positions (Fig. 3C and 4C).

Individual classification of accents

An individual modelling approach was developed to identify binary accents. Since other accentuation patterns are possible (Abecasis et al., 2005) beyond the binary default (Brochard et al., 2003), the model further tested for the presence of ternary accents. We focused on single-subject, mu-band peak amplitudes for STD tones in the first 8 positions of the auditory sequence in 80ms time-windows (proportional to the center frequency of interest; mu-band: 1/12Hz = 83ms) following the stimulus onset.

Single-tone mu-band amplitudes were concatenated to mimic an 8-tone auditory sequence (i.e., a trial). Next, single-subject and trial-level mu-band fluctuations (8 tones) were entered into a stepwise regression model (Fig. 5A; '*stepwiselm*' in Matlab) with 3 predictors: binary accents (values: 1, -1), ternary (1, -.5, -.5), and a constant term (ones). The winning model was chosen based on adjusted Eta-squared. Trials for which the winning model involved the binary predictor were labeled "binary". Similarly, trials for which the winning model involved the ternary predictor were labeled "ternary". The model thus allowed the combination of multiple predictors, but no interactions between terms. We accordingly interpreted (and labeled) the combination of binary and ternary terms as "combined". Lastly, trials in which grouping could not be clearly identified were labeled as "not classified". Session-level model results are provided in Suppl. Tab. 2, designated as "Preferences for accents" and expressed as the percentage of trials relative to the full number of auditory sequences (100 per session, per monkey). The session-level goodness of fit of the model is provided in the same table. The "Preferences for accents" across sessions and monkeys are provided in Fig. 5B.

Binary accent analyses

To confirm that the identified "binary" trials indeed showed binary accentuation patterns, we performed further analyses. First, we concatenated trials classified as "binary" and computed a trial-based single-tone pair-wise amplitude difference (its lower-triangle 2-D mean is provided in Fig. 5C). Namely, we calculated the amplitude difference between every tone (1-8 positions) along the auditory sequence independently for each sequence. Hence, we estimated the amplitude difference for the ^{1s}t and 2nd position, then to the third position, and so forth. Similarly, the amplitude for the 2nd position was compared to the 3rd, the 4th position, and so on. The result of this computation is a session-level pair-wise amplitude difference matrix, whose size is N trials x N positions-1 x N positions-1. Next, we isolated the pair-wise amplitude difference for tones in odd-positions (Fig. 5D; "odd-pos difference") and even-positions ("even-pos difference") and statistically compared them by means of 1000 permutations of odd-even labels. An FDR-adjusted p-value lower than .05 was considered statistically significant (Benjamini & Hochberg correction). These two variables were then combined into a distribution of "binary similarity". The binary similarity, thus, features the amplitude difference for tones in odd-numbered positions (1-3-5-7th) and the amplitude difference for tones on even-numbered positions (2-4-6-8th). In contrast, the binary dissimilarity was created by extracting the mean difference of tones in odd versus even positions (Fig. 5D). Finally, the binary similarity was statistically compared to the binary dissimilarity. Statistical testing was performed by means of 1000 permutations of odd-even labels, and an FDR-adjusted p-value lower than .05 was considered statistically significant (Benjamini & Hochberg correction).

Comparative analyses

In a prior study (Criscuolo, Schwartze, Henry, et al., 2022) we investigated rhythm processing capacities in humans, using a comparable experimental paradigm and analysis pipeline as here. Human participants only took part in two experimental sessions, hence we only focused on the first two experimental sessions of the monkeys for comparative data analyses (see Criscuolo, Schwartze, Henry, et al., 2022) for further details regarding the analysis procedure adopted in the human dataset).

From the human sample, we randomly selected 4 participants (gender-balanced, as for the monkeys). In monkeys as well as in humans, we extracted the 'individual preferences for accents' as calculated in the accent modelling. Next, we isolated 'binary' trials, performed

'binary similarity' and 'binary dissimilarity' analyses as described in the 'Binary accent analyses' paragraph. Lastly, we inspected the time-course of neural activity time-locked to STD tones and compared it across monkeys and humans (Fig. 6).

Ternary accent analyses

Exploratory analyses zoomed in ternary trials. While the 'binary trials' could only show two accentuation patterns (S-w or w-S), ternary beats can show at least three different accentuation patterns, i.e., the accent can either fall on the first (S-w-w), second (w-S-w), or the third position (w-w-S). To disentangle these three accentuation patterns from the distribution of "Ternary trials" identified during the "Individual classification of accents", we ran a second stepwise regression model. This model featured three predictors corresponding to the respective accentuation types, implemented as:1, -.5, -.5 (pattern 1), -.5, 1, -.5 (pattern 2) and -.5, -.5, 1 (pattern 3). The model did not allow interaction terms, and the winning model was chosen based on adjusted Eta-squared. The output of the model is provided in Fig. 5B (bottom right), as the percent distribution of three accentuation patterns across sessions and relative to the total number of auditory sequences (100 per session). Note that not all trials could be classified as pertaining to the three modelled accentuation patterns. Other accentuation patterns are possible in the ternary trials, which were not modelled here: for instance, a S-w-w pattern could be as well represented by a stair-case amplitude change (i.e., 1, -.75, -.25) or a shuffled version of it (i.e., 1, -.25, -.75). However, given that the stimulation rate in use is likely suboptimal to test ternary accentuations even in humans (Abecasis et al., 2005; Baath, 2015; Brochard et al., 2003; Fujioka et al., 2012; Poudrier, 2020), we did not build models to test all possible ternary accentuation patterns. Furthermore, it is important to note that the model in use here only uses the first 8 tones of the auditory sequence. This choice avoids the onset of DEV tones in later positions, which may disrupt ongoing accentuations, but inevitably leaves only up to two periods of a ternary accent (as compared to 4 repetitions of a binary accent). Consequently, even two small amplitude fluctuations with superimposed noise (inherent in EEG recordings) may drive the 'ternary' classification, but these trials may not necessarily reflect a true ternary accent. In turn, we expected a large proportion of 'ternary' trials to fail to be further classified as strictly reflecting the modelled patterns (1,-.5,-.5 (pattern 1), -.5,1,-.5 (pattern 2) and -.5,-.5,1 (pattern 3)). The small percentage of trials belonging to the three accentuation types (~2%) precluded further analyses due to insufficient statistical power to interpret results.

Resources and details

The datasets supporting the current study will be deposited in a public repository but are available from the corresponding author upon reasonable request. The code for analyses is available upon request. Further information and requests for resources should be directed to the Corresponding Author.

Results

Rhythm tracking

Macaque monkeys passively listened to isochronous equitone sequences presented at a stimulation rate of 1.67Hz and containing 13-to-15 frequent tones (standard; STD) and one amplitude-attenuated deviant tone (DEV). We tested *whether* and *how* their neural activity would show idiosyncratic signatures of rhythm tracking.

Macaque monkeys' neural activity encoded the timing of external events (Fig. 2A, B top for M1 and bottom for M2). The Fourier spectrum showed a power peak at the stimulation frequency (1.67Hz; Fig. 2A), indicating that neural activity responded timely to tone onsets. Next, we quantified the consistency of pre-stimulus phase in delta-band (centered at 1.67Hz) neural activity during a time-window preceding tone onsets (Fig. 2B) by means of mean vector length (MVL) analyses. This phase analysis focused on the ~60ms (proportional to the stimulation frequency: 1/1.67Hz/10) prior to tone onsets. Single-session trial- and channel-level MVL of STD tones preceding a DEV (pre-DEV) significantly differed from a random distribution (MVLs are plotted as kernel distributions in Fig. 2D; pre-DEV in blue; Suppl. Tab. 1-2 for statistics).

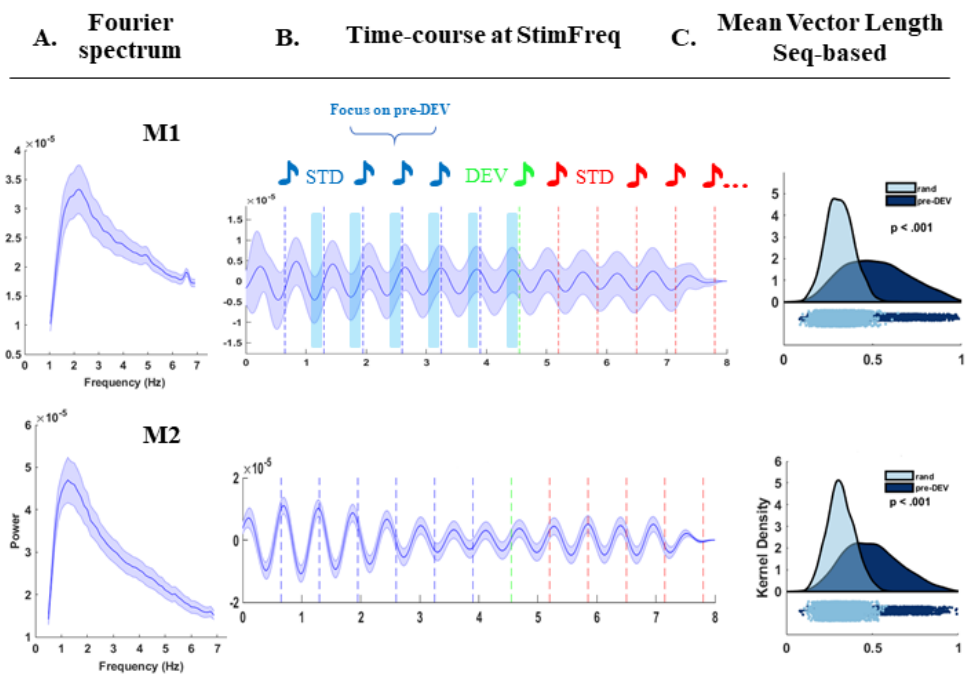


Figure 2 –- Rhythm tracking analyses

A: Fourier spectrum of neural activity along the entire auditory sequence. The plot displays the grand-average power in the frequency range from 1 to 7Hz. B: time-course of neural activity at the stimulation frequency. Vertical dotted lines indicate the onsets of STD tones prior- (blue) and post-DEV (red). The DEV onset is reported in green. Blue shades represent the standard errors. Light-blue rectangles indicate the pre-stimulus intervals of STD in which we performed phase analyses (not scaled). C: the kernel density distribution of mean vector length (MVL) calculated at the single-session and sequence-level and averaged across the fronto-central cluster of interest. These MVLs are based on the raw phase-angles for pre-DEV STD tones (blue) and are statistically compared to the MVL for random distribution of phase-angles. Single-session statistics are reported in Suppl. Tab. 2.

Accent processing

We tested whether participants' neural activity would sample the acoustic environment by superimposing binary accentuation patterns (S-w accents in odd-numbered versus even-numbered positions) onto the isochronous equitone sequences. Thus, we analyzed event-related responses (ERP) to STD tones in S and w positions, and further inspected the time-frequency representation of time-locked responses.

ERPs to STD tones in S-w positions did not differ statistically (Fig. 3A, 4A). However, STD tones elicited stronger N100 and P200 responses as compared to DEV tones (FDR-adjusted $p < .05$; Fig. 3A,4A, right), confirming the processing of an unpredicted amplitude-attenuated deviant tone.

The time-frequency representation plots of neural activity in response to STD tones mainly showed one event-locked response in the mu-band (8-15Hz; Fig. 3B for M1 and 4B for M2). In this frequency band, we compared event-locked fluctuations for STD tones in odd (S) versus even (w) positions along the sequence (Fig. 3C, 4C), corresponding to hypothetical S-w positions (blue and red, respectively). The result of the statistical comparison of S-w positions did not survive multiple comparison by FDR correction (FDR > .05).

To summarize, neither ERP nor TFR analyses revealed a binary accentuation, as STD tones elicited similar responses when they occurred in odd- and even-numbered positions along the auditory sequence. This result, however, may be associated with inter- and intra-individual differences in *when* and *how* accentuation patterns are superimposed onto the auditory sequences (Brochard et al., 2003). These hypotheses required a more adequate method to be tested: the novel accent modelling approach below.

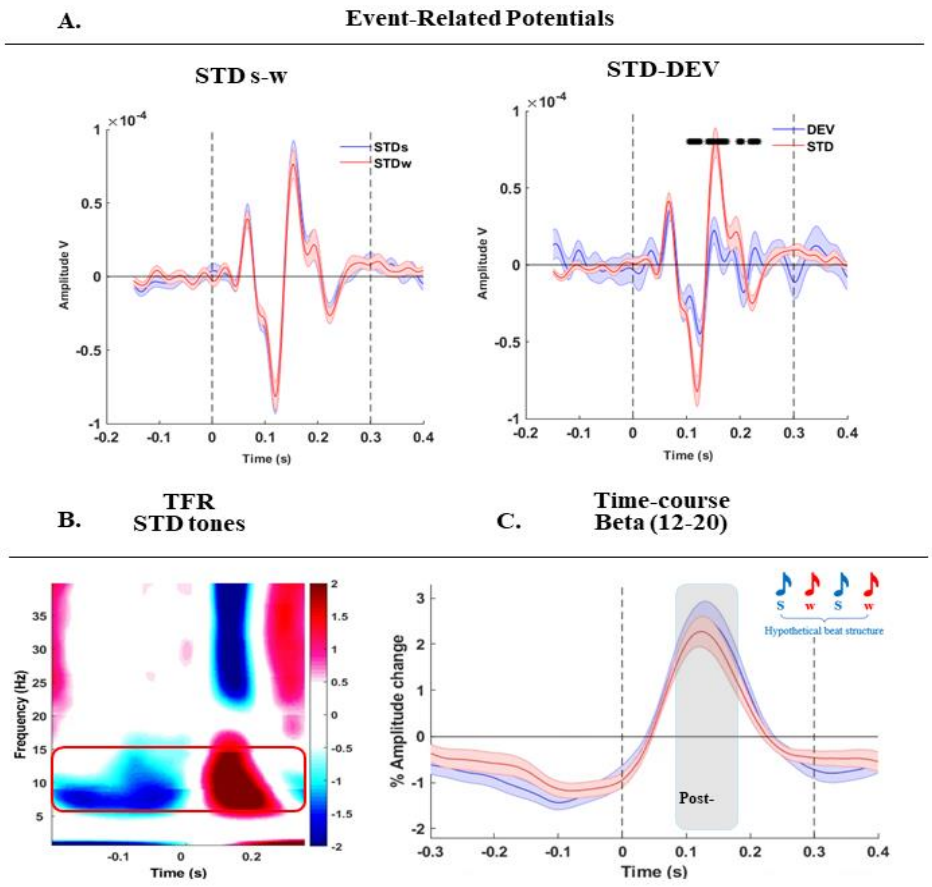


Figure 3 – ERPs and TFR data for monkey 1

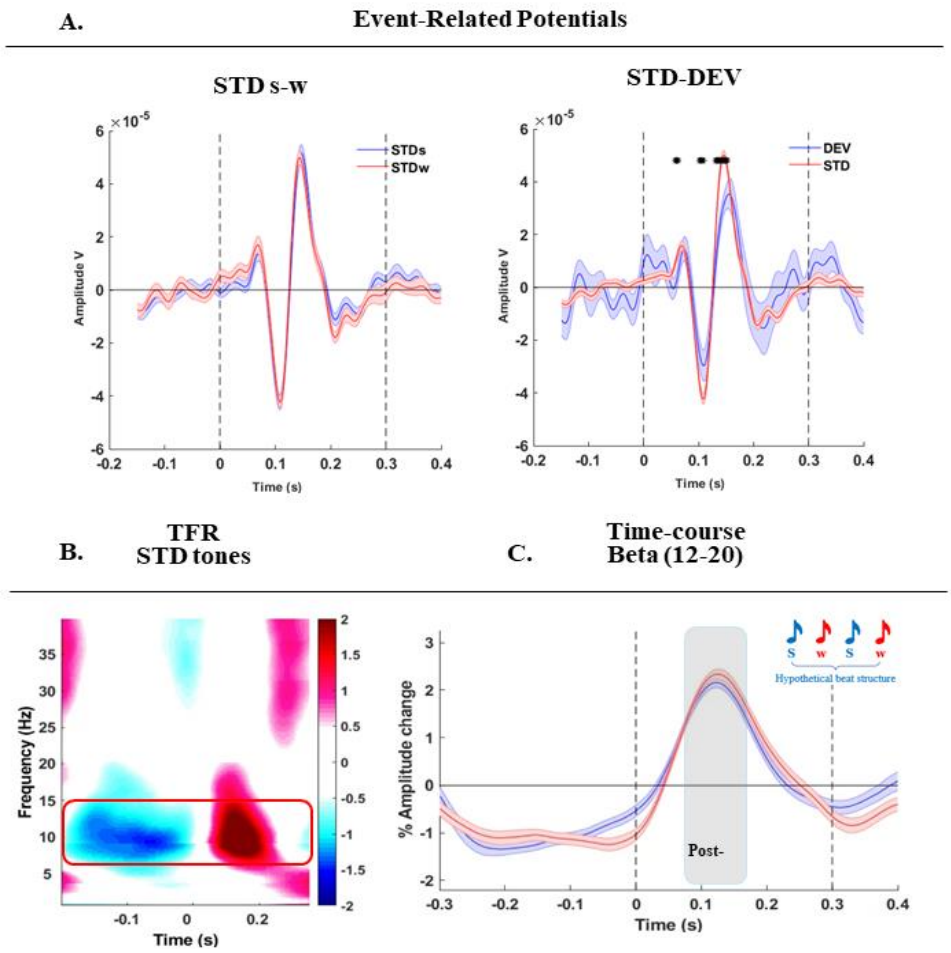


Figure 4 –- ERPs and TFR data for monkey 2

A: On the left, ERP responses for STD tones in S (blue) w (red) positions. On the right, ERP responses for STD (blue) and DEV tones. Stars indicate significant time-windows, as assessed by means of paired-sample t-tests (FDR-adjusted p <.05). B: grand-average time-frequency spectrum time-locked to STD tones (-.2 to .4s). The frequency range spans 1-40Hz with a frequency resolution of .25Hz. The red rectangle highlights predominant responses in the mu (8-15Hz) frequency range, on which we performed statistical comparisons. C: extracted time-course of mu-band activity in hypothetical S-w positions, time-locked to STD tones onsets, in blue for odd-numbered positions (Strong binary accent) and red for even-numbered positions (weak binary accent). Shaded colors indicate standard errors. On top, a grey rectangle delineates the time-window in which peak amplitude extraction is performed.

Accent modelling

To address the questions of whether (i) monkeys accentuate in a similar way, (ii) they always accentuate, and (iii) accentuation patterns influence DEV processing (Brochard et al., 2003),

we focused on trial-level data and modelled various accentuation patterns. We used a stepwise regression model to classify session-level, mu-band neural responses as best reflecting a binary, ternary, or absence of accentuation patterns. The model predicted tone-by-tone mu-band amplitude changes from three predictors: binary, ternary, and constant terms (Fig. 5A). Resulting preferences for accents are reported in Suppl. Tab. 3 and summarized in Fig. 5B. Note that most trials (~60%) did not reflect either binary or ternary accents. In the absence of perceptual reports, we cannot confirm whether this observation signals lack of sensitivity of our method, or whether monkeys did indeed not accentuate.

Next, we zoomed into "binary trials" and disentangled S-w from w-S accentuation patterns based on the single-trial β-coefficients obtained from the modelling (see methods). The resulting distributions are reported in Fig. 5B, bottom left. Similarly, we disentangled three possible accentuation patterns in the "ternary trials" (Suppl. Fig. 3). We performed a separate stepwise regression modelling using S-w-w, w-S-w and w-w-S accents as predictors (see methods). Distributions are reported in Suppl. Fig. 3.

Overall, this approach allowed showing that macaque monkeys' neural activity spontaneously superimpose accentuation patterns on identical tones embedded in isochronous equitone sequences. Importantly, the monkeys' neural activity seems to switch between binary, ternary, and other accentuation patterns over trials. Notably, however, in the majority of trials no consistent accentuation pattern was identified.

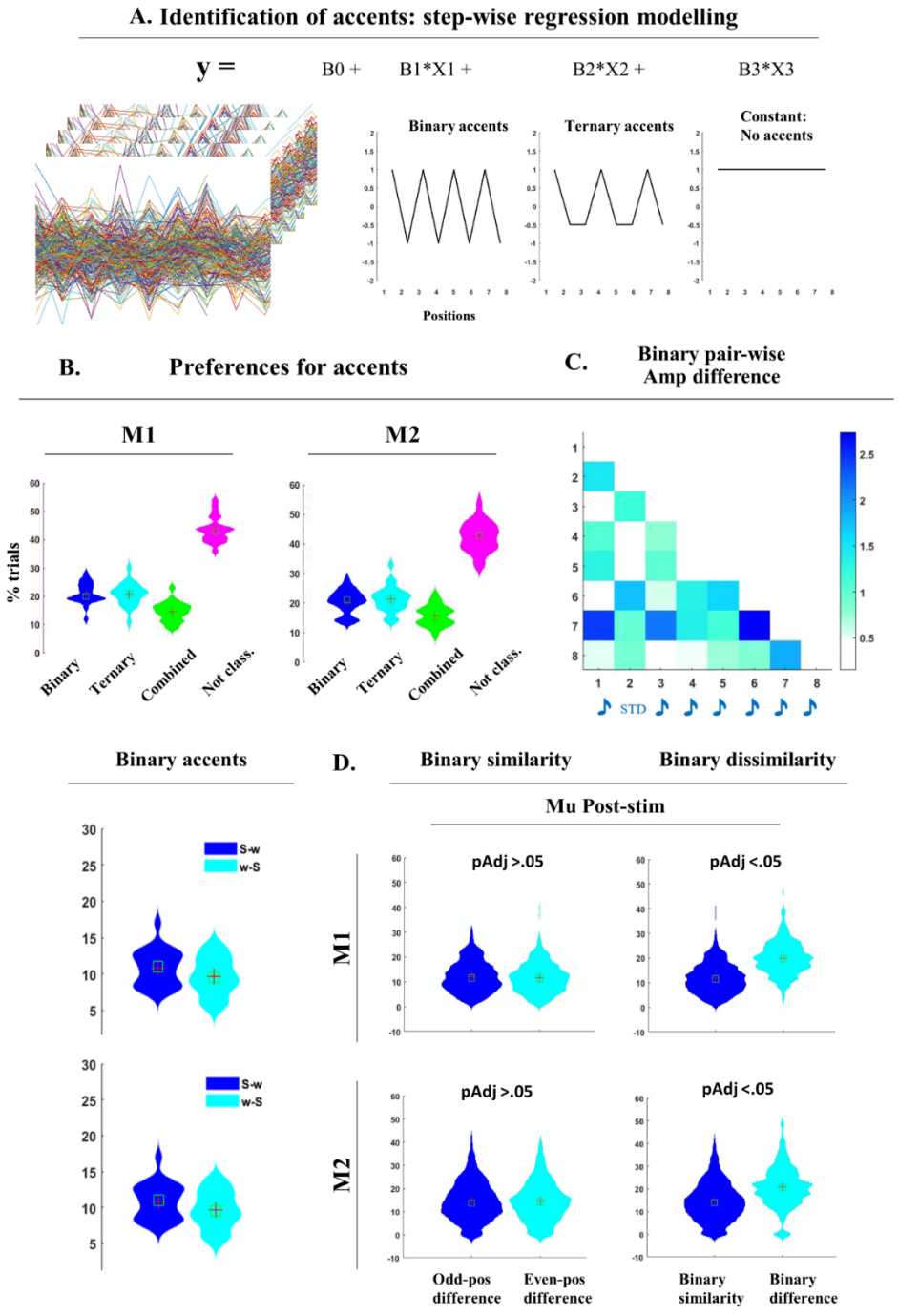


Figure 5 –- Modelling of individual accents and analyses on binary accents.

A: The modelling of accents was performed by means of stepwise regression modelling and using mu-band post-stimulus responses as the dependent variable. The predictors were a binary (1, -1), a ternary (1, -.5, -.5) and a constant term (ones). B: preferences for

accents, as reported from the modelling. In order, we plot the distribution of trials assigned to binary, ternary, combined (binary-ternary) accents, and 'not classified' (neither binary nor ternary) across the two monkeys. At the bottom, we zoom into binary trials and distinguish S-w accents from w-S accents based on trial-level Beta coefficients from the modelling (top for M1, M2 below). C: grand-average pair-wise difference for mu-band peak amplitudes across the first 8 positions of the auditory sequence in binary trials. D: on the left, the distribution of amplitude differences across odd-numbered positions (in blue) and even-numbered positions (cyan). The average of these two distributions forms the 'Binary similarity'. On the right, the 'binary similarity' (blue) and the mean amplitude difference of the odd- versus even-numbered position ('binary dissimilarity'; in cyan). Statistical testing was performed by means of 1000 permutations, and an FDR-adjusted $p < .05$ was considered as statistically significant.

Binary accents

After isolating trials showing binary accentuation patterns, we aimed to statistically test whether mu-band responses would significantly differ in S versus w positions. If so, neural responses to tones falling on odd-numbered positions should differ from those on even-numbered positions. However, there should be no differences for neural responses on the same positions: namely, tones falling on odd-numbered positions should elicit similar (i.e., non-significantly different) neural activity. In sum, we assessed whether this modelling approach delivers a meaningful classification of binary accents.

To this end, we isolated the binary trials and calculated the tone-by-tone pair-wise amplitude difference for mu-band post-stimulus activity across 8 positions in the auditory sequence and preceding the DEV tone. For visualization, the resulting matrix was averaged across trials and only the lower diagonal matrix is shown (Fig. 5C). The original matrix (all trials) was instead used to calculate metrics of "Binary similarity" and "Binary dissimilarity" (Fig. 5D; top for M1 and bottom for M2). The Binary similarity features two distributions: the amplitude difference for tones in odd-numbered positions (1-3-5-7th; "blue", labeled as "odd-numbered position difference") and the amplitude difference for tones in even-numbered positions (2-4-6-8th; cyan, labeled as "even-numbered position difference"). The two distributions did not significantly differ from each other. The respective values were then combined to compute a "Binary similarity" variable. For the "Binary dissimilarity" analyses, we calculated the amplitude difference for tones in odd- versus even-numbered positions (corresponding to on-beat versus off-beat "Binary difference") and statistically compared it to the "Binary similarity" (Fig. 5D). Statistical testing confirmed a significant difference (FDR-adjusted $p < .05$), indicating that mu-band post-stimulus amplitudes were significantly modulated according to a binary accent. The same procedure was independently repeated for both monkeys.

Taken together, these results confirmed that trials classified as 'binary' during the modelling did indeed show a consistent binary accentuation pattern. Mu-band amplitudes on STD tones in S positions significantly differed from those in w positions.

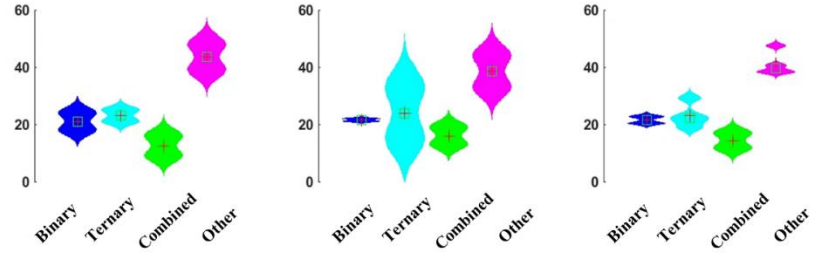
Comparative analyses of human and monkey data

Next, we set out to investigate similarities in rhythm processing between humans and macaque monkeys. We directly compared the two macaque monkeys with a subset of 4 datasets of participants taken from a prior human study (Criscuolo, Schwartze, Henry, et al., 2022). Critically, these human participants underwent EEG recording while listening to similar stimulus material as the monkeys. This allowed us to reproduce the modelling of accents in use here and to directly compare the two datasets.

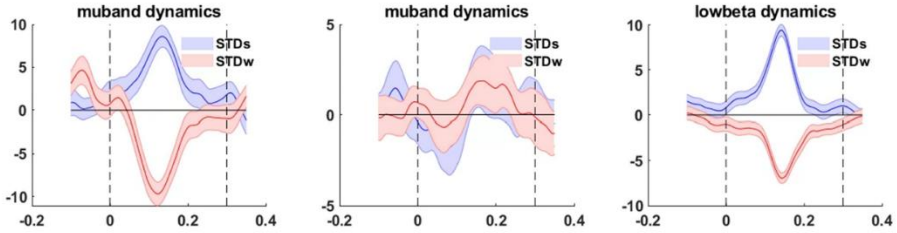
As human participants took part in only two experimental sessions, we focused on the first two experimental sessions of the monkeys as well. Details on the analysis procedure for the human dataset can be found in (Criscuolo, Schwartze, Henry, et al., 2022). In Fig. 6A, we show preferences for accents for M1, M2, and 4 human participants and below, the distribution of preferences for binary, ternary, and other accents (non-classified trials). Like humans, macaque monkeys showed the emergence of binary accentuations in 21% of the trials and ternary accentuations in 23% of the trials. From the selected binary trials, we then plotted the time-course of event-locked activity in the mu-band for M1 and M2 and low-beta for humans, and for STD tones on S-w positions (blue and red respectively; Fig. 6B). Comparable to human participants, both monkeys showed larger amplitudes in response to STD-S tones than for STD-w tones (Fig. 5). However, while in M1 and human participants binary accentuations were evidenced by a non-significant Binary Similarity but a significant Binary Dissimilarity, M2 showed such an effect later (Fig. 6C). We take this finding as additional evidence for the inter- and intra-individual variability across species in the *if, when,* and *how* accentuations occur.

A. Monkeys – Humans preferences for accents

	M1				M2				Humans				
	Binary %	Triplet %	Comb %	Other %	Binary %	Triplet %	Comb %	Other %	Binary %	Triplet %	Comb %	Other %	
Sess1	18	25	9	48	22	15	19	44	20	23	16	41	**Pt. 3**
Sess2	24	21	16	39	21	33	13	33	20	29	13	38	**Pt. 4**
									22	21	18	39	**Pt. 5**
									23	19	11	48	**Pt. 7**
Avg	22	23	12.5	43.5	21.5	24	16	36.5	21.3	23	14.5	41.5	**Avg**



B. Time-locked dynamics in binary trials



C. Binary accentuation effect

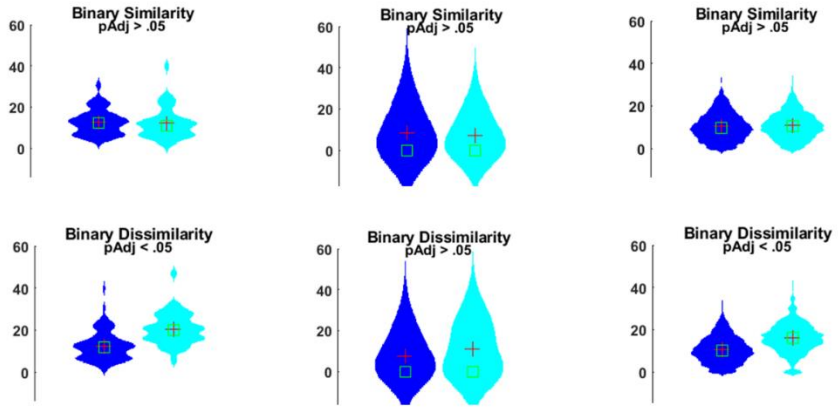


Figure 6 – Monkey-human similarities in rhythm processing.

A: distribution of preferences for accents for, from left to right, M1, M2, and 4 human participants selected from a separate human dataset (Criscuolo, Schwartze, Henry, et al., 2022). *B: The time-course of time-locked neural dynamics in the mu-band for M1 and M2, and in the low-beta band for human participants. In blue, the time-locked responses to STD tones on Strong positions and red for weak positions. C: Binary accent effect quantified by means of Binary Similarity and Dissimilarity metrics. While M1 and the four human participants showed comparable binary accentuations from the beginning, M2 showed the same pattern later (Fig. 5). Of note, M2 only showed significant binary accentuations after two recording sessions. This observation differentiates the one depicted in Fig. 5, where we denoted significant binary accentuations when pooling across data from all recording sessions (>20). Thus, monkeys similarly to humans tend to vary in how they subjectively employ binary accentuation patterns over time.*

Discussion

In this comparative EEG study, we set out to investigate the basic rhythm processing capacities of macaque monkeys and humans. All participants passively listened to isochronous equitone sequences, and we examined spontaneous neurophysiological activity that underlies the sampling of temporal regularities in the acoustic environment. We intentionally did not choose an active experimental task setting as it might enforce unspecific goal-directed behavior, and potentially confound genuine endogenous rhythm processing. We further suggest that the testing of task-independent neural behavior in non-human primates might be a quintessential step in understanding the phylogenetic trajectories of *basic* rhythm cognition.

The present results show that the macaque monkey's neurophysiological responses display the encoding of temporal regularities in the acoustic environment even during passive listening, and confirm prior task-active results (Ayala et al., 2017; Bartolo et al., 2014; Crowe et al., 2014; Gámez et al., 2018; Honing et al., 2018; Merchant et al., 2011; Merchant, Pérez, et al., 2013; Zarco et al., 2009). We further show that these neurophysiological responses go beyond the mere encoding of isochrony: neural activity in the mu-band indicated the superimposition of binary (strong (S)–- weak (w)) accentuations in a subset of trials, mirroring results in humans (Criscuolo, Schwartze, Henry, et al., 2022). Even though all tones were physically identical, in some trials tone-locked neural responses were modulated by a binary (S-w) or ternary (S-w-w) *subjective* accentuation, resembling the well-documented *tic-toc* phenomenon observed in humans (Abecasis et al., 2005; Baath, 2015; Brochard et al., 2003; Poudrier, 2020; Schmidt-Kassow et al., 2011). As this phenomenon emerged during passive listening, the superimposition of accentuations might represent the spontaneous sampling of the acoustic environment beyond the encoding of single event onsets or time-intervals.

Standard ERP and time-frequency analyses, relying on the averaging of neural activity over hundreds of trials, failed to show these binary accentuation patterns. In comparison, our novel trial-based analysis increased sensitivity to such accentuation patterns. These combined observations also support earlier human studies that reported large inter- and intra-individual

differences in *if*, *when,* and *how* participants accentuate (Baath, 2015; Poudrier, 2020). Hence, various accentuation patterns are possible: individuals may start accentuating at different time points (i.e., not necessarily from the beginning of an auditory sequence), may alternate accents over time (thus, over trials), or may not accentuate at all (if not instructed to do so). Thus, any trial-averaging procedure may inevitably overwrite these accentuation possibilities and masks out individual tendencies that influence the parsing of acoustic environmental rhythms.

While isochrony may not necessarily represent a (musical) rhythm, we propose it to be an ideal test-case for investigating the basic neurophysiology that underlies the encoding of temporal regularities. We further note that isochrony is present in a wide range of daily behavior, and its evolutionary advantage might lie in its simplicity: it allows generating temporal predictions (Ravignani & Madison, 2017). In turn, temporal predictability facilitates adaptive behaviours, rhythmic interactions, music, speech, and much more (Greenfield, Honing, et al., 2021).

Complementing results from task-active settings (Lakatos et al., 2008; Schroeder et al., 2010), we show that macaque monkeys can encode and track regularly timed event onsets with low-frequency neural oscillations, mirroring results in humans (42,62,63, see for an overview 29). Along with alpha-/beta-band rhythms, delta-band oscillations have been associated with internalised timing and motor-to-auditory top-down predictions, even in the absence of overt motor tasks (Abbasi & Gross, 2020; Arnal, 2012; Arnal & Giraud, 2012; Bartolo et al., 2014; Biau & Kotz, 2018; Engel & Fries, 2010; Fujioka et al., 2009, 2015; Saleh et al., 2010). Both rhythms are prominently found in cortical motor (A. Keitel & Gross, 2016) and subcortical (striatal) brain regions (Bartolo et al., 2014; Bartolo & Merchant, 2015), and their functional coupling underlies complex auditory processing and temporal predictions in humans (Arnal et al., 2015; B. B. Morillon et al., 2019; B. Morillon & Baillet, 2017). Amplitude modulations in the alpha-beta frequency bands are associated with the priming of auditory brain regions via feedforward anticipation of incoming auditory input (Bowers et al., 2013; Engel & Fries, 2010; Gehrig et al., 2012; Klimesch, 2012; Liljeström et al., 2015). Thus, recurrent information flow between motor and auditory circuitries might underlie the emergence of simple to complex rhythm and beat structure in audition (A. D. Patel & Iversen, 2014).

Cross-species differences in *complex* rhythm and beat processing have been commonly associated with neuroanatomical and -functional differences in the motor system, specifically in cortico-basal-ganglia-thalamo-cortical (mCBGT) circuitry, which is more developed in humans than in non-human species (Mendoza & Merchant, 2014; Patel & Iversen, 2014; Wilson & Cook, 2016). However, the current findings might indicate that *basic* rhythm

processing capacities not necessarily involve the mCBGT, or that they preceded neuroanatomical changes in the evolution of the human brain. However, given the absence of information on the neuroanatomical provenance in EEG signals, we refrain from speculations but motivate future studies to investigate this matter.

In summary, the current findings confirm that macaque monkeys have an adequate neural outfit to sample temporal regularities in the environment, and further show a human-like predisposition to parse regular acoustic input with accentuation patterns. These observations confirm that macaque monkeys have the fundamental building blocks that are necessary for DPS.

These unexplored parallels between humans and macaque monkeys motivate further cross-species investigations to advance better understanding of the phylogenesis of human rhythm cognition.

Conclusion

While passively listening to isochronous equitone sequences, macaque monkeys' neural oscillatory activity sampled the acoustic environment at multiple timescales. Delta- and mu-band oscillations encode the temporal regularity in auditory sequences, tracked sound-onsets, and parsed them with a superimposed accentuation pattern. These observations mirror basic rhythm processing in humans and confirm a complementary role of low- (delta) and high- (mu) frequency bands. As these basic rhythm processing capacities are linked to the development of complex sensorimotor skills in humans (e.g., speech and music), these findings highlight a basic and fundamental steppingstone in the phylogenetic trajectories of humans' rhythm cognition.

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Author contributions

H.M., M.S., S.A.K. conceptualized the study.

H.M., L.P., Y.A. collected data, performed, and interpreted audiogram test.

A.C., M.S., S.A.K planned and A.C. performed data analyses.

A.C., H.M., M.S., S.A.K wrote the manuscript.

Declaration of interests

The authors declare no competing interests.

Chapter 4

Neural and behavioral dynamics of encoding, production and synchronization with external rhythms in subcortical lesion patients

Neural and behavioral dynamics of encoding, production and synchronization with external rhythms in subcortical lesion patients

A Criscuolo, M Schwartze, S Nozaradan, SA Kotz

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Abstract

Acting in and adapting to a dynamically changing environment necessitates precise encoding of the temporal unfolding of sensory events around us and to the *time* of our own (re-)actions to them.

Cerebellar (CE) and basal ganglia (BG) circuitries play fundamental and complementary roles in the timing of sensory events. While the CE seems to encode the precise timing of sensory events (*when* an event occurs), the BG engage in generating temporal predictions (*when* a next event occurs). However, their contributions are rarely investigated in combination, as it is generally difficult to record data from respective patient groups in parallel.

Here we investigated the contributions and causal roles of CE and BG in sensory and sensorimotor timing processing. Healthy controls and patients with lesions in either CE or BG listened to isochronous auditory sequences while their EEG was recorded and later performed a tapping synchronization task. We characterized intra- and inter-individual variabilities, as well as group differences, in delta-band phase-coherence, power fluctuations, and dynamics of acceleration, deviation and stability while tuning delta-band oscillations and tapping to the rhythm of the auditory sequence.

Combined behavioral and neurophysiological results confirm that patients displayed heterogeneity and altered capacity to synchronize ongoing neural activity and behavior with temporal regularities in the acoustic environment. These results confirm and differentiate the causal roles of the CE and BG in temporal processing as well as in the production and synchronization with temporally regular sound events.

Introduction

Time is a fundamental dimension of human cognition. Every decision, every action, every sensory stimulus around us happens in time and at multiple timescales. Our capacities to encode the precise *timing* of events and to *time* our (re-)actions to them are pivotal for acting and adapting to a continuously changing dynamic environment. However, the environment displays some gradient of *temporal regularity* (Greenfield, Honing, et al., 2021): there are various periodicities within the body (e.g., the heartbeat and respiration; Criscuolo et al., 2022) as well as in simple and complex sensory inputs (e.g., music, speech) and in behavior (e.g., interpersonal interactions in the animal and human world; Greenfield, Aihara, et al., 2021). These temporal regularities (or *rhythm*) can enable individuals to anticipate *when* an event starts and when the next sensory event occurs. In turn, temporal anticipation can benefit *adaptive* behavior: we can dance to music because we know *when* the next beat falls, and we can synchronize with others because their movement timing is predictable. Yet what determines our capacity to adapt behavior in time? Do we differ in the *if* and *how* we adapt and synchronize with auditory rhythms?

We have previously proposed (Criscuolo et al., 2023) that synchronization depends on two fundamental lower level capacities that form a 3-node framework: detect, produce, and synchronize ('DPS') with rhythms (Criscuolo et al., 2023). Encoding is a prerequisite to detect rhythms. Human (e.g., Schroeder & Lakatos, 2009) as well as nonhuman animals (e.g., Lakatos et al., 2008) can do so by aligning endogenous neural oscillatory activity at multiple timescales (Criscuolo et al., 2023; Lakatos et al., 2005) to temporal regularities in the sensory environment. Encoding and detecting regularities allow generating predictions about *when* next events occur, thus enabling the *dynamic attending* (Large & Jones, 1999) of event onsets. Temporal predictions materialize as anticipatory neural activity (Arnal, 2012; Fujioka et al., 2009, 2012, 2015; Ross et al., 2018; Snyder & Large, 2005), which supports the predictive alignment of neural oscillations to event onsets, fosters sensory processing (Lakatos et al., 2013) and further allows for production and synchronization of behavior in a predictive manner (Bartolo & Merchant, 2015; Gámez et al., 2018). Thus, "adaptation by anticipation" (Fraisse, 1963; p. 18) is a mechanism for optimizing behavior and operates across sensory modalities (Arnal & Giraud, 2012; Cravo et al., 2013; Friston, 2005; B. Morillon et al., 2016; A.C. Nobre et al., 2012).

Fundamental to predictive temporal processes is the engagement of an extended motor system (Arnal, 2012; Fujioka et al., 2012, 2015), recruited to prepare and execute

predictive and synchronized behavior. The cerebellum (CE) and the basal ganglia (BG) are structures in an extended subcortico-cortical brain network that plays a pivotal role in temporal processing (Schwartze & Kotz, 2013). The CE encodes the precise timing (*when* an event onsets) of sensory events in the subsecond range (Ivry et al., 1988; Ivry & Keele, 1989; Ivry & Schlerf, 2008) and thus allows estimating the duration of temporal intervals (Grube, Cooper, et al., 2010a; Grube, Lee, et al., 2010; Knolle et al., 2012, 2013; Teki, Grube, & Griffiths, 2011; Teki, Grube, Kumar, et al., 2011) by quantifying the time elapsed between event onsets. The BG support the generation of temporal predictions (*when* the *next* event occurs) and use relative timing to extract the beat (Grahn, 2009; Grahn & Brett, 2009a; Schwartze et al., 2011a; Teki, Grube, Kumar, et al., 2011). Consequently, patients with BG lesions are less sensitive to temporal regularity in auditory sequences, potentially resulting in a less efficient prediction of incoming sensory information in basic (Schwartze et al., 2015) as well as in complex (syncopated rhythms; Nozaradan et al., 2017) sequences. In contrast, CE lesions tend to not impact the capacity to generate temporal predictions (Schwartze et al., 2016b) but alter the encoding of event onsets in basic and complex sound sequences (Nozaradan et al., 2017), ultimately resulting in delayed and variable early event-related responses in the EEG (Schwartze & Kotz, 2021). Altered encoding of event onsets and single time intervals (Grube, Cooper, et al., 2010b) further affects the production of and synchronization with rhythms (Ivry & Keele, 1989; Ivry, Keele & Diener, 1988). CE lesion patients displayed larger heterogeneity in self-paced tapping and reduced capacities to synchronize their tapping to temporally regular sequences and tempo changes (Schwartze et al., 2016a). On the other hand, BG lesion patients showed intact synchronization when tapping to an external rhythm but also variable tapping behavior, indicating difficulties in coordinating and adjusting their tapping specifically to slower tempo changes (Schwartze, Keller, et al., 2011b). Supporting prior lesion studies, these observations suggest intact single interval-based timing in the BG patients (Grube, Cooper, et al., 2010b; Teki, Grube, Kumar, et al., 2011), but impaired processing of temporal regularity (i.e., the hierarchical temporal structure of a sensory sequence, the beat) in music (Grahn & Brett, 2009b) and speech (Kotz & Schmidt-Kassow, 2015).

What underlies these dysfunctions? Can we relate difficulties in producing and synchronizing with external rhythms to specific neural dynamics? In other words, can the analysis of neural oscillatory activity causally show in what way the cortico-subcortical timing network differentiates the processing of temporal regularities in perception and action?

We report results from two experiments involving healthy controls (HC) and patients with focal lesions in either the CE or BG. Via a behavioral and an EEG experiment, we assessed sensory and sensorimotor capacities to encode, produce, and synchronize neural activity and overt behavioral responses with temporal regularities in auditory sequences.

Participants listened to isochronous auditory sequences while EEG was recorded. We assessed *if*, *when,* and *how* their neural activity reflected the temporal regularity of auditory sequences. We expected CE patients to show increased variability in the temporal encoding of tone onsets, while we hypothesized BG patients to have difficulties in generating temporal predictions. To test these hypotheses, we developed an extensive analysis pipeline designed to quantify the *tuning* of delta-band neural oscillatory activity towards the stimulation frequency. In order, (i) time-frequency representation analyses allowed us to test for group differences in the power of neural activity in the delta-band. Next, (ii) instantaneous frequency (IF) analyses were employed to test whether delta-band neural activity would tune to the stimulation frequency (*Sf*) of the auditory sequence (1.5Hz). Third, (iii) acceleration analyses quantified the dynamics of oscillatory activity over time, once transformed into IF. (iv) Acc values were further used to compute a metric of Stability (inversely proportional to the sum of dynamic changes in the Acc over time). Similarly, (v) from IF we derived a metric of Deviation, which quantifies the standard deviation of IF from the *Sf* over time. Lastly, (vi) we complemented these metrics with a measure of Shannon entropy (E) of Pow, IF and Acc. Overall, these methods allowed to test the hypotheses that CE lesions should causally impact the ability to encode the precise timing of event onsets (variability in the IF, low ITPC and Dev), while BG lesions should causally impact the capacities to process temporal regularities and generate temporal predictions (low delta power, heterogenous IF and Acc, resulting in low S).

In the behavioral experiment, we expected the patient groups to display difficulties in producing stable finger-tapping and to synchronize to regular auditory sequences presented at three different tempi. We hypothesized that CE patients would have difficulties in the precise encoding of event onsets and synchronizing behavior, especially with faster tempi, while BG patients were expected to have more difficulties producing and synchronizing with slower rhythms. To test these hypotheses, we conducted comprehensive within- and between-group analyses of individual dynamics of tapping, quantifying tapping rates, acceleration, entropy, and stability of the performance over time.

Materials & Methods

Participants

Thirty-three participants took part in the study and signed written informed consent in accordance with the guidelines of the ethics committee of the University of Leipzig and the declaration of Helsinki. Participants comprised two patient groups and one age- and gender-matched control group: 11 patients with focal lesions in the basal ganglia (BG; mean age 50.9, range = 30-64 years; 5 males), 11 patients with focal lesions in the cerebellum (CE; mean age 52.6, range = 37-64 years; 5 males), and 11 healthy controls (HC; mean age 52.1, range = 28-63 years; 5 males). Patients' demographics and lesion information are provided in Tab. 1, their anatomical MRI is provided in Fig. 1, and the results of their neuropsychological and cognitive assessment are provided in Suppl. Tab. 1.

The HC group was recruited via a database at the Max Planck Institute for Human Cognitive and Brain Sciences (Leipzig, Germany). All participants were right-handed and matched for years of education. None of the participants were professional musicians, and they reported no history of hearing or psychiatric disorders. All participants received monetary compensation for taking part in the study. Further information on the participants and lesions characteristics can be found in Nozaradan et al., (2017).

CE	*Age*	*Location*	*Additional locations*	*Etiology*	*Volume in cc*	*X*	*Y*	*Z*
	64	posterior cerebellar lobule	none	PICA infarction	7,1	89	37	26
	30	posterior cerebellar lobule	superior frontal gyrus, corpus callosum	ICH and AVM	48	77	38	35
	49	posterior cerebellar lobule, tonsil, vermis	none	PICA infarction	14,5	57	40	24
	53	anterior and medial cerebellar lobule, tonsil	none	PICA infarction	7,9	62	41	24
	39	anterior and posterior cerebellar lobule	none	cyst extripation	2,4	88	52	15
	62	posterior cerebellar lobule	thalamus	PICA infarction	9	111	69	37
	62	posterior cerebellar lobule	telencephalic white matter	PICA infarction	3,1	57	58	55
	59	posterior cerebellar lobule, tonsil	none	PICA infarction	3,6	110	38	30
	63	posterior cerebellar lobule	telencephalic white matter	PICA infarction	5,7	104	61	46
	37	vermis, deep cerebellar nuclei, peduncle	none	tumor postoperatively	8,8	84	49	37
	42	posterior cerebellar lobule	none	PICA infarction	0,3	121	48	27
BG								
	41	putamen, pallidum, caudate body, IC	corona radiata	MCA infarction	23,4	56	113	76
	59	putamen, pallidum, caudate head and body, IC	corona radiata	ICH	18,3	53	119	76
	52	putamen	none	ICH	2,8	104	99	74
	61	claustrum, putamen, pallidum, caudate body, EC, IC	corona radiata, thalamus	ICH	8,8	51	98	77
	37	putamen, caudate body, IC	none	MCA infarction	0,8	55	97	88
	50	putamen, caudate body, IC	corona radiata, corpus callosum	MCA infarction	6,7	54	110	81
	60	putamen	none	MCA infarction	0,5	47	102	64
	55	putamen, pallidum, caudate body	none	MCA infraction	3,0	102	101	77
	51	claustrum, putamen, EC	insula	ICH	14,8	106	102	78
	64	putamen, pallidum, caudate body, IC	none	MCA infaction	6,1	98	116	80
	49	putamen, caudate body	thalamus	MCA infarction	6,3	93	103	82

Table 1 – Individual patient history.

In order, from left to right, age, lesion location, secondary lesion location, lesion etiology, volume of the lesion in cc, and lesion coordinates (as provided by MRIcron). Top for cerebellar (CE) patients, and bottom for basal ganglia (BG) patients. Abbreviations: PICA = posterior cerebellar artery, ICH = intracerebral/-cerebellar hemorrhage, AVM = arteriovenous malformation, IC = internal capsule, EC = external capsule, MCA = Middle cerebral artery. The highlighted rows indicate patients for which both EEG and tapping data were used.

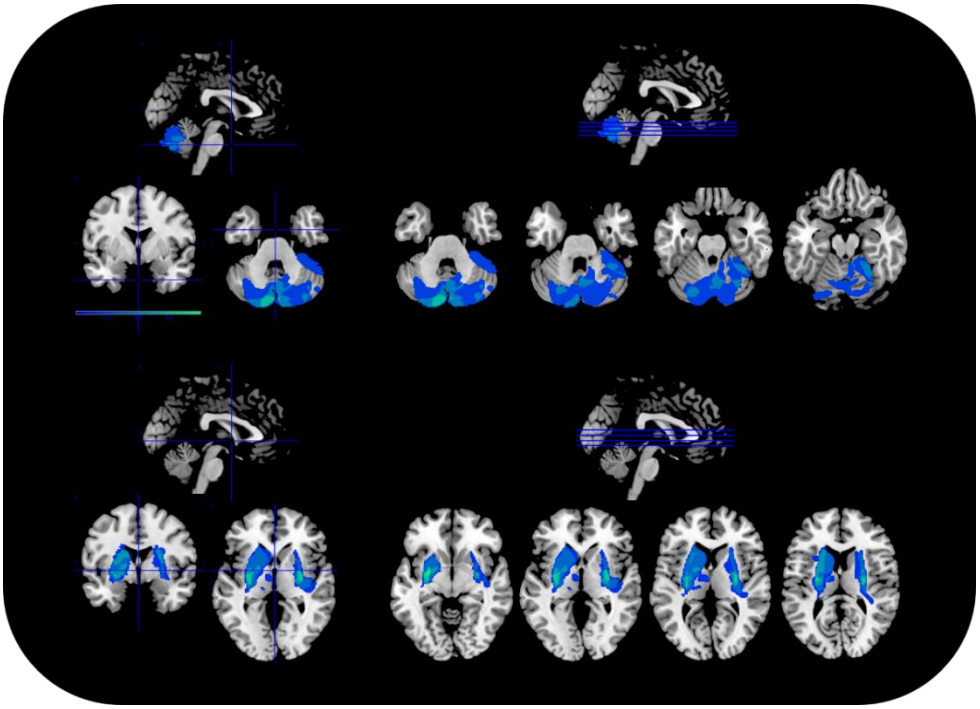

Figure 1 – Brain lesion delineation and overlap.

The figure provides the brain lesion delineation on a template anatomical MRI for basal ganglia (BG; top) and cerebellar (CE; bottom) patients. The figures were obtained by using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/), and display the lesion overlap color-coded in shades of blue (blue = minimal overlap; light blue high overlap; values range from 0 to 5).

EEG experiment: design and procedure

Participants listened to 96 sequences comprising 13-to-16 tones in a recording session of approximately 25min. Each sequence contained frequent standard tones (STD; F0 = 400Hz, duration = 50ms, ramp up and down = 10ms, amplitude = 70dB SPL) and one or two amplitude-attenuated deviant tones (DEV; amplitude 66dB). The inter-onset-interval between successive tones was 650ms, resulting in a stimulation frequency (*Sf*) of 1.54Hz, and a total sequence duration of 8.45-10.4s (13 to 16 tones * 650ms; Fig. 2A).

Participants were seated in a dimly lit soundproof chamber facing a computer screen. Every trial started with a fixation cross (500ms), followed by the presentation of an auditory sequence. The cross displayed on the screen served to prevent excessive eye movements during the presentation of the tone sequences. At the end of each sequence, participants were prompted to press a response button to indicate whether they had heard one or two softer

tones. After this response, there was an inter-trial interval of 2000ms. A session was divided into two blocks of approximately 10 minutes each, with a short pause in between.

EEG recording

The EEG was recorded by means of 59 Ag/AgCl scalp electrodes positioned according to the International 10-10 system with the ground placed on the sternum. Four additional vertical and horizontal electrodes monitored eye movements and were positioned on the outer canthus of each eye, and on the inferior and superior areas of the left orbit. The signals were amplified, low-pass filtered at 512Hz, digitized using a sampling rate of 1024Hz (64-channel high-speed amplifier, Biosemi, the Netherlands). Electrode impedances were kept below 5kΩ and the left mastoid served as online reference. Data were referenced to an average reference offline.

Data Analysis

EEG Preprocessing

EEG data were analyzed in MATLAB with a combination of custom scripts and functions and the FieldTrip toolbox (Oostenveld et al., 2011). Data were band-pass filtered with a 4th order Butterworth filter in the frequency range of 0.1-50Hz (*ft_preprocessing*). Eye-blinks and other artifacts were identified using independent component analysis. This semi-automated routine is composed of two steps: in the first iteration, '*fastICA'* (implemented in FieldTrip) was applied to decompose the original EEG signal into independent components (N= number of EEG channels -1). Components with a strong correlation (>.4) with the EOG time-courses were automatically identified and removed with '*ft_rejectcomponent*' before reconstructing the EEG time-course. In a second step, '*fastICA'* was used again, now with a dimensionality reduction to 20 components. These components were visually inspected via 'ft_*rejectvisual'* and marked as 'outliers' if their max values and z-scores were far from the distribution of other components. The 20 components were further visually inspected by plotting their topographies and time-series, and a second selection of 'outliers' was made. Taking into consideration the two visual inspections, we made a final decision on which components to remove. On average, 2 components were removed ('*ft_rejectcomponent*') before reconstructing the EEG time-series. In the next preprocessing step, artifact subspace reconstruction was performed as implemented in the '*pop_clean_rawdata*' function in

EEGlab, and with the 'BurstCriterion' parameter set to 20 (as recommended in the online EEGlab tutorials; all other parameters were set to 'off'). To further ensure the removal of potentially noisy channels and time-points, we implemented an automatic channel rejection and an artifact suppression procedure. To this end, the median variance across channels was calculated (excluding EOG channels), and channels exceeding 2.5*median variance were defined as 'outliers' and removed. Similarly, the artifact suppression procedure (see Criscuolo et al., 2023) interpolated noisy (>2.5*absolute median) time-windows on a channel-by-channel basis. Lastly, data were low pass filtered at 40Hz via '*ft_preprocessing*', segmented to each auditory sequence (starting 4s before the first tone onset and ending 4s after the last tone onset), and downsampled to 100Hz.

Fast-Fourier Transform and Inter-Trial Phase coherence

Fast-Fourier transform (FFT) analyses were conducted to test whether healthy participants and patients encoded temporal regularities in the auditory sequences. FFT analyses were performed at the single-participant, -channel and -trial level on 8s-long segments starting from the onset of the first tone in the auditory sequence and including a total of 12 tones. The resulting frequency resolution was .125Hz (1/8s = .125Hz). As in prior work (Criscuolo et al., 2023), a fronto-central channel (FC) cluster was used, encompassing the sensor-level correspondents of prefrontal, pre-, para-, and post-central regions highlighted in (Fujioka et al., 2012; Fujioka et al., 2015). The cluster included 14 channels: 'AFz', 'AF3', 'AF4', 'F3', 'F4', 'F5', 'F6', 'FCz', 'FC3', 'FC4', 'FC5', 'FC6', 'C3', 'C4'. Data from this FC cluster were not averaged at this stage. Next, the complex part of the Fourier spectrum was used to calculate inter-trial phase coherence (ITPC; Fig. 2B left). ITPC was obtained by dividing the Fourier coefficients by their absolute values (thus, normalizing the values to be on the unit circle), averaging, and finally taking the absolute value of the complex mean (for further documentation see https://www.fieldtriptoolbox.org/faq/itc/). For illustration purposes, the ITPC plots in Fig. 2B are restricted to 1-4Hz.

As the stimulation frequency of the auditory sequences was 1.5Hz, we restricted single-participant and -channel ITPC analyses at 1.5Hz only, and disregarded any other frequencies including (sub)harmonics of the stimulation frequency. Finally, single-participant and -channel data were pooled per group and visualized as violin plots in Fig. 2B (right). Group differences were statistically assessed by means of a 1-way ANOVA with a group factor

(*anova1* built-in in MATLAB), followed by post-hoc simple tests corrected for multiple comparisons via Tukey-Davis correction (*multcompare* built-in in MATLAB) in case of a significant (p <.05) main effect (Suppl. Tab. 2). Simple effects with a p-value below an alpha-corrected .05 were considered statistically significant.

Analyses of oscillatory dynamics

We employed several methods to analyze neural oscillatory activity pre-, during, and post-stimulation (listening periods). Details and parameters for each of the methods are provided in the respective sections below.

Time-frequency transform

After preprocessing, single-trial EEG data underwent time-frequency transformation (‘*ft_freqanalysis’*) by means of a wavelet-transform (Cohen, 2014). The bandwidth of interest was centered around the stimulation frequency (+/- 1Hz, i.e., .54 - 2.54Hz, thus obtaining a 1.54Hz center frequency), using a frequency resolution of .2Hz. The number of fitted cycles was set to 3. The single-trial approach results in ‘induced’ (as compared to ‘evoked’) responses. No averaging over channels, trials, or participants was performed at this stage. The resultant time-frequency transformed data was labeled as ‘Pow’.

Instantaneous frequency

After preprocessing, single-trial EEG data were bandpass-filtered with a 4th order Butterworth filter centered around the stimulation frequency (plus and minus 1Hz, .54 - 2.54Hz, obtaining a 1.54Hz center frequency; *ft_preprocessing*) and Hilbert-transformed to extract the analytic signal. Next, the instantaneous frequency (IF) at each time point (t), and for each channel, trial, and participant, was calculated with the following formula:

$$IF(t) = \frac{FS}{2\pi}\,\omega(t) = \frac{FS}{2\pi}\,\frac{d\theta(t)}{dt}$$

Where ω(t) is the derivative of the unwrapped phase (θ) at each time point (t), given the time-steps (dt) and FS is the sampling frequency.

Acceleration

Once calculated the single-participant, -trial, and channel-level IF, acceleration (Acc) was calculated as the first derivative of IF (or as the second derivative of the Hilbert-transformed signal). Thus, we employed the following formula:

$$Acc(t) = \frac{d\ IF(t)}{dt}$$

Stability

Once the single-participant, -trial, and channel-level Acc was obtained, Stability (S) was calculated as the inverse of the sum of absolute changes in Acceleration. Thus, we employed the following formula:

$$S(X) = \frac{1}{\sum_1^N |Acc|}$$

Deviation

Once the single-participant, -trial, and channel-level IF was obtained, we quantified the deviation (D) from the stimulation frequency. D was calculated as the square-root of the mean squared difference between the IF and the stimulation frequency (Sf):

$$D(X) = \sqrt{\frac{1}{N}\sum_1^N((IF\ - Sf)^2)}$$

Mean and Entropy Pre-, During, and Post-sequence

For each participant, trial, and channel, we calculated the mean and entropy of Pow, IF and Acc in three time-windows of interest: pre-sequence ('Pre'; -4 to 0s), during the sequence ('Dur'; 0 to 8.45s), and post-sequence ('Post'; 8.45 to 12.45s). Shannon entropy (E) was calculated with the following formula:

$$E(X) = -\sum_{x\ \epsilon X} p(x) \log\ p(x)$$

Where Σ denotes the sum over the variable's possible values and p is the probability of each value (x) in the time-series (X).

Latency

For each participant, trial, and channel, we estimated how long it took for the IF to tune to the *Sf* (1.5Hz). The search was performed within the first 8s of listening (0-8s) of each trial, and by using a narrow frequency criterion (*Sf* ± .2Hz).

Statistical comparisons

Group differences were statistically assessed for each of the above-mentioned metrics by means of a 1-way ANOVA with a group factor (*anova1* built-in in MATLAB), followed by post-hoc simple tests corrected for multiple comparisons (Tukey-Davis correction) (*multcompare* built-in into MATLAB) in case of a significant (p <.05) main effect. Simple effects with a p-value below an alpha-corrected .05 were considered statistically significant and are reported as horizontal black lines on top of Fig. 3B. The ANOVA tables and simple tests are provided in the Supplementary materials (Tab. 3-10).

Tapping experiment

The same participants also performed the tapping experiment. However, not all could complete the tapping task. We therefore present data from 7 matched participants per group. The participants who took part in both experiments are highlighted in Tab. 1.

For the tapping experiment, participants listened to the same auditory stimuli as the ones employed in Nozaradan et al., 2017. They were composed of 12 intervals of 200ms and comprised pure tones (1000Hz) with 10ms rise and fall times and silent intervals (Fig. 4A). Such shortest inter-onset intervals (IOI) define a basic stimulation frequency (*Sf*) of 5Hz. The sequences were further presented at two more tempi: double ('x2', resulting in a 10Hz *Sf*), and quadruple ('x4', resulting in a 20Hz *Sf*) base tempo. Each sequence (12 intervals) was looped continuously for 33s, resulting in a total duration of ~5.5min.

Participants were asked to tap with the index finger in time with the perceived beat in an auditory stream and were instructed to start tapping as soon as they perceived the beat. Differently from the EEG experiment, this task required participants to process the rhythm, extract the salient periodicity from the acoustic sequence and coordinate their movements to it.

Tapping was performed on a response pad while the forearm and elbow were fixed on an armrest cushion to avoid excessive movements. Taps did not trigger any sound, and the latency of each finger tap (i.e. the time of contact of the finger onto the pad) was registered with millisecond accuracy and recorded in Presentation (NBS, Berkeley, USA).

Tapping data analysis

Based on tapping time data, we obtained the inter-tap-interval (ITI) as the difference between successive tap onsets. Next, we calculated the Shannon entropy and the Stability in ITI with the same formulas as described above. Lastly, we obtained the tapping frequency (Freq) as the inverse of the ITI (1/ITI).

Individual data were pooled for each group (Fig. 4B-C). We then performed two main statistical comparisons: within-group and between-group differences. For the latter, between group differences were assessed for the basic tempo, 'x2' tempo, and 'x4' tempo. In Fig. 4C, we display from left to right the group data for the ITI, Freq, and Stability, color coded per group. For the within group assessment, the same variables were displayed per group, assessing differences across tempi (color coded per tempo; basic, 'x2' and 'x4').

Between and within group differences were statistically assessed only for the ITI by means of a 1-way ANOVA with a group factor (*anova1* built-in in MATLAB), followed by post-hoc simple tests corrected for multiple comparisons by Tukey-Davis correction (*multcompare* built-in in MATLAB) in case of a significant (p <.05) main effect. Simple effects with a p value below an alpha-corrected .05 were considered statistically significant and are reported as horizontal black lines on top of Fig. 4. The ANOVA tables and the simple tests are provided in the Supplementary materials (Tab 11-16). No statistical comparisons were performed on the other metrics due to low statistical power (one value per subject, resulting in 7 values per group).

Link between Tapping – EEG data

Despite the low number of participants, exploratory analyses aimed to assess a possible link between tapping and EEG data by means of Pearson correlation. We correlated the EEG metrics of ITPC, Pow E, IF E, Acc E, Stability, Deviation, and Latency with tapping metrics of Entropy and Stability. Correlations were assessed at the single-participant level, and independently for the three tempi. Finally, the results were visualized by means of circular graphs in Fig. 5 (rho values are provided in Suppl. Fig. 27).

Data and code Availability

The analysis code in use will be stored in an open repository.

Results

In this study, we investigated how sensory and sensorimotor capacities are shaped by temporal regularities in auditory sequences comparing HC, CE, and BG patients. Hence, we report results from two experiments: first, participants listened to isochronous auditory sequences while EEG was recorded continuously (Fig. 2). Next, the same individuals performed a tapping task, in which they synchronized their tapping to regular auditory sequences presented at three different tempi (Fig. 4).

EEG experiment

In this experiment, we adopted two methodological approaches. First, we employed Inter-Trial-Phase Coherence (ITPC) analyses to investigate *if* and *how* HC, BG and CE participants encoded temporal regularity in auditory sequences. Second, analyses of neural oscillatory dynamics assessed *if*, *when,* and *how* participants' neural activity *tuned in* and *out* of temporal regularity in acoustic sequences. Details for each methodological approach can be found in the respective methods section above. Results for each method are discussed below, in two separate paragraphs.

Inter-Trial Phase coherence (ITPC)

While participants listened to isochronous auditory sequences presented at a *Sf* of 1.5Hz (Fig. 2A), their neural activity encoded the temporal regularity, as shown by the coherence peaks at 1.5Hz in the ITPC spectrum (Fig. 2B). A distinct peak at 1.5Hz was present in the ITPC spectrum for all groups (Fig. 2B, left). However, statistical analyses revealed a significant group difference (Fig. 2B, right): HC (dark blue) showed stronger coherence at the *Sf* than both CE and BG groups (lighter shades of blue). The one-way ANOVA revealed a significant group effect ($p < .001$; Supp. Tab. 2), and post-hoc simple t-tests revealed higher coherence in HC than in both CE and BG groups, but no significant difference between CE and BG (Suppl. Tab. 2; corrected for multiple comparisons).

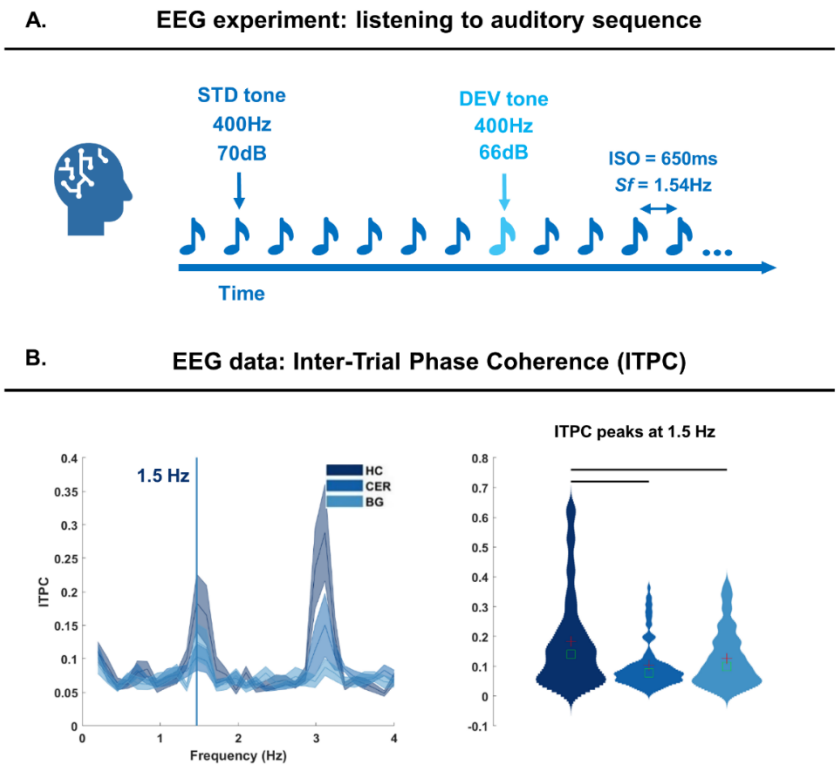

Figure 2 – Experimental design of the EEG study, and Inter-Trial Phase Coherence analyses.

A: experimental design: participants listened to 96 isochronous auditory sequences presented at a fixed Stimulation frequency (Sf) of 1.54 Hz (inter-stimulus onset (ISO) of 650ms). The sequences included frequent standard (STD; pitch 440Hz, loudness 85dB) and infrequent amplitude deviant (DEV) tone (amplitude 66dB). B: Inter-Trial Phase Coherence (ITPC) analyses. The ITPC plot features frequency in Hz on the x-axis and the ITPC values on the y-axis. Healthy controls (HC), cerebellar (CE) and basal ganglia (BG) patients' data are provided in shades of blue (from dark to light blue). The vertical blue line signals the ITPC peak at 1.5Hz. These peaks were extracted and plotted on the right, via means of distribution plots. Here, statistical comparisons assessed group differences in ITPC values at the stimulation frequency (1.5Hz). The black horizontal lines report significant differences between the groups, after correction for multiple comparisons.

Neural oscillatory dynamics of rhythm processing

Single-participant estimations

Each of the metrics mentioned above were estimated at the single-participant and –trial level, as illustrated in Fig. 3A: the time-course of Hilbert-transformed data, IF and Acc (solid line = mean over channels; shaded bars report the standard error (SE) over channels). The dashed pink line on the IF plot, reports the *Sf*. On the right side, the distribution of IF and Acc in the

‘Pre-‘, ‘Post-’ and ‘Dur-‘(ing) the listening periods (color-coded in shades of blues), and pooling across the FC channel cluster. The time-series of IF and Acc were further used to estimate D, the deviation from the *Sf*, and S, the stability of the neural signal. Finally, we obtained the Latency (not visualized here), the first crossing point of IF through the horizontal *Sf* line. The single-participant and -trial figures (33 participants x 96 sequences) can be provided upon reasonable request.

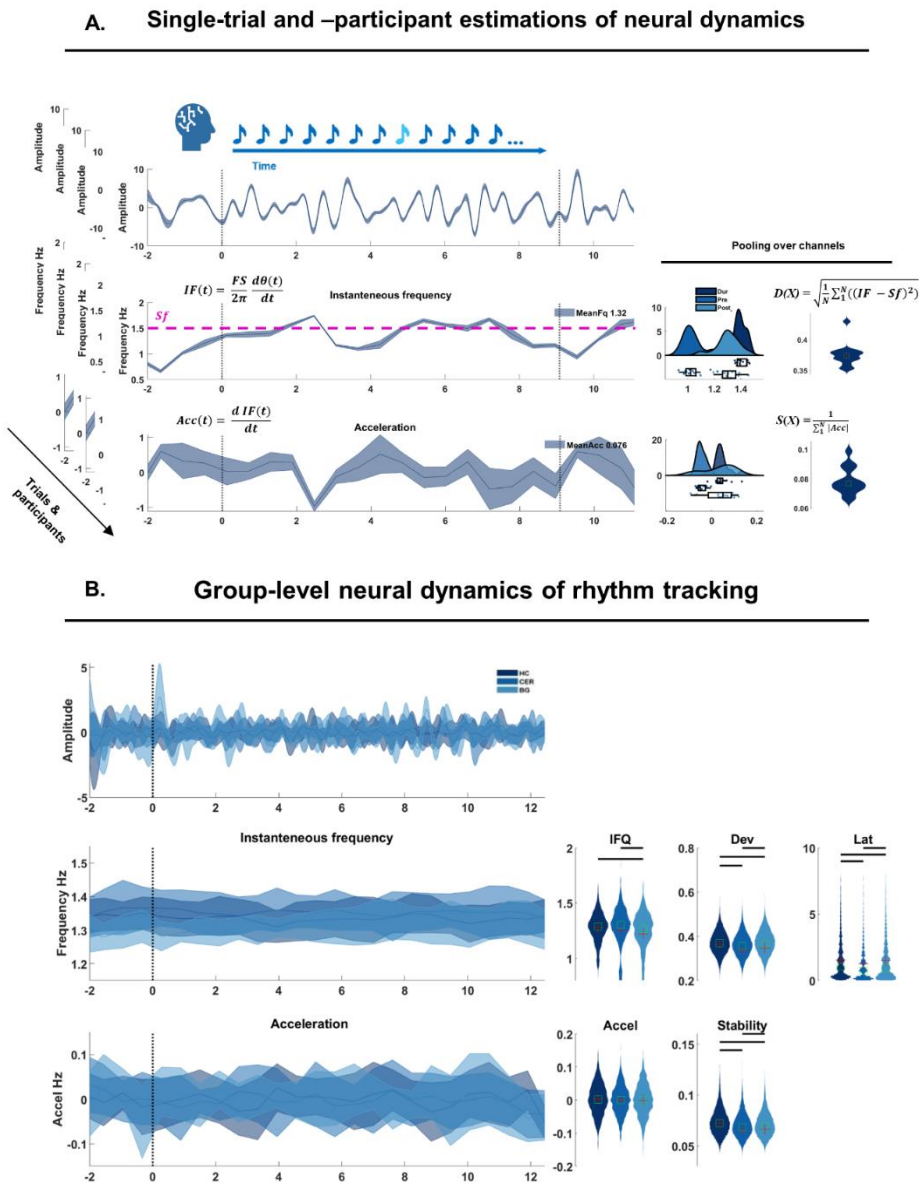

Figure 33 – Analyses on neural dynamics of rhythm processing.

A: We estimated, at the single-participant and -trial levels, the instantaneous frequency (IF) and Acceleration (Acc; time-courses on the left side). The pink dashed line on top of the IF indicates the stimulation frequency (Sf). The distribution plots on the right side are obtained by pooling data points over channels and averaging over time. IF and Acc were also used to calculate metrics of Deviation (D) and Stability (S). The violin plots on the right side show the resultant D and S over time, and pooling over channels. B: mirroring the layout of A, the group-level data (color-coded in shades of blue) reporting on the left the time-courses of neural oscillations in the delta frequency band (top), the estimated IF (middle) and Acc (bottom). On the right side of the IF time-courses, violin plots of the IF pooling over trials and participants and averaging across the FC cluster of interest. Next to it, the estimated Dev values, and the Latency. Next to the time-courses of the Acc, violin plots of the Acc pooling over trials and participants and averaging across the FC cluster of interest. Next to it, the estimated S values. The thick black horizontal lines on top of the violin plots report significant group differences ($p < .001$, corrected for multiple comparisons).

Group visualization

Individual data were then pooled into 3 groups: HC, CE, and BG patients. The group-level data is provided in Fig. 3B and mirrors the layout of Fig. 3A.

On the right side, the violin plots show (in order) the IF and Acc, obtained by averaging data during the listening window (0-8s) and across channels, and by pooling single-participant and -trial data. Next to it, are the distributions of Dev, S and latency obtained by averaging over channels, and pooling over participants and trials. Note that for readability, Fig. 3 focuses on the listening period ('Dur') only, avoiding visualizations of Pre- and Post-listening periods. Similarly, Fig. 3 excludes data from Entropy analyses. Statistical comparisons are provided in Suppl. Tables, while additional figures are stored in a personal drive, and can be provided upon reasonable request by the authors.

HC's Pow and IF was like that of CE patients, but significantly different from BG patients (Suppl. Tab. 2,4). HC's Dev and Lat were higher than both patients' groups (Suppl. Tab. 9,10). There were no significant differences in Acc, but HC had a significantly higher S as compared to the two groups (Suppl. Tab. 8).

In contrast, CE patients showed the lowest Dev and Lat (Suppl. Tab. 9,10), comparable Acc (Suppl. Tab. 6) and the lowest S (Suppl. Tab. 8).

Finally, BG patients' neural activity showed higher power (Suppl. Tab. 2) and lower IF (Suppl. Tab. 4) during listening as compared to both HC and CE. Their Dev, Lat, and S was higher than CE but lower than HC (Suppl. Tab. 8,9,10).

Tapping experiment

Participants listened to auditory sequences at 3 rates (basic tempo, 'x2' and 'x4' tempo; Fig. 4) and were asked to synchronize their tapping to the perceived beat and try to keep tapping at a comfortable rate. Within- and between-group comparisons assessed tapping behavior and variability over time. Starting from the within group analyses (Fig. 4B), HC's ITI followed an inverse U-shape, whereby ITI increased from the basic to the 'x2' tempo and decreased for the highest rate ('x4' tempo; Suppl. Tab. 15). The 'x4' showed the shortest ITI as compared to the other two tempi, thus resulting in the highest tapping frequency. Tapping stability tended to increase linearly over the tapping rates.

CE patients' tapping behavior was comparable to the one found for HCs: their ITI showed an inverse U-shape, whereby the ITI was significantly longer in the 'x2' tempo as compared to the basic and 'x4' tempi, and the latter had the shortest ITI (Suppl. Tab. 16). Thus, the resulting tapping frequency increased across rates, and so did the tapping stability.

Finally, the BG patients showed a negative linear relationship between tapping speeds and ITI, whereby the ITI were longest for the basic tempo and shortest for the 'x4' (Suppl. Tab. 17). Thus, their resulting tapping frequency followed a U-shape across tempi, and their stability increased with 'x4' tempo.

Moving to between-group differences (Fig. 4C), BG patients' ITI were largely variable across individuals, as revealed by both within- and between-group analyses. In fact, some of the patients tapped at high frequencies, and others at a slow frequency, especially at the basic tempo. However, the average ITI at basic tempo was significantly longer than for the other two groups, who did not significantly differ from each other (Suppl. Tab. 12). CE patients showed longer ITI and high stability at 'x2' (Suppl. Tab. 13), and higher ITI at 'x4' tempo (Suppl. Tab. 14) as compared to the other two groups. BG had the lowest ITI at 'x2' tempo, and the lowest stability at 'x4' tempo. HC had the lowest ITI and the highest stability at 'x4' tempo.

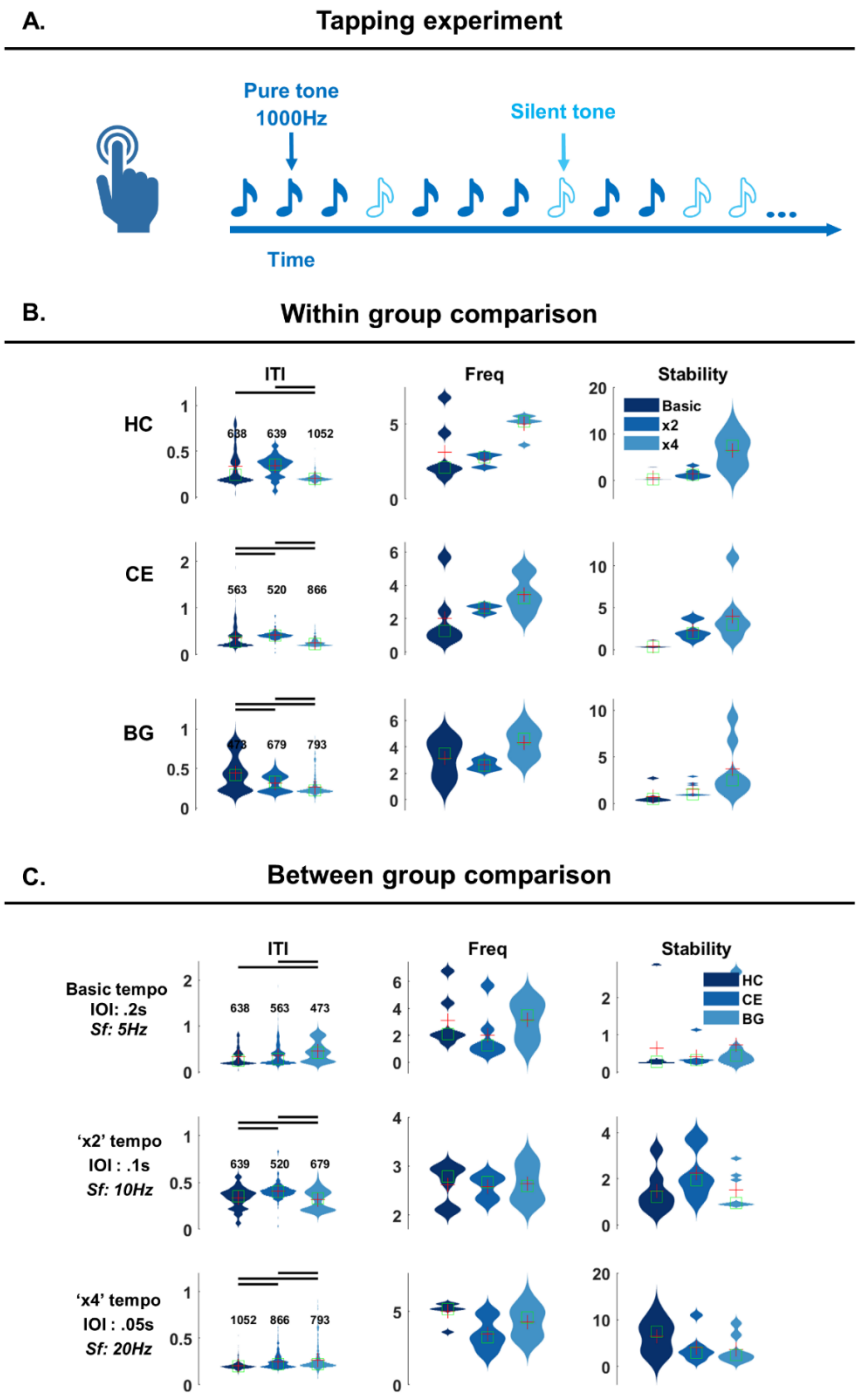

Figure 44 – Tapping experiment and group comparisons.

A: experimental design: participants listened to auditory sequences at three different speeds and were asked to synchronize their tapping to the perceived beat, while keeping the tapping at a comfortable rate. These sequences included pure tones at 1000Hz and silent tones. The inter-onset-intervals (IOIs) varied from the basic tempo (IOI: .2s) to the 'x2' tempo (IOI: .1s) and 'x4' tempo (IOI: .05s), resulting in stimulation frequencies (Sf) of 5, 10 and 20 Hz respectively. B: Within group comparisons statistically assessed the difference in inter-tap-intervals (ITI) per group (each row), and across speeds (the three distributions per plot). Thick, black, horizontal lines report significant differences across tempi, per group. Next to ITI, we also estimated the tapping frequency (Freq) and tapping stability (in order). C: Between group comparisons statistically assessed the difference in ITI across groups (the three distributions per plot), per tempo. Thick, black, horizontal lines report significant differences across groups, per tempo. Next to ITI, we also estimated the tapping frequency (Freq) and tapping stability (in order).

Link between Tapping - EEG

Further analyses assessed the link between Tapping Entropy (Tap E; light blue) and Tapping Stability (Tap S; dark blue) with the metrics derived from the individual's EEG data analyses (Fig. 5). Given the low number of participants per group, these correlations present exploratory analyses, and no conclusions are drawn on these observations. The correlation strength (rho values) is represented in Fig. 5 with the thickness of the line connecting each node. Rho values below .5 were masked out. Positive and negative rho values are also provided in Suppl. Tab. 18.

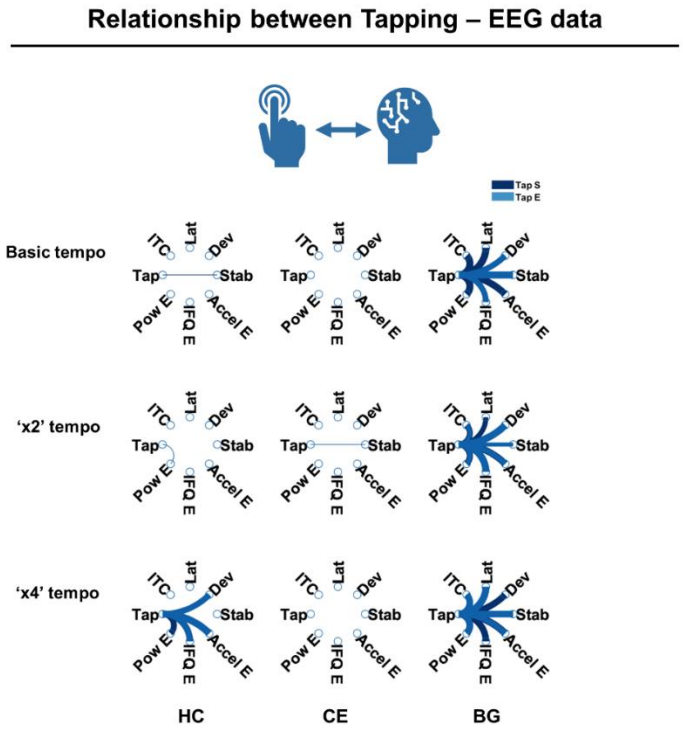

Figure 5 – Relationship between Tapping and EEG data.

Exploratory analyses assessed the link between tapping metrics of stability (Tap S; dark blue) and Shannon entropy (Tap E; light blue) with EEG-derived metrics of Inter-trial-coherence (ITC), power entropy (Pow E), entropy in instantaneous frequency (IFQ E), acceleration entropy (Accel E), Acceleration Stability (Stab), Deviation (Dev) and Latency (Lat). Correlations were performed independently per groups (organized column-wise) and tapping speeds (organized in rows).

Discussion

We investigated the causal contributions of the cerebellum (CE) and the basal ganglia (BG) to sensory and sensorimotor processes underlying the detection, production and synchronization ('DPS') with basic auditory rhythms. Using EEG, we assessed the neural dynamics of temporal processing, unravelling group differences in *when, if,* and *how* healthy controls (HC), CE, and BG lesion patients process temporal regularities. Next, a behavioral experiment probed their capacity for DPS when tapping to temporally regular acoustic sequences at different rates.

Starting from the behavioral experiment, we found significant group differences across tapping rates. CE patients showed similar tapping rates as HCs for the basic rate and more stable tapping than the other groups for the 'x2' rate, where they tapped faster. However, the tapping at 'x4' was slower and more variable than for the other two groups, and their stability was lower than that of the HCs. Analyses of delta-band neural dynamics revealed that CE patients' delta power and instantaneous frequency were comparable to the HCs. However, they showed lower stability and reduced phase coherence, confirming preserved yet deteriorated sensitivity to temporal regularity in the acoustic sequences. These observations are in line with previous evidence, where CE patients showed intact sensitivity to the temporal structure of auditory sequences (Schwartze & Kotz, 2021), but heterogenous encoding of the precise timing of event onsets (Grube, Cooper, et al., 2010b; Nozaradan, Schwartze, et al., 2017), ultimately affecting the production of and synchronization with rhythms especially at faster rates (Ivry & Keele, 1989; Ivry, Keele & Diener, 1988; Schwartze et al., 2016).

Compared to HCs and CE patients, BG patients' tapping frequency did not follow the increase in tempo rates but followed a U-shape. Large inter-individual variability was present especially at the basic tempo, with some patients tapping very fast while others tapped more regularly. BG patients' tapping stability was lower than that of the other groups in the fastest tempo. In line with these observations, EEG results for delta-band neural activity revealed stronger power variations, reduced instantaneous frequency, stability, and phase coherence in BG patients when listening to isochronous auditory sequences. We consider that altered sensory encoding of temporal regularity might have influenced the patients' capacity to

produce and synchronize efficiently with an external rhythm. These findings are in line with previous results showing altered processing of salient periodicities in BG patients (Nozaradan, Schwartze, et al., 2017) even in simple auditory sequences (Schwartze et al., 2015), and confirm that the heterogeneity in tapping behavior and difficulties in adapting to tempo changes are related to BG dysfunctions (Schwartze, Keller, et al., 2011b).

Although exploratory, correlation analyses further revealed a link between tapping behavior (entropy and stability) and brain-derived metrics of dynamics (e.g., power entropy, acceleration, stability), specifically for the BG patients. However, given the small sample size and low statistical power, we refrain from any speculative interpretations of these preliminary results.

The newly employed methods allowed characterizing the role of delta-band oscillations in basic rhythm processing: we showed that delta oscillations fluctuate over time, *tuning in* and *out of* perceived acoustic regularity in auditory sequences by dynamically accelerating and slowing down from silence to listening periods. These observations support the *dynamic attending* hypothesis (Mari Riess Jones & Boltz, 1989; Large & Jones, 1999), and confirm the role of low-frequency oscillations (Schroeder & Lakatos, 2009) in detecting, producing, and synchronizing with temporal regularities in an auditory environment. On the other hand, the current approach also confirmed the fundamental role of the BG and CE in an extended cortico-subcortical-cortical network underlying rhythm and timing processing (Criscuolo, Pando-Naude, et al., 2022; Kasdan et al., 2022; Kotz et al., 2018; Schwartze & Kotz, 2013). In fact, we showed that while the healthy brain could flexibly and dynamically respond to and synchronize with sensory inputs, patients with lesions in the BG and CE did not. Patients showed a degree of heterogeneity and deteriorated capacity to synchronize ongoing neural activity to temporal regularities in the acoustic environment, which ultimately resulted in altered capacity to produce stable tapping and to synchronize behavior with external rhythms. Differently from our hypotheses, however, we could not clearly dissociate CE from BG timing functions. We argue that our experimental setup and/or the adopted analytical approach may have played a role. For instance, use of isochronous auditory sequences as opposed to complex auditory rhythms may represent the first limitation, as these stimuli may have been suboptimal to dissociate CE-related sensory timing computations from BG-related temporal predictions. Secondly, differently from the typical tone-locked analysis approach, we here investigated the neural dynamics of rhythm tracking at the sequence-level. This choice allowed us to characterize the frequency, acceleration, and stability of neural waves tuning towards auditory

rhythms. However, such approach does not provide an indication of inter-individual variability in the amplitude and latency of event-related responses to each tone onset along the sequence. Third, we have previously discussed that BG and CE are part of a widespread cortico-subcortical network engaging in rhythm processing. Thus, a lesion in these subcortical regions may not necessarily impact basic rhythm processing. In fact, we know from the animal literature that there are neurons in the cortex acting as 'neural chronometer' encoding the passage of time and the precise timing of sensory events (Merchant et al., 2011; Merchant, Harrington, et al., 2013; Merchant, Pérez, et al., 2013). These cortical neurons may take over timing computations as a functional reorganization mechanism after subcortical brain lesions, ultimately preventing to characterize the link between focal subcortical lesion and impaired timing functions. Finally, another limitation lies in the difficulty to distinguish fine-grained timing processing in absence of spatio-temporally resolved data. In this perspective, this research field would benefit from a more accurate characterization of the time-course, strength and directionality of information flow during rhythm processing. Such approach would allow to monitor the interplay and the causal relationship between cortico-subcortical regions, as well as between the BG and CE. Furthermore, it would enable to characterize the frequency-specificity and directionality of influence of some timing computations. Existing literature suggests delta-, as well as beta-band activity to be prominent in subcortical and cortical brain regions (Bartolo et al., 2014; Bartolo & Merchant, 2015; A. Keitel et al., 2017; A. Keitel & Gross, 2016) and to be linked to predictive priming of sensory regions (Arnal, 2012; Engel & Fries, 2010). In other words, the anticipatory alignment of beta-band activity to the *when* of salient events (Fujioka et al., 2012, 2015) couples with bottom-up delta-band activity (Abbasi et al., 2018; Arnal et al., 2015; Merchant et al., 2015; Saleh et al., 2010) to instantiate motor-to-auditory predictions in support of adaptive behavior. Thus, our focus on scalp activity and on delta-band activity only prevents a full characterization of bottom-up and top-down mechanisms of temporal processing and prediction. Altogether, we encourage future studies to complement the current findings with investigations of beta-band activity, with a particular focus on event-related dynamics and beta-delta functional coupling. Such a complementary approach would deepen our understanding of the neurophysiological mechanisms underlying intra- and inter-individual variabilities in the capacities to detect, produce and synchronize with temporal regularities in the sensory environment, and to ultimately produce adaptive behavior.

Conclusions

The capacities to encode the precise timing of the sensory events around us, and to time our (re-)actions to changes in the environment are pivotal to act and adapt in a dynamically changing environment. In this study, we explored the rich and variegated landscape of neural oscillatory dynamics, and assessed *if, when* and *how* neural oscillations processed the temporal regularity in acoustic sequences. BG and CE lesions impacted the neurophysiological encoding of the rhythm and further affected the ability to produce and synchronize behavior (tapping) to external stimuli.

Author contributions

S.A.K., M.S., C.O., S.N., conceptualized both or one part of the study.

S.A.K., M.S., C.O., collected the data.

A.C. designed and performed data analyses.

A.C., S.A.K., M.S., S.N., interpreted the results and wrote the manuscript.

Declaration of Competing Interest

The authors declare no competing interests.

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Chapter 5

Cognition through the lens of a body-brain dynamic system

Cognition through the lens of a body–brain dynamic system

A Criscuolo, M Schwartze, SA Kotz

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Abstract

Continuous interactions between physiological body-brain rhythms influence how individuals act, perceive, and evaluate their environment. Despite increasing interest, the intricate interface between breathing, cardiac, neural rhythms, and cognitive function remains poorly understood. By evaluating current theoretical and empirical implications, we derive an integrative framework of a *body-brain dynamic system* that combines a hidden hierarchical structure with dynamical state transitions. We propose that body-brain signals can interchangeably drive state- and task-specific coupling mechanisms which influence cognitive functions. The dynamical nature of this framework parallels the intrinsic variability of human behavior, and ultimately aims at better understanding how individuals act in and adapt to a dynamically changing environment.

Keywords

Body-brain interaction, respiratory rhythm, cardiac rhythm, neural oscillations, human behavior, dynamic system

Reciprocal influence of body and brain rhythms on behavior?

The question whether there is any systematic relationship between the body and the brain (or the 'mind') represents a longstanding debate, dating back to Hippocrates. In the Platonic dialogues we also read:

"…the great error of our day in the treatment of the human body, … [is] that physicians separate the mind from the body."

Stepping back from Descartes' and Newton's reductionist principles, recent research confirms that multiple physiological activities of the body and the brain share a cyclic (quasi-)periodic (Klimesch, 2018) nature and display systematic patterns of *(a)synchronous oscillatory dynamics* and/or *mutual dependencies*.

Although the most evident body rhythms such as respiration and heart rate (HR) are considerably slower (roughly 0.25Hz and 1.25Hz, respectively) than the most frequently studied neural rhythms (1-50Hz; Fig. 1A-B) and quite variable across the lifespan (Fleming et al., 2011), empirical evidence confirms their tight link to neural and cognitive functions. Body rhythms might directly influence neural spiking and oscillatory activity and thereby modulate information processing (Critchley & Garfinkel, 2018; H.-D. Park et al., 2014), perception, action, cognition, and emotion regulation (Azzalini et al., 2019; Ebert et al., 2002; Heck et al., 2017; Ito et al., 2014; Kluger, Balestrieri, et al., 2021; Kluger & Gross, 2021; Monti et al., 2019; Nakamura et al., 2018). Stimulated by these recent developments, we propose that the combined assessment of rhythmic body-brain signals is critical to advance a holistic understanding of how individuals solve the fundamental task of continuously evaluating, reacting, and adapting to a dynamically changing environment (Critchley & Harrison, 2013; Varga & Heck, 2017).

Bridging the gap between current empirical research and existing theoretical propositions, we propose an integrative framework to holistically examine the body-brain-behavior interface. The central tenet of this *body-brain dynamic system* (BBDS) is to regard the body and the brain as partially independent *subsystems* that dynamically transition from *decoupled* to *coupled* states in a context-specific manner. We propose that an emergent hidden non-static hierarchical organization (see section 'An integrative framework') modulates neurocognitive function, continuously supporting the optimization of adaptive behavior. In contrast to static hierarchical conceptions, we reason that body-brain coupling instantiates a transient state that

is interchangeably driven by either the body or the brain according to environmental contingencies (Fig. 2).

The first challenge for this framework is, that while appealing, observed links between body-brain rhythms and behavior are mostly correlational in nature, and thus do not provide causal evidence. Second, research has primarily focused on the isolated influence of respiratory or cardiac rhythms on brain activity or behavior, precluding a more inclusive stance on the body-brain-behavior interface. Existing holistic perspectives, instead, tend to focus on (self-)consciousness, but not overt behavior (Critchley & Garfinkel, 2018; Park & Tallon-Baudry, 2014). With a broader perspective, the 'binary hierarchy body brain oscillation theory' (Klimesch, 2018) was among the first to propose the existence of a body-brain frequency architecture governed by binary (sub)harmonic relationships (***frequency coupling*** and ***cross-frequency coupling,*** see Glossary). This theory accounts for inter-individual variability in body-brain rhythms (e.g., heart rate and spontaneous alpha band activity) and subjective rate preferences in overt behavior (e.g., spontaneous walking rate), and has stimulated key questions that define the starting point for the proposed BBDS framework:

(i) Are body-brain rhythms continuously coupled over time?

(ii) If body-brain coupling is not a constant phenomenon, which rhythm(s) drive it?

(iii) Do psychophysiological states (e.g., resting versus active states) dynamically influence body-brain rhythms or are these constrained by static harmonic relationships?

(iv) Is cognition (e.g., the allocation of attention over time) influenced by body-brain rhythms and vice versa? If so, how?

(v) Finally, what exactly is the functional role of body-brain interactions?

Guided by these questions and bridging the gap between current theory and empirical findings, the goal of the BBDS is to provide a dynamic perspective on the body-brain interface, focusing on breathing and cardiac rhythms to explain how such intricate interactions enable individuals to efficiently act in and adapt to a dynamically changing environment. Rather than a formal description of system dynamics, the BBDS develops a framework and motivates future research to implement and test model predictions (see Outstanding Questions).

To this end, the BBDS embraces the natural variability of human behavior across multiple cognitive functions and promotes a holistic approach to the study of both neurotypical individuals and neurological disorders (see Box1).

Brain rhythms

Neurophysiological activity is characterized by periodic fluctuations in the excitability of neuronal populations (Buzsáki et al., 2013). Rhythmic oscillatory activity is usually clustered (with some flexibility in the bandwidths) in multiple frequency bands, ranging from delta (1-4Hz), theta (4-8Hz), alpha (8-12Hz), beta (12-25Hz) and gamma (from 25Hz onwards). These oscillations and their relation to cognitive function have been extensively studied in the domains of attention (Lakatos et al., 2008), sensorimotor behavior (Merker et al., 2009), speech (Giraud & Poeppel, 2012) and music [18], while aberrant neural oscillatory activity is linked to dysfunction thereof (Uhlhaas et al., 2018). Current evidence suggests that neural rhythms adhere to a specific spatio-temporal organization whereby ***functional coupling*** across space, time, and frequency is associated with local cytoarchitectonic structure, specific anatomical connectivity as well as with cognitive function (A. Keitel & Gross, 2016). For example, the coordination of excitability changes across neuronal populations might render perception an essentially rhythmic function (see ***perceptual cycles***), which at least partially depends on the phase and rate of the respective oscillations (Large & Jones, 1999; Schroeder et al., 2010; Schroeder & Lakatos, 2009). However, little is known about the joint influence of other physiological oscillations, such as respiratory and cardiac rhythms on cognitive function. Thus, the question arises: is human behavior modulated by the interaction of body-brain rhythms? And if so, how?

Respiratory rhythms and their influence on brain dynamics and behavior

Two main control systems regulate respiratory muscles (Plum, 2008). One exerts unconscious, autonomic, and continuous control of respiration meeting the body's metabolic demands. This pathway comprises the brainstem, reticular formation, pons, and medulla. The other system, comprising sensorimotor and limbic forebrain structures (Belyk et al., 2020), facilitates the top-down control of respiration, allowing among other functions to coordinate speech and complex motor acts.

A widespread cortico-limbic network actively tracks human breathing (Herrero et al., 2018). Activation of olfactory and limbic regions, including the amygdala and hippocampus, aligns with the inspiration phase (see ***phase-locking***) of the respiratory cycle (Zelano et al., 2016). Voluntary control of breathing engages primary sensory and motor cortices, the supplementary motor area, cerebellum, thalamus, caudate nucleus, and globus pallidum, bilaterally, as well

as the medulla (McKay et al., 2003). Notably, breathing is also modulated by covert motor behavior, for instance during imagery (Decety et al., 1993) and listening to music (Bernardi et al., 2006). People tend to align their breathing with a perceived musical rhythm (Haas et al., 1986) as a form of ***respiratory entrainment***. Consequently, the phase-alignment with external stimuli influences visuo-spatial (Kluger, Balestrieri, et al., 2021; Perl et al., 2019) and memory performance (Nakamura et al., 2018; Zelano et al., 2016). Conversely, psychophysical states can modulate breathing. For instance, states of anxiety, depression, anger, stress, and other negative or positive emotions are linked to specific respiratory patters (Jerath & Beveridge, 2020) and conscious control of breathing, e.g., slowing, can induce changes in heart rate variability ((Gross et al., 2016; Stark et al., 2000)) and in brain activity (Zaccaro et al., 2018). This evidence points to an active interface of psychophysical states, breathing, and cognitive function. However, which mechanisms govern these intricate relationships, and what defines breathing-cognition coupling functionally? Moreover, what does cardiac activity add to the equation?

Cardiac rhythms and their influence on brain dynamics and behavior

The alternation of systole (ventricular contraction) and diastole (ventricular relaxation) gives rise to the cardiac cycle and the heart rhythm. The heartbeat (HB) does not display the regularity of a metronome but rather acts more like a dynamic pacemaker (Shaffer et al., 2014) driven by both sympathetic (acceleration) and parasympathetic (vagus) nerves.

"when the heart is affected, it reacts on the brain; and the state of the brain again reacts […] on the heart; so that under any excitement there will be much mutual action and reaction between these" – Charles Darwin (Darwin, 1998).

Research shows that noradrenergic neurons in the locus coeruleus may influence neurovascular coupling and cerebral blood flow (Iadecola, 2017), from health to pathology (Sean Giorgi et al., 2020). Similarly, HR modulates thalamic activity, resulting in global brain and cognitive effects ranging from emotion regulation (Balzarotti et al., 2017) to attention and working memory performance (Hansen et al., 2003). Evidence further highlights a specific phase relationship between the cardiac cycle and information processing. Hence, visual perception is modulated by heartbeat-locked neural responses (Park et al., 2014), the so-called heartbeat-evoked potential (HEP). Consequently, reaction times in response to auditory (Louisa Edwards et al., 2007) and visual (McIntyre et al., 2007) stimuli increase around the ***R-peak***. In turn, HEP modulated both early (P50) and later (N100, P300) event-related

potentials (ERP) of the EEG in response to somatosensory stimuli (Al et al., 2020). Hence, somatosensory stimuli are likely better detected during diastole than systole [48], and detection is inversely related to the amplitude of the preceding HEP, similarly to what has been observed for visual stimuli (Al et al., 2020; Park & Blanke, 2019b). However, this link is likely bi-directional, as cognitive functions such as attention, emotional processing, and social cognition, as well as the underlying brain activity, similarly impact interoception and HEP (Adolfi et al., 2017; Coll et al., 2021; Park & Blanke, 2019b).

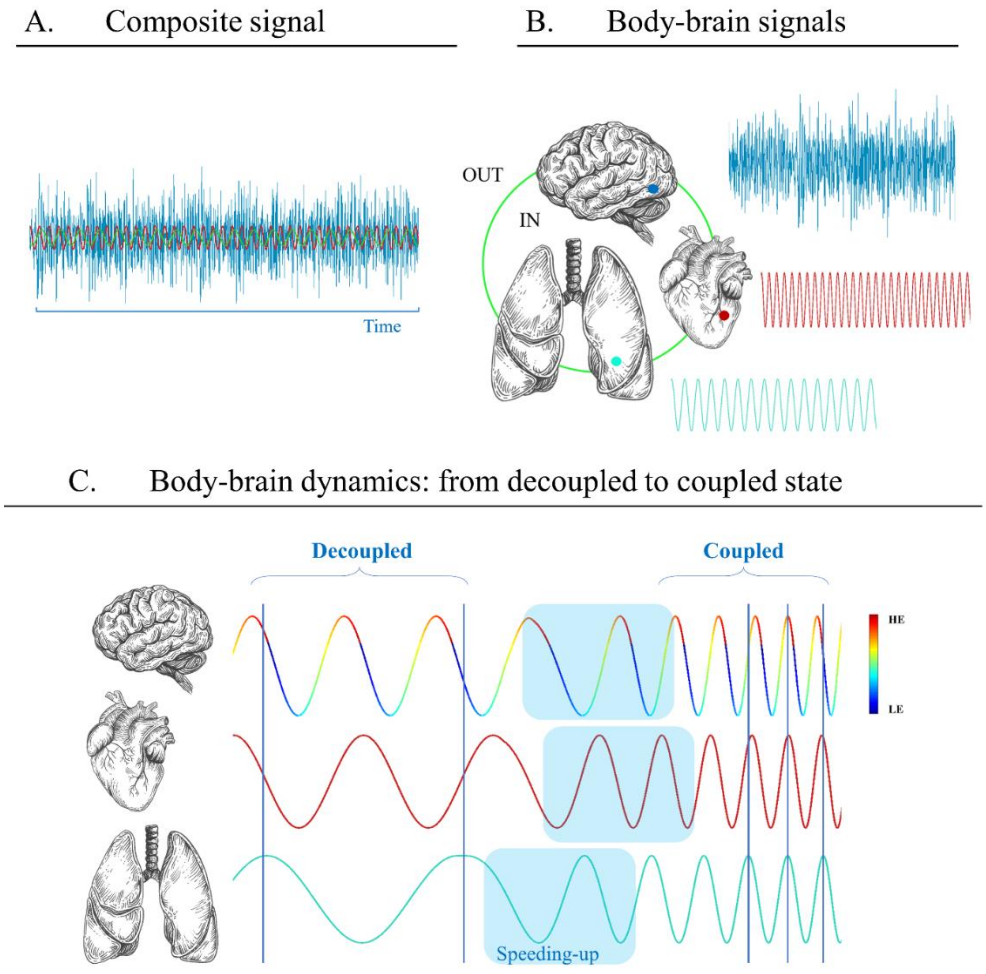

Figure 1 – A framework for the body-brain dynamic system.

A: a composite signal including brain (blue), heart (red) and respiratory (light blue) activity. B: brain-heart-lungs are partially independent subsystems, and a boundary (the physical extent of the body) separates them from the outside (OUT). Like an open system, the three subsystems share and exchange information with the external environment (input) and jointly deliver output (perception and action) via transformation processes (e.g., information processing). C: body-brain signals might switch from decoupled to coupled states to optimize behavior. We hypothesize that changes in breathing rates (e.g., speeding-up) might drive state transitions and induce changes in the rate and phase of the other signals. Signal dynamics can then be quantified by circular statistic tests (e.g., phase-locking values). Thus, phase-locking might be highly variable in decoupled states, while coupled state might show a preferential clustering. Of note, some variability in the coupling patterns might still be present, but a prominent phase-angle optimizes behavior. Brain activity is plotted with a color-code ranging from low-excitability (-LE) to high-excitability (HE). This refers to the concept of perceptual cycles, namely that there are (sub-)optimal windows for information processing that depend on the excitability phase in which signals are presented. The traces in the figure are based on data simulated for illustrative purposes using MATLAB.

The Influential ***predictive coding theory*** (Friston, 2005) offers a potential explanation to these findings, suggesting that the brain predicts and attenuates responses to rhythmically regular signals to optimize resource allocation to non-predicted sensory input (Seth & Friston, 2016). Consequently, the perception of sensory input oscillates at the HR, leading to the suppression of activity in response to events that fall on the low-excitability phase in the heart cycle (Al et al., 2020; Park et al., 2014). Alternatively, the ***neural subjective frame"*** suggests that (pre-attentive) updating of internal body states modulates self-awareness and sensation (Park & Tallon-Baudry, 2014). Accordingly, the brain might switch attention from interoceptive to exteroceptive signals, and this transition parallels HEP modulations (García-Cordero et al., 2017; Petzschner et al., 2019). Supporting this notion, oscillations during interoception (35-110 Hz) differ markedly from those during exteroception (1-35 Hz) in the insula, amygdala, somatosensory cortex, and inferior frontal gyrus (Petzschner et al., 2019). Interestingly, exacerbated HEP modulations are observed in disease and are associated with dysregulated behavior, impaired cognition, and atypicalities in brain volume and connectivity of allostatic networks (Birba et al., 2022; Fittipaldi et al., 2020; Salamone et al., 2021).

Taken together, these findings highlight bidirectional influences between heart activity, brain function, and behavior. However, how do HB and respiration relate to each other? Generally, the HB accelerates during inspiration (respiration rate (RR) decreases) and slows down during expiration (RR increases). These fluctuations of HB in relation to the breathing cycle are part of the phenomenon known as *heart-rate variability* and are influenced, among other factors, by the baroreflex and the sympathetic nervous system. The heart rate depends on breathing rhythms and tidal volume (depth of ventilation) and relates to breathing cycles approximately with a 4:1 ratio (4 HB within one respiration cycle) (Perry et al., 2019; Schäfer et al., 1998; Shaffer et al., 2014). Yet, little is known about how respiratory-cardiac coupling influences brain activity and cognition. Similarly, conceptual frameworks for the dynamics of such a

comprehensive body-brain system are largely lacking. In other words, how can the interactions between respiratory, cardiac, and brain activity, and their consequences for behavior, be characterized and explained?

An integrative framework

Earlier work has reviewed and discussed evidence of how visceral input modulates brain activity and subjective experiences of (self-) consciousness, as in the cases of intero- and exteroception (Azzalini et al., 2019; Park & Blanke, 2019a; H. D. Park & Tallon-Baudry, 2014). Similarly, others have discussed the modulatory influence of breathing on brain activity, perception, and action (Kluger, Balestrieri, et al., 2021; Kluger & Gross, 2021; Varga & Heck, 2017).

Bridging the gap between current empirical research and existing theoretical propositions, the *body-brain dynamic system* (BBDS) provides a dynamic perspective on body-brain interactions and describes how such an interface enables individuals to efficiently act in and adapt to a continuously changing environment. This integrative framework promotes a holistic approach to the study of the body-brain-behavior interface and motivates future research for its formal implementations (see Outstanding Questions). The focus of the BBDS is on respiratory and cardiac rhythms alongside with brain activity and behavior. For simplicity, we disregard in the current discussion other bodily (or visceral) signals apart from respiratory and cardiac signals, but conceivably, integrating such signals into the framework may follow the same principles (Azzalini et al., 2019).

A dynamic body-brain system

The proposed framework is inspired by *systems theory* and considers interactive body-brain rhythms within a *dynamic system*.

The BBDS focuses on three key elements: the brain, the lungs, and the heart, which constitute interconnected but partially independent subsystems. A boundary (the physical extent of the body) separates this system from the external environment (Key Figure; Fig. 1B). Like any open system, the three subsystems share and exchange information with the external environment (input) and jointly deliver output (perception, action) via transformation processes (e.g., information processing). The BBDS generates unique testable predictions: it is characterized by at least two states, a coupled and a decoupled state (Fig. 1C). In neurotypical behavior, the functional coupling of the body and the brain is not invariantly

maintained but can be dynamically and adaptively achieved whenever contingencies demand it. Thus, in wakeful states and in the absence of overt behavior, a largely decoupled system state is considered the default. In this scenario, autonomic centers regulating breathing and local cardiovascular centers modulating HB, dominate. When (re)acting, attending, and sensing the environment, the system can transition into a coupled state, influenced by top-down regulatory centers. This transition is achieved through changes in the rate and phase of internal signals, which tend towards preferred phase-coupling to optimize behavior (Fig. 1C). Although body-brain coupling is not a constant feature of the system, the endogenous predisposition to achieve phase-alignment unveils a hidden non-static hierarchical organization. Thus, a directional organization is established that drives dynamic state transitions, which can be initiated by multiple physiological rhythms interchangeably (i.e., respiration or cardiac) in specific contexts. Methodologically, the assessment of body-brain interfaces resembles current state-of-the-art analyses of neural entrainment. Hence, transient changes in coupling strength can be analogously quantified by circular statistics (Wolpert & Tallon-Baudry, 2021) (Fig. 1C) on a trial-by-trial basis. Consequently, *variability* in body-brain signals is the key mechanism for the dynamical aspect of the system, supporting the flexible interaction between the three sub-systems (lungs, heart, brain) and rapid adaptation to environmental contingencies, ranging from predictable to unpredicted events. Critically, this concept of flexible and adaptive interactions is supported by empirical evidence, showing that HB is prone to variability in healthy participants (Bigger et al., 1992), neural oscillatory signals can display state and task-specific timely responses (Mierau et al., 2017) and that respiration control modulates neural network activity and behavior (Herrero et al., 2018; Kluger & Gross, 2021). Thus, the proposed functional implication of the body-brain interface is to prepare the organism to dynamically allocate metabolic and cognitive resources required for behavioral contingencies. To do so, predictive processes allow exploiting prior knowledge and inform how to prepare the organism to better (re-)act in the environment. Thus, breathing and HR are dynamically modulated to optimize perceptual, behavioral (Balzarotti et al., 2017) and memory performance (Nakamura et al., 2018; Zelano et al., 2016).

This perspective can be exemplified by scenarios in which successful behavior demands timely body-brain adaptation. We differentiate between at least two types of behavior that are characterized by *strictly rhythmic* or *clustered* body-brain-behavior relations in a coupled state (Fig. 2). Motor acts like speaking, laughing, singing, playing a wind instrument, or shooting

a ball are all preceded by a short preparatory inspiration, and behavior preferentially unfolds during the longer lasting and progressive expiration phase (Fig. 2A).

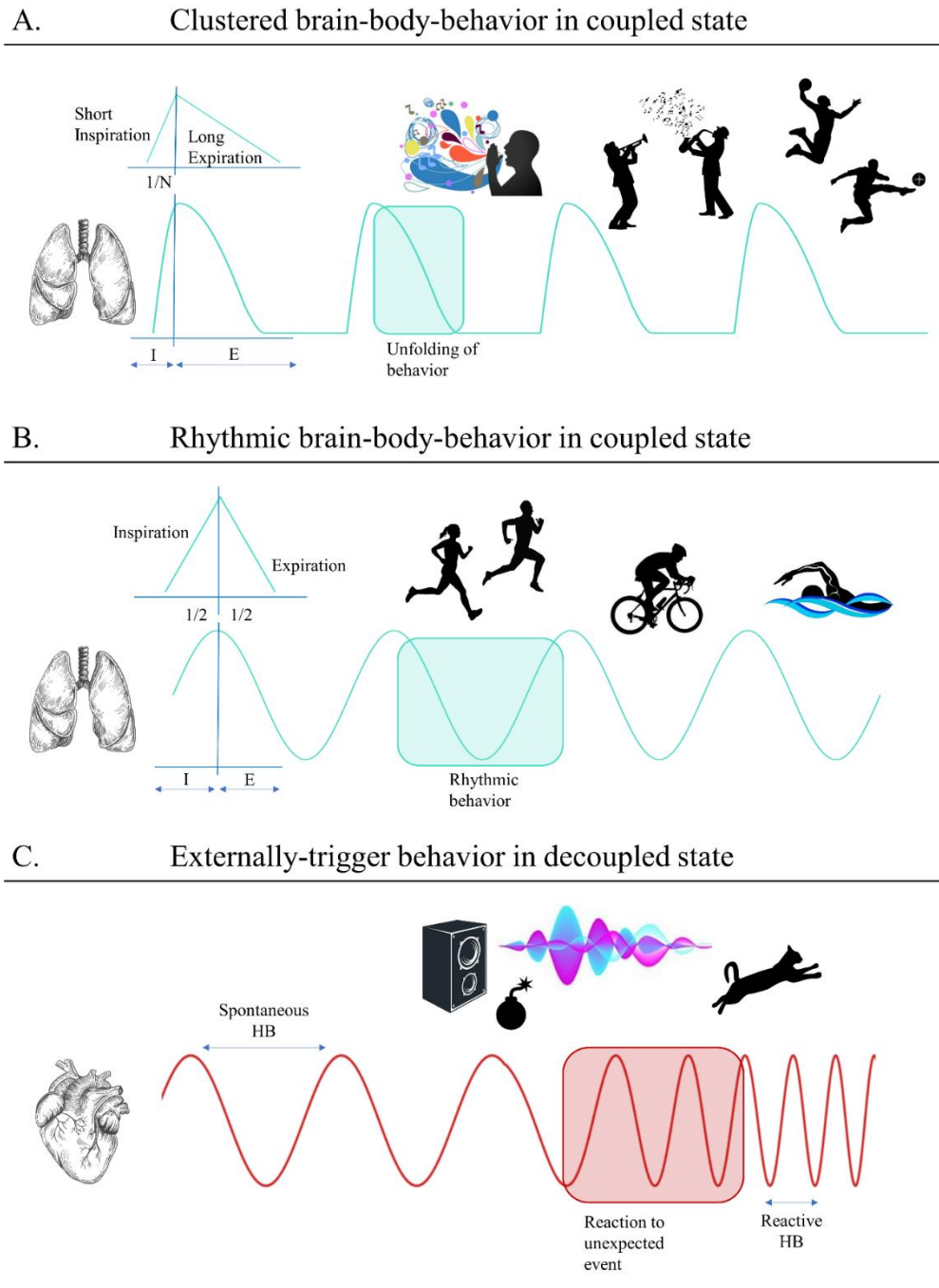

Figure 2 – Body-brain-behavior relationship in coupled and decoupled states.

A. In clustered body-brain-behaviors, motor acts such as speaking, laughing, singing, playing a wind instrument, or shooting a ball would tend to unfold during the long-lasting expiration phase of the breathing cycle. Here, the phase-relationship between body-brain-behavior is not regular but would depend on the motor act performed and physiological needs (e.g., need of oxygen).

B. In rhythmic body-brain-behaviors, motor acts such as running, cycling, or swimming tend to establish a clear phase-relationship with the breathing cycle. The unfolding of behavior relative to body-brain rhythms is more precise as compared to clustered body-brain-behaviors.

C. Externally triggered behaviors let body-brain rhythms transition from decoupled to coupled states. In this case, the heart signal is the driver of body-brain coupling via speeding-up its pace. The traces in the figure are based on data simulated for illustrative purposes using MATLAB.

These actions can be characterized by a *clustered body-brain-behavior relationship*: signal coupling is not achieved by a 1:1 phase relationship, but by 1: N phase clustering. Hence, the sequela of motor acts unfolds in one expiration phase, accompanied by variability in HB and brain activity. This idea translates to the brain's ***readiness potential***, which displays preferential phase-locking at the end of the inspiration phase, while behavior tends to cluster at the expiration phase (Park et al., 2020). Notably, respiration-action coupling is absent in unpredicted externally triggered actions (Park et al., 2020), where action planning is missing (decoupled state). Conversely, more stable rhythms are generated during continuous actions such as walking, running, or cycling. Here, the body-brain-behavior relationship reveals a highly regular pattern, characterized by stable intervals between inspiration-expiration phases (Fig. 2B). Likewise, motor movements and HB tend to phase-synchronize with breathing, establishing a *rhythmic* body-brain cycle.

In this view, breathing seems to emerge as the driver of body-brain coupling in both *rhythmic* and *clustered* behaviors. Indeed, motor planning cannot preclude breathing control, and the organism exploits these body-brain dynamics to improve motor coordination, attention, and perception. Empirical evidence further supports this role as breathing modulates heart activity and induces brain-breathing coherence in a widely distributed brain network (Herrero et al., 2018; Kluger & Gross, 2021). Top-down regulatory effects are likely achieved by synchronizing activity within cell assemblies and coordinating network interactions, ultimately regulating cortical excitability, and shaping sensory encoding, memory, and behavior (Heck et al., 2016; Heck et al., 2017; Kleinfeld et al., 2014; Martin & Ravel, 2014). We further propose that coupled states are reinforced by sensorimotor feedback loops to reduce noise (variability) in body-brain-behavior phase-locking.

However, the BBDS is not assumed to rely on a single driver, which would imply a strict functional hierarchy. Indeed, unpredicted events and externally triggered actions may engage

cardiac rhythms as the primary driver (Fig. 2C). For instance, a loud and unpredictable sound may drive a sudden increase in HB. Such alerting signals may initiate a cascade of physiological processes, aiming at raising alertness and preparing the body for action. Consequently, body-brain coupling would aim to optimize a timely behavioral response and is achieved via a dynamic interplay between subcortical (autonomic) and cortical (top-down control) brain centers.

We have discussed so far how body-brain dynamics determine how individuals successfully act in a dynamic environment and adapt to it. A critical pending question, though, concerns how perception and other cognitive functions are influenced by body-brain dynamics.

In line with other neurocognitive accounts of multisensory perception (Large & Jones, 1999; Schroeder et al., 2010; Schroeder & Lakatos, 2009), the BBDS considers that sensory processing, allocation of attention, and perception unfold continuously, but in discrete units. Thus, while sensing the environment, attention is dynamically and flexibly allocated to prioritize specific locations, features and/or streams. In turn, the likelihood of perceiving a stimulus is modulated by the phase-relationship between the attended event and underlying neural activity, establishing so called '*perceptual cycles*' (VanRullen, 2016). The *high-excitability phase* of neural activity represents an optimal window for processing information, while neural responses to events falling on the *low-excitability phase* are suppressed. The BBDS proposes to extend this principle beyond neural activity in isolation to incorporate bodily physiological signals as conjunct determinants of 'perceptual cycles'. It thus follows that body-brain rhythms establish high- and low-excitability cycles, influencing the likelihood of sensory processing and perception (Azzalini et al., 2019; Kluger, Balestrieri, et al., 2021; Park et al., 2014). Supporting this view, neural activity time-locked to HB before stimulus onset predicts visual detection (Park et al., 2014), and respiration-locked alpha modulations influence visuo-spatial processing (Kluger, Balestrieri, et al., 2021). Other cognitive functions may be similarly influenced by body-brain coupling, ranging from memory (Nakamura et al., 2018; Zelano et al., 2016) to interoception (Park & Blanke, 201°a) and emotional processing (Jerath & Beveridge, 2020). For instance, memory encoding and retention may be enhanced when stimuli are presented during the body-brain high-excitability cycle and performance may be worse elsewhere.

To conclude, the BBDS embraces the variability in human behavior and proposes that cognition necessitates intrinsically variable body-brain interactions to adapt to an ever-

changing environment. A certain degree of variability in coupling states is well-documented in human EEG and respiratory signals and might support cross-domain generalization within such a framework. A static hierarchical model (Klimesch, 2018) might not sufficiently describe dynamic transitions from decoupled to coupled body-brain states, nor psychophysical changes observed from rest to motion. In contrast, the proposed differentiation of *planned* and *externally triggered actions* and of *rhythmic* and *clustered* body-brain coupled states suggests a flexible body-brain functional architecture, whose dynamics can be characterized by patterns of task- and state-specific evolution in body-brain phase-locking.

Concluding Remarks and Future Directions

Bridging the gap between empirical evidence and theoretical perspectives, we propose a novel framework for a ***body-brain dynamic system*** (BBDS), which aims to integrate the dynamical nature of body-brain rhythms with the inherent variability of human behavior. The BBDS framework thus promotes the combined assessment of physiological body rhythms (respiratory and cardiac) and brain rhythms as valuable sources of information to explain how individuals act in and adapt to a dynamically changing environment. This quest promises to advance our understanding of human perception, action, and cognition in neurotypical individuals and in neurological disorders, but necessitates appropriate experimental paradigms and analytical tools (see Outstanding Questions).

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Declaration of interest

None to declare.

Glossary

- **Brain readiness potential**: in the context of EEG measurements, the brain readiness potential is a metric associated with motor preparation.
- **Cross-frequency coupling**: Cross-frequency coupling is a concept that describes the co-variation in the dynamics of two or more neural signals oscillating at different frequency bands (e.g., delta-beta coupling).
- **Cycl**e: when referring to periodic signals (neural oscillations, respiration, heart activity), a full cycle includes a repeated pattern in time. In the case of a sinusoidal wave, both the high- and low-excitability phases describe a full cycle, which is periodically repeated in time.
- **Directional causalit**y: in the analysis of brain activity, directional causality measures the influence exerted by one signal on one or more other signals which are functionally coupled. It can be estimated by granger causality and/or other metrics relying on the information theory framework.
- **Entrainmen**t: in physics, entrainment refers to a mechanism of active alignment of two oscillators, whereby the signals are independently oscillating at their individual rates before and after a transient moment of alignment.
- **Functional couplin**g: in the context of EEG measurements, functional coupling describes the co-variation in the dynamics of two or more signals (e.g., from two brain regions) and can be obtained through various metrics of amplitude or phase changes.
- **Heart-beat evoked potential (HEP)**: The HEP is an event-related EEG response reflecting body-brain interaction.
- **Hierarchical functional organization:** this term refers to the presence of a structured pattern of functional coupling that can be mathematically quantified. Thus, elements at higher levels of the hierarchy interact with signals at lower levels and vice versa. Note that correlational evidence might suffice for this organization to take place. However, the model can be extended by means of measures of directional causality.
- **Perceptual cycles**: given that oscillatory brain activity is characterized by alternating instances of high- and low-excitability phases, cognition might be a cyclic process with (sub-)optimal moments for information processing and perception.

- **Phase-locking**: when examining neural oscillations, phase-locking describes a precise relationship between the phase of a signal with another signal or event. For instance, brain activity in the beta-frequency band can be phase-locked to the occurrence of an acoustic event.
- **Predictive coding framewor**k: this view postulates the inherent predictive nature of neural activity. Hence, the brain constantly generates predictions about events in the (internal and external) environment and a continuous process of learning updates current knowledge via prediction error signals (signaling the (mis-)match between expected and actual outcomes).
- **R-peak**: the R-peak corresponds to the maximal deflection observed in the periodic electrocardiogram signal.

Box 1 – Translational aspects of body-brain research

An interesting aspect of the body-brain integrative approach lies in the potential characterization of individual capacities as a prerequisite for personalized training or interventions. Clinicians and therapists have long asked how to improve standard protocols (Kotz & Gunter, 2015) as treatment outcomes vary significantly (Bella et al., 2017). Specification of individual capacities, including behavioral and cognitive measures together with brain, respiratory, and cardiac activity, may reveal a pivotal link between cognitive dysfunctions (e.g., attention deficits, dysfluent speech) and altered body-brain coupling. Thus, a better understanding of the causal relationships between body-brain-behavior could factor into early diagnosis and the development of individualized trainings. For example, breathing control techniques, along with metronome-timed speech training (Kell et al., 2009), are found to improve speech fluency in people who stutter. In these scenarios, the processing of external (music) rhythms and the volitional control of respiration may superimpose a temporal pattern through which behavior can unfold efficiently (Fig. 2). Through this mechanism, external rhythms provide a means to temporally (re-)structure altered body-brain-behavior. For instance, the speech production rate may align with the rate of externally presented rhythms. Alternatively, volitional control of breathing may facilitate sensorimotor coordination for speech production. Similar mechanisms may underlie the beneficial effects of rhythm training in dyslexia (Goswami, 2017), gait performance, time perception, and sensorimotor timing abilities in Parkinson's disease (Bella et al., 2015; Benoit et al., 2014). Interestingly, the known modulatory effects of musical rhythm on blood pressure and cardiac activity (Bernardi et al., 2006, 2009) might foster post-stroke interventions (Särkämö et al., 2014).

Overall, these observations lead to the critical consideration that many clinical settings could benefit from an integrative body-brain-behavior approach. However, this requires a better understanding of the underlying functional and causal mechanisms linking body-brain physiology to behavior and general cognition.

Outstanding questions box

- Are body-brain interactions steadily present over time or transient?
- Which neuroimaging methods and experimental paradigms would enable testing the directionality and causal influence of body-brain signals on behavior?
- Is signal synchronization (e.g., phase-locking or concurrent amplitude changes) the only pre-requisite for describing body-brain functional coupling? Would metrics of causality (e.g., granger causality) deepen current understanding of the link between body-brain and behavior?
- What are the generators of body-brain synchrony? What drives body-brain coupling and what is its functional role?
- Is it possible to modulate the activity of body-brain oscillators to influence cognitive functions?
- Is the influence of body-brain dynamics restricted to a specific sensory modality (e.g., vision or audition), cognitive function (e.g., speech processing) or can we rather speak of a cross-domain functional mechanism?
- Can body-brain analyses enrich individual neurocognitive profiling along the spectrum from health to pathology? If so, would they inform prevention and intervention?
- Which type of formal implementation (e.g., metastability, chaotic system, turbulence) would better describe body-brain interactions and predict their influence on cognitive functions?

Chapter 6

General Discussion

General Discussion

The *leitmotiv* of this thesis is *time*: physical time, the brain's implementation of time, the psychological *sense of time*, and finally, time in the body. Thus, I asked: how do we use time to orient ourselves in the world? How do we implement time processing for general cognition? Are there inter-individual and cross-species differences in timing cognition? Does our bodily physiological activity contribute to our sense of time and influence timing processing?

To address these questions, we here focused on a specific aspect of timing cognition: the capacity to process and detect temporal regularities in the sensory environment. In the first part of the thesis, I investigated the basic neural mechanisms by which we process and predict the *timing* of sensory input in our environment. My approach combined comparative and translational perspectives as I performed basic (Chapter 2), evolutionary (Chapter 3), and clinical (Chapter 4) research. Overall, I discussed that the capacity to act and adapt in a dynamically changing environment depends on our abilities to *encode* and *predict* the precise *when* of sensory events, and to timely coordinate our (re-)actions by generating *predictions* about the *timing* of future events.

In Chapters 2 to 4, I systematically assessed the neural oscillatory dynamics underlying these fundamental timing functions. Participant- and trial-level analyses allowed exploring the rich and variegated nature of neural waves while *encoding* and *attending* auditory streams. I discussed that neural waves implement a *dynamic* and *active sampling* of sensory streams, thereby processing the temporal *regularities* in isochronous auditory sequences and generating *expectations* about the *when* of future events. Furthermore, I demonstrated that the continuous flow of auditory input is *discretized* in consecutive moments of high- versus low-salience. Our brain does more than simply process isochrony: active sampling sometimes takes the form of *accentuations*. Thus, individuals differ in the *if, when,* and *how* they sample the acoustic environment, and further show intra-individual variabilities in their tendencies to superimpose binary, ternary, and other accentuation patterns onto isochronous auditory sequences. The alternation of high- versus low-salience moments impacted the processing of *deviants*, thus showing that accentuations influence other cognitive functions beyond rhythm processing. In Chapter 3, I discussed that rhythm tracking and accentuations are already present in nonhuman animals, macaque monkeys. Our ancestors' neurophysiological activity showed striking similarities to humans', in which they could encode temporal regularities, generating temporal predictions, and superimposing accentuations to foster deviance processing. As these *timing* computations are phylogenetically linked to the development of

higher-order cognitive functions such as music and speech processing in humans, these results bridge a gap in evolutionary literature and can motivate new cross-species investigations on rhythm cognition. Next, in Chapter 4, I demonstrated that the basal ganglia (BG) and the cerebellum (CE) play fundamental roles in rhythm processing: lesions in either of these two subcortical structures causally altered the capacities to precisely encode the *timing* of sensory events and to generate temporal expectations, ultimately impacting the ability to produce and synchronize behavior to external rhythms.

In the second part of the thesis, I introduced a novel perspective on brain functioning. In Chapter 5, I proposed that the brain may not be functioning in isolation, but constantly interfaces with physiological fluctuations in bodily signals to inform cognition. Thus, I surveyed evidence for how breathing, cardiac, and gastrointestinal signals influence brain activity, information processing, perception and action. Bridging the gap between these fragmented research lines, I argued in favor of a fundamental shift in our experimental paradigms, so to allow for a more holistic assessment of body-brain physiological interactions and their influence on neurocognitive functioning. In this perspective, we proposed a novel framework for a Body-Brain Dynamic System (BBDS), characterized by systems of dynamic oscillators transiently shifting from body-brain decoupled to coupled states to coordinate information processing and behavior. The core tenet of the BBDS is that body-brain physiological rhythms shape individual rhythms: perceptual rhythms (e.g., individual attentional rhythms, and preferences for listening at specific rates) as well as behavioral rhythms (e.g., individual preferences for walking, running, reading, speaking at specific rates). In this formulation, the BBDS puts the individual in the spotlight and allows to explore inter-individual differences finally holistically in cognition, from health to pathology.

Physical time

Starting from the physical understanding of time, we have seen that we use *oscillations* to quantify the passage of time. In fact, our modern measure of seconds is derived from the frequency of electromagnetic radiation of caesium atoms, thus the label *atomic clock.* The fluctuations between energy states of caesium atoms as well as the swinging of our grandma's pendulum clock, trace oscillations. Oscillators can be characterized by frequency (the rate; relative to the period of the oscillation), amplitude (the magnitude; the width of swinging of the pendulum), and phase (the state of the oscillation; the *precise* position along the wave).

The inherent periodicity of oscillators allows discretizing the continuous flow of time into a measurable and predictable unit (an oscillatory cycle), ultimately producing a *sense of time*. In turn, we can use the sense of time to determine the *when* of unfolding events in our sensory environment, and we can reliably quantify the time elapsed from moment A to moment B. As such, time is what allows organizing multimodal sensory input at multiple timescales (e.g., speech and music audio-visual input) into coherent perceptual representations. The *sense of time* further allows to describe *motion* and *dynamics* in a variety of physical phenomena. For instance, time is employed to quantify the motion of particles, their velocity, acceleration, energy and other fundamental properties. These *dynamics* can be quantified by *calculus*, a mathematical technique which allows to describe the rate of change of something (e.g., the motion of particles) by subdividing the continuous flow of time into infinitesimal quantities.

Altogether, we can argue that time plays a fundamental role in our lives. Time allows to describe almost any physical phenomena in the natural sciences. Similarly, the *sense* of time temporally organizes and structures our reality into a coherent percept, allowing us to make sense of the world. *Ordo ab chaos*.

Time in the brain

How does our brain generate the *sense* of time? How do we use this *internal time* to process the *timing* of sensory input in our environment?

In Chapter 1, I discussed that brain cells, neurons, in highly specialized cortico-subcortical circuitries are time generators and time processing machines. In fact, these neurons act as self-sustained endogenous oscillators, generating an *internal* sense of time, and capable of dynamically tracking and adapting to the *timing* of sensory input around us. Neural waves, indeed, possess an *endogenous rhythm* (i.e., they oscillate at a specific *eigenfrequency*), which resembles an *internal clock*. This clock, however, is not fixed but becomes a timekeeper that encodes external rhythms (i.e., the *timing* of sensory events) by *tuning-in* and *-out* with the timing of environmental stimuli. The capacity to *couple* internal to external oscillations is fostered by *predictions*: since most of our sensory reality displays gradients of temporal *regularities*, our brain employs temporal patterns to generate predictions about the *when* of next events. Thus, once the brain has detected regularities in my speech (e.g., there are 3-4 syllables per second, defining a syllable rate), it forms expectations about the *when* of the next incoming sounds. In this context, delta and beta (δ-β) oscillatory rhythms seem to play a

crucial role in processing and predicting timing. I then discussed that β-δ waves form an adaptive neural code to integrate bottom-up sensory processing with top-down predictions. Hence, in the case of audition, β-δ cross-frequency coupling mediates audio-motor interactions, temporally pacing the flow of information between auditory and motor regions.

This framework was tested in chapters 2 to 4, where I characterized the basic mechanisms by which neural waves implement rhythm processing in the general population (Chapter 2), in a comparative dataset with macaque monkeys (Chapter 3), and in a clinical population comprising stroke patients with lesions in the BG and CE (Chapter 4).

Neural waves encode temporal regularities

How do we use neural waves to process environmental rhythms? In Chapters 2-4 I explored the basic neural oscillatory mechanisms of auditory rhythm processing. I hypothesized that individuals may differ in the *if, when,* and *how* they process temporal properties in auditory sequences, thus I dedicated particular attention to characterize intra- and inter-individual variabilities.

The starting point was testing these hypotheses in the general population. Healthy young individuals listened to isochronous auditory sequences while we recorded their electrical brain activity via electroencephalography (EEG). The analysis pipeline explored single-participant and -trial data, thus enabling us to dive into intra- and inter-individual variabilities in rhythm processing. First, Fourier and Inter-Trial Phase Coherence (ITPC) analyses demonstrated that individuals encoded the temporal regularity of auditory sequences, as revealed by clear amplitude and coherence peaks in the Fourier and ITPC spectra, respectively. Next, we performed so-called 'rhythm tracking' analyses to investigate the phase relationship between endogenous neural oscillatory activity in the δ-band and the onset of individual tones within the auditory sequence. These analyses indicated an overall phase coherence at the single-trial level as demonstrated by mean vector length analyses (i.e., a metric of phase coherence in circular statistics). The high coherence before stimulus onset might suggest a mechanism of predictive alignment towards expected tone onsets. However, we also characterized large intra- and inter-individual variabilities in δ-band pre-stimulus phase. In fact, in contrast to well-established lines of evidence, here δ-band oscillations did not always align their high-excitability peak to tone onsets. In contrast, pre-stimulus δ phase scattered around the unit circle.

How to explain these discrepant observations? In Chapter 2, we discussed the possibility that individuals do not always track auditory rhythms if not instructed to do so. This argument is supported by previous evidence showing random pre-stimulus δ phase for ignored (as opposed to attended) auditory streams (Lakatos et al., 2013), and a gradual phase-shift and clustering of δ phase along the auditory sequence (Lakatos et al., 2005). To note, however, most of the classical studies documenting a phase effect of low-frequency oscillations on cognition (Lakatos et al., 2005, 2008, 2013) focused on stimulus onsets (0ms) rather than on pre-stimulus time-windows. We chose to look into a 60ms pre-stimulus window, aiming at anticipatory phase-alignment while avoiding a potential stimulus-induced phase-reset. In fact, a stimulus onset typically triggers phase-reset and evoked responses, which might bias phase estimates and derived metrics (e.g., coherence). Hence, previous studies showed that the δ phase is 0 at stimulus onset and coherent over stimulus repetitions (Lakatos et al., 2008). Another difference lies in the recordings: while prior studies employed invasive recordings, in EEG the phase effects are sometimes flipped (e.g., as a result of volume conduction), thus showing improved auditory processing on the rising phase of δ-band activity (e.g., Henry & Obleser, 2012) as opposed to the trough (Lakatos et al., 2005, 2007, 2008). However, there is complementary EEG evidence documenting a behavioral advantage (e.g., detection performance) for stimuli presented along both the peak and trough of ongoing δ-band activity (Busch & VanRullen, 2010; Cravo et al., 2013; Henry & Herrmann, 2014; Henry & Obleser, 2012; Mathewson et al., 2009; Schroeder & Lakatos, 2009; Stefanics et al., 2010). These contradictory results raise concerns about the *real* role of δ-band activity in information processing. In fact, a recent comprehensive review by Keitel et al., (2022), highlighted that there is scarce and contradicting evidence on the link between pre-stimulus oscillatory amplitude and phase and cognition, and often there are small effect sizes. While differences in experimental setups and methodologies (recording types ((non-)invasive), time-windows, channel selection (a single EEG channel (e.g., Cz) or a channel cluster), processing pipelines (e.g., re-referencing)) may partially account for these discrepant results, in the current work we emphasize the role of *variability*. In particular, we characterized large intra- and inter-individual variabilities in the *if* and *how* people predictively align their δ-band oscillatory activity to isochronous tone onsets. We further discuss that if variability emerges in such basic experimental setup, it may play a functional and adaptive role in cognition (Criscuolo et al., 2024). In turn, the need to dedicate more attention to single-participant and trial fluctuations.

Beyond the 'rhythm tracking' approach, 'accentuation analyses' further revealed that individuals spontaneously superimposed accentuation patterns onto auditory sequences. Thus, although identical, successive tones were differentially processed as a function of a binary (Strong – weak; S-w) and ternary (S-w-w) accentuation pattern in a subset of trials. In fact, single-participant and -trial modeling of β-band neural oscillations revealed individual preferences for binary, ternary, and other accentuation patterns. In turn, the tone-locked β-band responses were fluctuating as a function of a S-w or S-w-w patterns. Moreover, the superimposed accentuations influenced deviance processing: event-related responses to deviant (amplitude attenuated) tones were stronger in the accentuated as compared to the non-accentuated positions along the auditory sequence. These results support the *dynamic attending* theory (Large & Jones, 1999), according to which our brain dynamically samples the sensory environment, and further expands prior evidence on the phenomenon of subjective accentuation (Abecasis et al., 2005; Baath, 2015; Brochard et al., 2003; Poudrier, 2020). In this perspective, accentuations may serve to parse and segment continuous sensory streams into predictable, coherent and finite units (Bolton, 1984; Mari R. Jones, 1976; Schroeder & Lakatos, 2009) and to allocate attentional resources to salient sensory events with the scope to optimize perception (Nobre & Van Ede, 2018; Shalev et al., 2019).

Overall, this chapter shed new light on the basic neurophysiological mechanisms of temporal processing: I confirmed the complementary roles of δ-β waves in basic rhythm processing and the existence of intra- and inter-individual variabilities in the *if, when,* and *how* individuals encode, predict, and sample the acoustic environment.

A cross-species comparison

Are there cross-species (dis)similarities in rhythm cognition? Are our close ancestors, macaque monkeys, capable of processing temporal regularities similarly to humans?

Charles Darwin noted that: "*The perception, if not the enjoyment, of musical cadences and of rhythm is probably common to all animals and no doubt depends on the common physiological nature of their nervous system*".

Comparative research demonstrated that the capacities to detect, produce and synchronize with rhythms is present in vocal learning animals (e.g., parrots; Patel et al., 2009), but not in others: macaque monkey were shown not to detect and synchronize with human-made

(musical) stimuli (Honing et al., 2012, 2018). Thus, the hypothesis that some aspects of rhythm cognition may be species-specific (Fitch, 2013; Patel, 2008; Patel, 2006), and dependent upon neuroanatomical differences between humans and other nonhuman animals (Merchant & Honing, 2014; Patel & Iversen, 2014) arose. However, one may ask if the use of human-made complex rhythms is adequate to test evolutionary hypotheses of temporal processing capacities. Another question is whether a finger tapping task (as the one typically employed in these studies) fits the ecological reality of the animal, who probably never tapped before (and surely not along a human-made musical rhythm). Thus, in chapter 3 I argued that a more fundamental question in comparative rhythm cognition could be: do nonhuman animals have the neurophysiological predisposition to *encode* temporal regularities in the environment?

To address this question, I mirrored the experimental approach adopted in Chapter 2. Hence, two macaque monkeys listened to isochronous auditory sequences while EEG was continuously recorded. The monkeys did not undergo any training specifically designed for this study, as there was no task involved. The monkeys were seated in a monkey chair, they were free to move, and passively listened to identical tones presented in isochronous auditory sequences for more than 20 recording sessions. Fourier analyses demonstrated that macaque monkeys' neural activity encoded the temporal regularity of the auditory sequences similarly to humans, as revealed by amplitude peaks centred at around the stimulation frequency. Next, 'rhythm tracking' analyses showed predictive phase alignment of δ-band oscillations towards expected tone onsets, as indexed by the mean vector length. Similar to what I discussed for humans in Chapter 2, however, there were large intra- and inter-individual variabilities in the phase alignment, and a portion of trials did not show signs of tracking (the phase coherence as indexed by the mean vector length did not reach statistical significance). These observations support previous evidence showing that macaque monkeys' neural activity encodes and synchronizes with temporal regularities in the sensory environment (e.g., Lakatos et al., 2008). At the same time, however, the single-trial approach allowed demonstrating that there are variabilities in the *if, when,* and *how* δ-band oscillations track rhythms in the macaque. Similarly, single-trial modelling of β-band oscillations revealed that macaque monkeys employ accentuations in a subset of trials. As in humans, binary (S-w) and ternary (S-w-w) accentuation patterns sample the acoustic environment, superimposing adjacent temporal windows of high- versus low-salience. Here, as well as in Chapter 2, I discussed that accentuations were not visible when averaging event-related potentials (ERP) and event-

related time-frequency signals. The typical tendency to average across hundreds of trials had probably masked out trial-level accentuations, ultimately leading to the view that monkeys are not capable of superimposing accentuations. Instead, despite documented neuroanatomical and -functional differences in the motor system, and specifically in the cortico-basal-ganglia-thalamo-cortical (mCBGT) circuitry (Mendoza & Merchant, 2014; Patel & Iversen, 2014; Wilson & Cook, 2016), we confirmed comparable neurophysiological signatures of rhythm processing in macaque monkeys. As in humans, a δ-β neural code implements different aspects of temporal processing, ultimately allowing to encode, track and predict temporal regularities in the sensory environment.

The causal role of subcortical circuitries

Where in the brain can we ascribe such exquisite time processing capacities?

Human's excellent timing and rhythm processing and production abilities have long been associated with neuroanatomical changes along the dorsal auditory stream, and extending into premotor, neostriatal, and basal ganglia areas throughout evolution (Balezeau et al., 2020; Rauschecker & Scott, 2009). However, others have argued in favor of a more prominent role of sensorimotor (i.e., auditory and motor) regions (Balasubramaniam et al., 2021; Wiener et al., 2019) as these areas are engaged in rhythm processing and production in both humans (Chen et al., 2008; Grahn & Brett, 2007; Kotz et al., 2018; Wiener et al., 2010) and nonhuman animals (Cisek, 2019; Mendoza & Merchant, 2014; Merchant & Honing, 2014; Sohn et al., 2019). Furthermore, as sensorimotor regions phylogenetically preceded the development of higher-order brain regions, they must have played a significant role in the capacity of organisms to adapt to the environment.

The motor network being discussed here is an extended cortico-subcortical-cortical network engaging BG and CE. The BG and CE have been associated with various aspects of rhythm cognition, including the capacities to extract salient periodicities in auditory sequences and to encode the precise *timing* of sensory events. Causal evidence further exists, demonstrating that patients with lesions in these brain regions had difficulties with processing, producing, and synchronizing with rhythms. What remained unclear, however, is what exactly changes in the neural dynamics of the patients' brains: are neural oscillations not encoding the temporal regularities of sensory streams?

In Chapter 4, I expanded our previously adopted experimental approach by developing a novel methodological procedure to characterize the neural oscillatory dynamics of rhythm processing. Leveraging on the notions built in Chapter 1, I applied *calculus* to describe parameters as the velocity (in this case, instantaneous frequency; IF) and acceleration (Acc) of neural waves while tracking auditory rhythms, and further derived metrics of neural stability (S), deviation (Dev) and entropy.

As in Chapters 2 and 3, healthy ageing individuals (healthy controls; HC), and stroke patients with lesions in either the BG or CE listened to isochronous auditory sequences while their EEG was recorded. ITPC analyses revealed that BG and CE patients encoded the temporal regularity in auditory streams, but less precisely than HC. By exploring trial-level neural dynamics in the δ-band, I further revealed group differences in the power, IF, S, and Dev. CE patients' δ-band power and IF were comparable to HC, supporting the notion that these patients conserved intact sensitivity to the temporal structure of auditory sequences (Schwartze & Kotz, 2021). However, the lower stability and phase coherence may indicate heterogenous encoding of the precise timing of event onsets (Grube, Cooper, et al., 2010b; Nozaradan, Schwartze, et al., 2017). BG patients showed larger variabilities in power, reduced IF and S as compared to HC potentially indicating altered encoding of the temporal regularity.

The assessment of neural data was complemented with a behavioral task in which participants were asked to tap along with auditory sequences presented at three different rates. Here, CE patients tapped faster than other groups at the intermediate tempo, and much slower at the fastest tempo, further displaying more variability and reduced tapping stability as compared to HO. Thus, the reduced capacity to precisely encode the *when* of auditory events affected the production and synchronization to rhythms, confirming previous findings (Ivry & Keele, 1989; Ivry, Keele & Diener, 1988; Schwartze et al., 2016). BG patients, instead, showed large inter-individual variabilities already at the basic tempo, and a reduced tapping stability at faster tempo. These results confirm the previously documented heterogeneity in tapping behaviors in BG and the difficulties in adapting to tempo changes (Schwartze, Keller, et al., 2011b).

Altogether, these results substantiate the role of low-frequency neural oscillatory dynamics (Schroeder & Lakatos, 2009) to detect, produce, and synchronize with temporal regularities in the sensory environment. Hence, I demonstrated that δ-band oscillations pre-exist and outlast auditory sequences and tend to tune-in and -out with the perceived acoustic regularity

by accelerating and slowing down over time. Moreover, I confirmed the fundamental role of BG and CE as part of an extended cortico-subcortical-cortical network underlying rhythm and timing processing (Schwartze & Kotz, 2013). In fact, lesions in either the BG and CE causally impacted the capacities to precisely encode the timing of sensory events, process temporal regularities, as well as to produce and synchronize rhythmic behavior.

Time in the body-brain system

In Chapter 1, I elaborated on the use of oscillations to characterize physical time, and on the use of time to characterize motion and dynamics in natural sciences. Next, I discussed that in cognitive neuroscience we similarly employ oscillations, i.e., neural oscillations, to understand how process time and temporal regularities. Thus, in Chapters 2-4 we have seen how a δ-β neural code implements different aspects of temporal processing, allowing to encode, track and predict temporal regularities in the sensory environment. However, in Chapter 1 and later in Chapter 5, I also discussed the existence of other endogenous oscillators in the body: a frequency architecture of body physiological signals exists, ranging from the slow circadian rhythms, to gastrointestinal, breathing and cardiac rhythms. Thus, similarly to what I discussed for brain waves, I proposed that cardiac, breathing and gastrointestinal signals can be viewed as self-sustained oscillators, generating endogenous rhythms (e.g., heart rate) and processing timing in the environment (e.g., aligning cardiac activity to musical beat). I then suggested that body physiology may provide an *internal clock* marking the flow of time and which is employed as internal reference to generate and influence the *sense* of time. As for brain rhythms, bodily waves differ across individuals, and dynamically change within the same person during rest, perception (e.g., listening to music) and action (e.g., during sports). These observations lead to new experimental questions: does body physiology influence brain activity and cognition? Does body physiology play a role in inter-individual variabilities in behaviors? And more on the methodological side, can body-brain interactions be described by dynamic systems?

In Chapter 5 we introduced a new conceptualization of a Body-Brain Dynamic System (BBDS). The BBDS holistically examines the body–brain–behavior interface and aims at exploring intra- and inter-individual variabilities in neurocognitive functions and behaviors. In the BBDS, the body and the brain are viewed as partially independent subsystems, having their own physiological roles within the organism (e.g., oxygen supply). The subsystems,

however, can dynamically transition from decoupled to coupled states in a context-specific manner. While not necessarily always coupled, body-brain waves tend to achieve coupling to optimize behavior. Not only breathing (Heck et al., 2016; Ito et al., 2014; Kluger, Balestrieri, et al., 2021), but gastrointestinal (Azzalini et al., 2019; Mayer, 2011), and cardiac (Park et al., 2014; Park et al., 2016) signals modulate neural excitability and perception, consciousness (Park & Blanke, 2019), emotion regulation (Damasio & Carvalho, 2013), memory (Zelano et al., 2016), and action (Park et al., 2020).

How do body waves influence brain and behavior?

'Take a deep breath, listen' (Chapter 1). At the beginning of the thesis, I introduced this example, which clearly illustrates how we control physiology (in this case, breathing) to focus attention and augment sensory processing. In our daily experience, we employ top-down breathing control to enhance information processing, but what we do not notice is its influence on other physiological signals. First, respiration influences cardiac activity, inducing the well-known phenomenon of *heart rate variability* (Perry et al., 2019; Schäfer et al., 1998; Shaffer et al., 2014). As sensory processing, e.g., auditory (Edwards et al., 2007) and visual (McIntyre et al., 2007) processing, is enhanced around the *R-peak*, breathing-to-cardiac interaction represents an endogenous mechanism to foster cognition, potentially achieved by timely allocating metabolic resources. At the same time, a 'respiration modulated brain oscillatory network' exists (Kluger & Gross, 2021), which encompasses temporal, hippocampal, brainstem, and cerebellar regions, as well as motor, prefrontal, and posterior areas. Breathing couples with many complex motor behaviors such as speaking, singing, or laughing (McFarland, 2001; McKay et al., 2003) as well as walking, cycling, running (Bechbache & Duffin, 1977; Bramble & Carrier, 1983; Folinsbee et al., 1983; Hill et al., 1988; Jasinskas et al., 1980; Kohn et al., 2016; B. Rassler & Kohl, 1997), and rowing (Mahler et al., 1991). Thus, breathing control seems to be a mechanism to temporally coordinate action and structure the sequela of motor plans within the respiratory cycle. We proposed both *clustered* and *rhythmic* body-brain-behaviors to be possible, each characterized by different coupling patterns between these three elements. Thus, speaking may adhere to *clustered* behaviors, as a short inspiration is followed by a long expiration during which speech sounds unfold. Jogging, instead, fits better in the *rhythmic* behaviors as there is a tight correspondence between the motion of motor effectors (hands and legs) with the breathing cycle. What is fascinating is

that this research perspective opens to the investigation of daily behaviors and demands for ecologically valid experimental setups: daily acts of speaking, playing a musical instrument, doing sports fundamentally rely on body-brain -behavior coupling, but have yet to be characterized as such.

Individual body-brain rhythms influence inter-individual variability

Another debate surrounds the question of whether individual physiological rhythms influence individual cognitive and behavioral rhythms. For instance, individuals differ in their preferred tempo when listening to music and speech, with some preferring faster rates (e.g., speeding up a podcast), while others prefer slower rates (e.g., they avoid techno music). Similarly, there are individual differences in walking and speaking rates, and some individuals tend to comfortably jog and swim faster than others. Are these differences paralleled and explainable as a function of inter-individual differences in breathing and heart rates? Namely, do slower respiratory and heart rates determine slower walking and speaking rates? The link between individual body-brain rhythms and behavioral rhythms is currently being investigated in an ongoing pre-registered research line (Criscuolo et al., 2022b), where we test a number of spontaneous behaviors (e.g., reading, speaking, walking) while continuously monitoring bodily and brain activity. In the same research line, we test inter-individual differences in rhythms of perception: by letting participants passively listen to basic (isochronous) and complex (speech and poems) auditory sequences, we aim at better understanding how body-brain waves sample, encode, and predict temporal regularities in the acoustic environment. Once more, we leverage on the *dynamic attending* framework and expand its focus so to include bodily waves into the equation. Do bodily rhythms influence how we sample and process sensory information in the acoustic environment? How do heart and breathing rates act and interact with perceived temporal regularities? Can we expand the δ-β neural code for timing processing so to include the influence exerted from body waves?

Perhaps even before that, how to assess the dynamics of body-brain interactions from rest to cognition? How to achieve body-brain coupling as described in the BBDS?

We argued that body-brain interactions and the transition from decoupled to coupled states demand for systematic assessments of the strength and directionality of influence between body-brain signals, at multiple timescales. As these signals are characterized by a periodicity,

a dynamic system of coupled oscillators could describe each signal's dynamic, on the one hand, and signals interactions on the other. Thus, we hypothesized the transition from decoupled to coupled states to let a body-brain frequency architecture emerge. This architecture is argued not to be hierarchical, as the *driver* of coupling could either be the top-down control of breathing, or bottom-up heart rate changes.

However, can everyone control body-brain coupling efficiently? What is the influence of cardiovascular and respiratory disorders on brain activity and cognition?

Translational research showed a link between respiratory diseases in childhood (Campbell et al., 2017; Goodwin & Buka, 2008; Maric et al., 2020) and heightened risks for anxiety disorder and major depression in adulthood. Furthermore, breathing impairments were associated with early manifestations of Parkinson's disease (Morley & Duda, 2011), even in the 'pre-motor' diagnosis (Maric et al., 2020). Other psychiatric disorders (Quadt et al., 2018; Tumati et al., 2021), anxiety, depression (Paulus & Stein, 2010), and autism (Garfinkel et al., 2016) were also linked to an altered sensitivity to bodily visceral inputs. Altogether, this evidence suggests that a holistic assessment of body-brain interactions may help to better understand pathological conditions characterized by altered body physiology. However, in the healthy as well as in clinical populations, research has been limited to assessing one bodily signal next to brain activity and/or behavior, thus preventing the holistic characterization of body-brain dynamics and their conjunct influence on cognition.

To conclude, in Chapter 5 I discussed that the BBDS draws a tight link between bodily physiological rhythms, brain activity, and behavior. Fluctuations in body-brain interactions instantiate a rhythmic mode of perception and may be described by a system of body-brain dynamic oscillators. I argued that the time is ripe for a fundamental shift in how we study neurocognitive functions. Body-brain interactions demand for more attention and offer novel perspectives to foster our understanding of cognition in health and pathology. The BBDS paves the way for a plethora of novel and holistic research questions on human functioning; and I hope to pick up the right ones in my future research.

To start off with, I have introduced two novel research lines: the first targets the link between individual body-brain rhythms and behavioral rhythms (Criscuolo et al., 2022b), while the second aims at developing a holistic bio-feedback training to modulate neurocognitive functions and emotional states (Criscuolo & Kotz, 2023). As such, this research aims at expanding the traditional neurofeedback setups so to include bodily physiological activity and

body-brain interactions next to the assessment of brain activity in isolation. Thus, I hypothesized that a holistic biofeedback approach designed to train the capacity to focus on interoceptive signals and increase body-brain coupling will increase the efficacy of existing neurofeedback trainings in improving attention, anxiety and wellbeing.

‘Take a deep breath, listen’: Body-Brain Waves may be generating your own internal clock, sampling the sensory environment and coordinating perception and action within your own heart beats. If so, cognition and inter-individual differences may be better understood from the lens of a body-brain dynamic system.

What have we learned?

Ordo ab chaos

In this thesis, I have discussed that time processing is fundamental to achieve a coherent perceptual representation of our sensory environment. Chaotic multivariate sensory inputs of different spatial provenance and at multiple temporal scales converge into a coherent percept by using our *sense of time*.

Timing cognition in waves

The continuous flow of time is discretized into measurable and compact units by using oscillations of an atomic clock. Our *endogenous* sense of time is similarly associated with oscillations of brain activity, i.e., fluctuations in the excitability of neuronal populations. In Chapters 2-4 I demonstrated that neural waves encode, track and predict temporal regularities in the acoustic environment in healthy young and ageing individuals as well as in macaque monkeys. Cross-species similarities in basic rhythm cognition speak in favor of a fundamental role of basic *timing* throughout evolution. Lesions in the BG and CE in humans, however, causally impact temporal processing, and further alter the capacities to produce and synchronize with rhythms.

Time and timing are not fixed: variability

In this thesis I dedicated particular attention to intra- and inter-individual variabilities, typically neglected by pooling and averaging data across trials and participants. This approach allowed for interesting discussions: for instance, in Chapter 2 and 3 I showed that standard ERP and time-frequency analyses relying on the averaging of neural activity over hundreds of trials failed to show the presence of binary accentuations. In contrast, single-trial modelling revealed fluctuations: there were binary, ternary and other accentuations, on a subset of trials. In those trials, identical tones were differentially processed in function of S-w accents, and the accentuations further influenced deviance processing. These observations reveal a more variegated picture than previously thought: there are intra- and inter-individual differences in the *if, when,* and *how* participants sample the acoustic environment, and in the *if, when,* and *how* they processed temporal regularities at all. In the comparative study (Chapter 3), this systematic approach was even more important: evolutionary hypotheses on cross-species

similarities are usually tested by employing human-made stimuli and by training the animal to perform human-like behavior (e.g., synchronizing to complex musical rhythms). Leaving out the discussion on whether humans themselves enjoy (and are capable of) having to precisely tap along with music for long experimental sessions, these manipulations surely do not match an animal's ecological reality. Thus, I argued that a quintessential step in understanding the phylogenetic trajectories of *basic* rhythm cognition is the testing of task-independent neural behavior in non-human primates. In absence of specific task instructions, the animal may or may not be attentively listening to the auditory sequences at all. However, *if* the animal's brain still shows to be processing the temporal regularities in the acoustic environment, that provides evidence for an endogenous predisposition to process rhythms. In turn, one may speculate on the evolutionary role of rhythm cognition: what is its functional and adaptive role? In this context, single-trial analyses were fundamental to show the capacity of macaque monkeys' neurophysiological activity to encode, track and predict temporal regularities and sample the acoustic environments via accentuations patterns, in absence of task instructions.

Large intra- and inter-individual variabilities were also observed in 'rhythm tracking' analyses across Chapters 2-4. Healthy young individuals and macaque monkeys showed large variability in the *if, when* and *how* they aligned their neural waves to the rhythm of auditory tones. A portion of trials did not show phase coherence (as indexed by mean vector length), our proxy for the hypothesized predictive phase alignment. More exhaustive analyses on the dynamics of neural tracking in Chapter 4 similarly showed large heterogeneity in the velocity and acceleration of neural waves while *tuning* to auditory rhythms. While healthy participants displayed more stable neural dynamics as compared to stroke patients, they still showed variability.

What influences such variability?

In Chapter 5, I discussed that investigating the brain in isolation may be reductionist. The body hosts a plethora of endogenous oscillators, each fluctuating at its eigenfrequency. Neural waves, circadian, gastrointestinal, cardiac and respiratory rhythms may represent internal clocks ticking at different frequencies, mutually interacting, and forming a body-brain frequency architecture. I, thus, discuss that body-brain rhythms resemble dynamic oscillators sampling our sensory environment at multiple timescales, dynamically attending and

coordinating motor production and synchronization. Importantly, individuals differ in their physiology: your cardiac and breathing rates make you unique. Furthermore, your cardiac and breathing rates let your internal clock tick at your unique rhythm. Consequently, variability in body-brain rhythms and their dynamic interaction may instantiate inter-individual variabilities in sensory processing, perception and action.

However, how much do we know about inter-individual variabilities in bodily and behavioral rhythms (e.g., individual walking and speaking rates)? How much do we know about body-brain interactions and their influence on general cognition? Unfortunately, still little, but in recent years there has been a steep increase in interest in the topic and many research labs across the world are investigating various aspects of cognition in relation to body-brain interactions. While still young, this field of research promises to advance our understanding of neurocognitive functions, in health and cognition. And we are joining this journey with two exciting research lines in both basic (Criscuolo, Schwartze, & Kotz, 2022b) and translational (Criscuolo & Kotz, 2023) research.

Is isochrony processing a valid scenario for testing rhythm cognition?

While I acknowledge that isochronous auditory sequences may not necessarily represent a 'realistic' stimulus, in Chapter 3 I proposed it to be an ideal test-case for investigating the basic neurophysiological mechanisms underlying the processing of temporal regularities. In the absence of other temporal, spectral, and semantic information (i.e., as in complex rhythms, in music and speech), I have isolated the neural dynamics encoding a sequence of tones onsets and their predictable periodicity. While perhaps perceived as minimalistic (or simplistic), I note that isochrony (or gradients of temporal regularity) is present in a wide range of daily behaviors (e.g., walking), environmental stimuli (e.g., speech), and physical phenomena (e.g., motion of particles). Thus, understanding basic rhythm cognition is a fundamental stepping stone allowing investigations of more complex rhythms. Furthermore, in light of the discussion on variability above, starting with simple stimuli may be a better strategy as compared to investigating the processing of complex stimuli. In fact, variability may scale with task and/or stimulus complexity ultimately compromising the signal to noise ratio of the neural dynamics under investigation.

Can *timing* modulate other cognitive functions?

We discussed that internal time generation and time processing are fundamental to structure cognition: the *sense of time* allows to coherently process multisensory information, coordinating perception and (re-)action. When timing is altered, as in BG and CE patients, sensory processing is affected, as well as the capacities to produce and timely synchronize behaviors.

While we here tested the processing of basic rhythms (isochronous auditory sequences), and the production of simple behaviors (finger taps), we argue that these lower-levels functions are fundamental for higher-order cognitive functions and behaviors such as music and speech processing and production. Indeed, speech processing relies on a frequency architecture of brain waves (Giraud & Poeppel, 2012; Rimmele & Keitel, 2023), encoding and predicting the timing of speech sounds (phonemes, syllables, words). Similarly, speech production requires the planning and coordination of a sequela of motor movements, along with the prediction of upcoming sensory input (Hickok, 2012; Hickok & Poeppel, 2007). When some of these timing and predictive computations are altered, dysfluencies occur as in the case of stuttering (Sengupta et al., 2017). In fact, diverse developmental speech and language problems, ranging from dyslexia to stuttering, and with frequent comorbidity with motor and attention disorders, have been linked to genetic liability for 'atypical rhythms' (Niarchou et al., 2021). This large-scale genome-wide association study unravelled the fundamental influence of genetic factors on endogenous timing mechanisms. In particular, the abilities to process temporal regularities, predict, and synchronize to temporal patterns seem to have a genetic substrate which influences neurodevelopmental processes.

Can we use *timing* in rehabilitation?

Rhythmic training has been largely employed as a tool to improve speech and language processing, as well as motor coordination. For instance, rhythmic trainings proved to be effective in improving speech fluency (Toyomura et al., 2015), as well as reading skills (Bonacina et al., 2015). Similarly, music exposure (Nombela et al., 2013; Nombela et al., 2013) and dance (Earhart, 2009) seem to improve gait (speed and fluency of coordination) in Parkinson's disease (PD) patients. The predominant idea is that rhythmic training and music exposure may stimulate and provide a regular temporal frame, an *internal clock*, which is otherwise altered in these conditions (Goswami, 2011). What is usually neglected, however, is the bodily perspective: the aforementioned genome-wide study (Niarchou et al., 2021)

further unveils shared genetic architecture between timing processes and two other bodily rhythms, respiration and circadian rhythms. In PD, for instance, motor deficits usually co-exist with respiratory (Mehanna & Jankovic, 2010) and cardiovascular (Ziemssen & Reichmann, 2010) problems, pointing towards a *central timing* deficit. And while music and rhythm training are sometimes effective, large inter-individual differences exist, whereby some PD patients show no improvement or even worsening of symptoms when exposed to auditory stimuli (Nombela et al., 2013; Thaut et al., 1996). Altogether, these observations strengthen the link between various body-brain rhythms, timing capacities, and general cognition, ultimately reinforcing the need for more individualized, systematic and holistic assessments of body-brain interactions and individual variabilities.

Conclusions

In this thesis, I investigated the basic neurophysiological mechanisms to process and predict temporal regularities in the sensory environment. I performed basic, comparative and translational research and demonstrated that the capacities to detect, produce and synchronize with rhythms in the acoustic environment rely on neural dynamics in the δ-β frequency-bands. δ-band neural waves encode and track auditory rhythms via adaptive mechanisms of frequency- and phase-tuning, generally referred to as *entrainment*. Thus, I characterized cross-species similarities in neurophysiological mechanisms of basic rhythm processing, and further confirmed the fundamental role of subcortical brain regions in rhythm cognition. In fact, focal lesions in either the BG or CE causally impacted the capacities to precisely encode, produce and synchronize with external rhythms. Next to δ-band activity, we demonstrated that β-band oscillations sample the acoustic environment by superimposing accentuation patterns onto isochronous auditory sequences. These β-band dynamics were present in humans as well as nonhuman animals, confirming shared capacity to process rhythms beyond isochrony in our close ancestors, macaque monkeys. Overall, these observations speak in favor of an evolutionary role of rhythm cognition in the phylogeny of higher-order cognitive functions, such as music and speech in humans. Finally, I expanded the research line to other physiological rhythms: bodily activity. I discussed that bodily physiological signals resemble endogenous oscillators and may interact with brain waves modulating general cognition. Thus, I proposed the novel framework of the Body-Brain Dynamic System to analytically characterize body-brain interactions and their causal role in influencing intra- and inter-individual variabilities in neurocognitive functions and behaviors. Altogether, I discussed that *timing* in the body-brain system interacts with *timing* in the sensory environment, ultimately modulating our capacities to detect, produce and synchronize with rhythms, and influencing the abilities to act and adapt in a dynamically changing environment.

Appendix

Summary

From pre-Socratic to modern philosophers, many have debated about the role of the *sense of time* in our experience of the world. What is *time*, and how do we use it to structure our perception? Drawing a tight link between the use of *time* in physics and natural sciences and the *sense of time* in cognitive neuroscience, the research summarized in this thesis aims at understanding how our brain generates a *sense of time*, and how we employ *time* to coordinate perception and action.

With a series of basic, comparative and translational studies reported in Chapters 2 to 4, I discuss that neurophysiological activity in the brain may provide an exquisite sense of time: neural waves represent an internal ticking clock, generating an endogenous representation of time and able to keep track of the precise *timing* of external events. Thus, we discussed that neural waves at multiple time-scales (e.g., delta (δ; 1-4Hz) and beta (β; 12-20Hz)) encode the *when* of incoming sensory information, and predictively track the *when* of future sensory inputs by generating *predictions*. These expectations are formed by *detecting* temporal *regularities* in environmental stimuli: leveraging on learnt temporal *patterns,* neural waves prepare the organism to process the *next* stimuli, thus optimizing sensory processing, perception, and (re-)action. These so-called *dynamics of attending* are thought to play a fundamental role in our capacities to act and adapt in a dynamically changing environment. They rely on an extended cortico-subcortical network involving basal ganglia (BG) and cerebellum (CE), and are putatively linked to the development of higher order cognitive capacities in humans, such as music and speech.

Thus, in our research we asked: (i) do our close ancestors, macaque monkeys, process auditory temporal regularities similarly to humans? Next, (ii) can lesions in the BG and CE impact the capacities to encode, produce and synchronize with rhythms in the sensory environment?

In Chapter 2, we identified an adaptive δ-β neural code sampling the sensory environment by encoding, tracking and predicting basic auditory rhythms. In Chapter 3 we argued that striking similarities between humans and nonhuman animals (macaque monkeys) support the notion of shared basic rhythm cognition, challenging existing evolutionary hypotheses on the evolution of language and music in humans. Finally, in Chapter 4 we demonstrated that the δ-band neural computations employed to precisely encode the timing of auditory input are altered in BG and CE patients, who showed difficulties in processing the precise

when, as well as in tracking and predicting upcoming sensory inputs. These difficulties were further reflected in behavioral data, showing impaired ability of these patients to produce and synchronize their own behavior (tapping) to externally presented rhythms.

Expanding this research line, in the second part of the thesis (Chapter 5) we discussed that the *sense of time* is further influenced by bodily physiological activity: heartbeat, respiration and gastrointestinal rhythms provide yet another level of *time* in the body, next to brain activity. We thus, argued, that these complementary rhythms in the body and the brain may form a dynamic system of coupling oscillators, influencing sensory processing, perception and action. Our formulation of the Body-Brain Dynamic System (BBDS) incorporates the variability of human behavior, and explains it in function of inter-individual variabilities in physiological rhythms, as well as in body-brain coupling states. The BBDS opens to a plethora of new investigations on neurocognitive functioning in healthy and clinical populations: what is the modulatory influence of (altered) cardiovascular, respiratory and gastrointestinal activity on brain functioning and cognition? Some of the hypotheses formulated in the framework in Chapter 5 are tested in our new ongoing research line, in which we directly assess the link between body-brain rhythms, their dynamic coupling, and individual behavioral rhythms (e.g., rhythm of walking, speaking, listening preferences).

Altogether, the results presented in Chapters 2-4 speak in favor of a fundamental role of δ-β neural waves in rhythm processing, strengthen the notion that there exist similarities between human and nonhuman animal's rhythm cognition, and confirm the causal role of BG and CE structures in rhythm processing and production.

The second research line introduced in Chapter 5, suggests to expand the horizon of cognitive neuroscience research so to include body physiology and body-brain interactions in the equation. As such, our novel framework argues in favor of a fundamental shift in how we study human brain and behavior: holistic, systematic, individual assessments are critical to advance our understanding of human cognition, in health and pathology.

To conclude, we discussed that time generation and time processing, in the body and the brain, are fundamental to structure cognition: the *sense of time* allows to coherently process multisensory information, coordinating perception and (re-)action. *Ordo ab chaos*.

Nederlandse samenvatting (Dutch summary)

Van pre-Socratische tot moderne filosofen hebben velen gedebatteerd over de rol van het tijdsbesef in onze ervaring van de wereldlijke realiteit. Wat is tijd en hoe gebruiken we het om onze waarneming te structureren? Door een nauwe link te leggen tussen het gebruik van tijd in de natuurkunde en natuurwetenschappen enerzijds, en het tijdsbesef in de cognitieve neurowetenschappen anderzijds, heeft het onderzoek samengevat in deze scriptie tot doel te begrijpen hoe onze hersenen een gevoel van tijd genereren, en hoe we tijd gebruiken om perceptie en actie te coördineren.

Met een reeks basis-, vergelijkende en translationele studies gerapporteerd in Hoofdstukken 2 tot 4, bespreek ik dat neurofysiologische activiteit in de hersenen mogelijk een voortreffelijk tijdsbesef biedt: neurale golven vertegenwoordigen een interne tikkende klok, genereren een endogene representatie van tijd en zijn in staat om de precieze timing van externe gebeurtenissen bij te houden. We hebben besproken dat neurale golven op meerdere tijdschalen (bijv. delta (δ; 1-4Hz) en beta (β; 12-20Hz)) het 'wanneer' van binnenkomende sensorische informatie coderen, en voorspellend het 'wanneer' van toekomstige sensorische input volgen door voorspellingen te genereren. Deze verwachtingen worden gevormd door het detecteren van temporele regelmatigheden in omgevingsstimuli: door te profiteren van geleerde temporele patronen, bereiden neurale golven het organisme voor om de volgende stimuli te verwerken, waardoor sensorische verwerking, perceptie en (her)actie worden geoptimaliseerd. Deze zogenaamde dynamiek van aandacht wordt verondersteld een fundamentele rol te spelen in onze capaciteiten om te handelen en aan te passen in een dynamisch veranderende omgeving. Ze steunen op een uitgebreid cortico-subcorticaal netwerk dat betrokken is bij de basale ganglia (BG) en het cerebellum (CE), en worden verondersteld te zijn verbonden met de ontwikkeling van hogere cognitieve capaciteiten bij mensen, zoals muziek en spraak.

Dus, in ons onderzoek vroegen we ons af: (i) verwerken onze naaste voorouders, makaakapen, auditieve temporele regelmatigheden op dezelfde manier als mensen? Vervolgens, (ii) kunnen laesies in de BG en CE de capaciteiten beïnvloeden om ritmes in de sensorische omgeving te coderen, produceren en synchroniseren?

In Hoofdstuk 2 identificeerden we een adaptieve δ-β neurale code die de sensorische omgeving bemonstert door basisauditieve ritmes te coderen, volgen en voorspellen. In Hoofdstuk 3 betoogden we dat opvallende gelijkenissen tussen mensen en niet-menselijke dieren (makaakapen) de notie van gedeelde basisritmecognitie ondersteunen, bestaande evolutionaire hypothesen over de evolutie van taal en muziek bij mensen uitdagend. Ten slotte toonden we in Hoofdstuk 4 aan dat de δ-band neurale berekeningen die worden gebruikt om de timing van auditieve input nauwkeurig te coderen, worden veranderd bij BG- en CE-patiënten, die moeite hadden met het verwerken van het precieze 'wanneer', evenals met het volgen en voorspellen van aankomende sensorische inputs. Deze moeilijkheden werden verder weerspiegeld in gedragsgegevens, waarbij een verminderd vermogen van deze patiënten om hun

eigen gedrag (tikken) te produceren en te synchroniseren met extern gepresenteerde ritmes werd aangetoond.

Door deze onderzoekslinie uit te breiden, bespraken we in het tweede deel van de scriptie (Hoofdstuk 5) dat het tijdsbesef verder wordt beïnvloed door lichamelijke fysiologische activiteit: hartslag, ademhaling en gastro-intestinale ritmes bieden nog een ander niveau van tijd in het lichaam, naast hersenactiviteit. We betoogden dus dat deze complementaire ritmes in het lichaam en de hersenen een dynamisch systeem van koppelende oscillatoren kunnen vormen, dat de sensorische verwerking, perceptie en actie beïnvloedt. Onze formulering van het Body-Brain Dynamic System (BBDS) omvat de variabiliteit van menselijk gedrag en verklaart dit in functie van interindividuele variaties in fysiologische ritmes, evenals in toestanden van koppeling tussen lichaam en brein. Het BBDS opent naar een overvloed aan nieuwe onderzoeken naar neurocognitieve werking bij gezonde en klinische populaties: wat is de modulerende invloed van (veranderde) cardiovasculaire, respiratoire en gastro-intestinale activiteit op hersenfunctie en cognitie? Sommige van de hypothesen geformuleerd in het kader van Hoofdstuk 5 worden getest in onze nieuwe, lopende onderzoekslinie, waarin we rechtstreeks de link tussen lichaam-hersenen ritmes, hun dynamische koppeling en individuele gedragsritmes (bijv. loopritme, spreekritme, luistergewoonten) beoordelen.

Al met al spreken de resultaten gepresenteerd in Hoofdstukken 2-4 voor een fundamentele rol van δ-β neurale golven in ritmeverwerking. Ze versterken de notie dat er overeenkomsten zijn in het ritmebegrip tussen mensen en niet-menselijke dieren en bevestigen de causale rol van BG- en CE-structuren in ritmeverwerking en -productie.

De tweede onderzoekslinie geïntroduceerd in Hoofdstuk 5, suggereert het horizon van cognitieve neurowetenschappelijk onderzoek uit te breiden om lichaamsfysiologie en lichaam-hersenen interacties in de vergelijking op te nemen. Als zodanig betoogt ons nieuwe kader voor een fundamentele verschuiving in hoe we menselijke hersenen en gedrag bestuderen: holistische, systematische, individuele beoordelingen zijn cruciaal om ons begrip van menselijke cognitie, zowel in gezondheid als in pathologie, te bevorderen.

Ter afsluiting bespraken we dat tijdscreatie en -verwerking, in het lichaam en de hersenen, fundamenteel zijn om cognitie te structureren: het tijdsbesef maakt het mogelijk om multisensorische informatie coherenter te verwerken, perceptie en (her)actie te coördineren. Ordo ab chaos.

Impact addendum

What is the main purpose of the research described in the thesis and what are the main results and conclusions?

The research summarized in this thesis aimed at understanding how we encode and process the *timing* of sensory input, and how we employ timing computations to efficiently coordinate perception and action. With a series of basic, comparative and translational studies reported in Chapters 2 to 4, I showed that neurophysiological activity in the brain provides an exquisite *sense of time*: neural waves represent endogenous oscillators, produce an *internal clock*, and are capable of tracking the precise *timing* of sensory input. Thus, I discussed that neural waves at multiple timescales (e.g., delta (δ; 1-4Hz) and beta (β; 12-20Hz)) encode the *when* of incoming sensory information, and predictively track the *when* of future sensory inputs by generating *predictions*. These so-called *dynamics of attending* are thought to play a fundamental role in our capacities to act and adapt in a dynamically changing environment.

Thus, in our research we demonstrated similarities in basic rhythm cognition between humans and nonhuman animals, macaque monkeys. Next, we provided causal evidence for a fundamental role of BG and CE in the capacities to encode, produce and synchronize with rhythms in the sensory environment. Expanding this research line, in the second part of the thesis I discussed that bodily physiological activity interacts with and influences neurocognitive functions. Heartbeat, respiration and gastrointestinal rhythms provide yet another level of *time* in the body, next to brain activity. Thus, I advanced the new framework the Body-Brain Dynamic System (BBDS) to analytically examine and characterize body-brain interactions and their influence on sensory processing, perception and action.

What is the (potential) contribution of the results of this research to science?

Altogether, the results presented in Chapters 2-4 speak in favor of a fundamental role of δ-β neural waves in rhythm processing, strengthen the notion that there exist similarities between human and nonhuman animal's rhythm cognition, and confirm the causal role of BG and CE structures in rhythm processing and production.

The second research line introduced in Chapter 5, suggests expanding the horizon of cognitive neuroscience research so to include body physiology and body-brain interactions into the

equation. As such, our novel framework argues in favor of a fundamental shift in how we study human brain and behavior: holistic, systematic, individual assessments are critical to advance our understanding of human cognition, in health and pathology.

To conclude, I discussed that time, in the body and the brain, is fundamental to structure cognition: the *sense of time*, and the capacities to track and sample sensory input, allow to temporally organize multisensory information into a coherent percept, and ultimately allow to act and adapt in a dynamically changing environment. *Ordo ab chaos*.

Conceptual and methodological advances

Across chapters, we have dedicated particular attention to intra- and inter-individual variabilities: we have developed new methodological approaches to explore variability in individual brain data, and to characterize time-varying dynamics of neural oscillatory activity. Brain functioning and behavior are variegated, multifaceted, complex, dynamic phenomena (or systems) which cannot be summarized into group averages. The typical tendency to aggregate data across individuals and hundreds of experimental trials leaves out systematic assessments of *what* happens *moment to moment*, as well as *what* determines observed behaviors. We discuss that this approach has failed and will inevitably keep on failing in understanding human cognition and disorders: future research has to dedicate more attention to the individual and his/her unique body, brain, behavioral variabilities.

These formulations may not have an immediate impact on society and ongoing scientific research, but hopefully contribute to and motivate a movement *towards* novel holistic and individualized research and therapeutic approaches. In fact, the findings on intra- and inter-individual variabilities (Chapters 2-4) have raised substantial interest in the neuroscientific community. Similarly, the framework provided by the BBDS (Chapter 5) is of cross-disciplinary interest and has been welcomed with great enthusiasm by a large crowd of scientists of different backgrounds.

Public outreach and education

This work has been presented publicly in more than 10 internal conferences and more than 10 talks in research groups across the world. Importantly, this research has reached both the

neuroscientific community, as well as the general public via in-person events, as well as through an active presence on social media (e.g., Twitter, LinkedIn, Facebook) and websites (e.g., the BAND-lab and Waves conference). Our work has further attracted the interest of NeuroTech companies, who are in contact with us to explore future applications of mobile body-brain imaging setups in future research lines. What I am mostly proud of, however, is that I recently went back to my secondary school in Salerno (southern Italy) to discuss my research on rhythm. There is where I started to play music, and where my journey to becoming a professional musician started, some years ago. It was a great pleasure bringing there my own research on rhythm and music, and meeting the sparking interest in the crowd: my family, my teachers, and many more school teachers across the Province and Campania region.

Finally, our research is being published in high-impact factor journals, a process which allowed us to receive high-standard feedback and advice to further improve the quality of our work. Through the PhD, however, I have learnt that the publication process sometimes suffers from subjective views, egoistic interests (e.g., you cannot provide evidence against a reviewer's theory) and significant delays (it may take a year to go through revisions). Consequently, receiving fair, critical and timely feedback often remains an utopia.

My research lines have also inspired my teaching: I try to convince my students that the focus on the individual and individual variabilities is important to advance science. Thus, across BSc and MSc courses, I often engage in critical discussions with students discussing the *why* and *how* examining variability is important, in healthy and clinical populations. The *how* is further implemented in my programming and signal processing courses, during which I offer ad-hoc examples on how to analyze and visualize single-participant and -trial data, and how to summarize findings with statistics.

About the author

Curriculum vitae

Publication list

Talks and Conference contribution

Antonio was born and raised in the sun and blue of the Amalfi Coast, in southern Italy. He is originally from Salerno, where he studied music and bassoon and graduated at the Conservatory in 2013. He pursued his BSc studies at the University of Bologna, and his Master's studies of music at the Conservatory of Cesena. During the third year, he moved to Aarhus (Denmark) at the Center for Music in the Brain for his internship and thesis. Later, he enrolled in the Research Master in Cognitive Neuroscience at Maastricht University. In the second year, he moved to Oxford (United Kingdom) for his internship and thesis. Since 2020, he is a PhD student at Maastricht University. During his PhD, he attracted a mobility grant from the Royal Netherlands Academy of Arts & Sciences, which allowed a research visit of a few months at the Max Planck Institute for Empirical Aesthetics in Frankfurt (Germany). Furthermore, he acquired three smaller scale grants to attend and present his research at international conferences. Among these, a travel grant from the Italian Association of Cognitive Sciences. Besides his research and teaching activities, Antonio is the founder and organizer of the WAVES series: a series of internal conferences, summer schools, and workshops on Body-Brain Waves in his hometown, Salerno.

Publication list

Peer-reviewed articles

2024	Variability allows for adaptation in dynamic environments. A Criscuolo, M Schwartze, SA Kotz *Physics of Life Reviews*
2023	Individual neurophysiological signatures of spontaneous rhythm processing A Criscuolo, M Schwartze, MJ Henry, C Obermeier, SA Kotz *NeuroImage*
2023	Macaque Monkeys and Humans Sample Temporal Regularities in the Acoustic Environment A Criscuolo, M Schwartze, L Prado, Y Ayala, H Merchant, SA Kotz *Progress in Neurobiology*
2022	Cognition through the lens of a body–brain dynamic system A Criscuolo, M Schwartze, SA Kotz *Trends in Neurosciences*
2022	An ALE meta-analytic review of musical expertise A Criscuolo, V Pando-Naude, L Bonetti, P Vuust, E Brattico *Scientific reports*
2021	Neural tracking of speech: top-down and bottom-up influences in the musician's brain KD Kandylaki, A Criscuolo *Journal of Neuroscience*
2019	On the association between musical training, intelligence and executive functions in adulthood A Criscuolo, L Bonetti, T Särkämö, M Kliuchko, E Brattico *Frontiers in Psychology*

Book chapters

2023	Fundamentals of Electroencephalography and Magnetoencephalography A Criscuolo, E Brattico Language Electrified: Principles, Methods, and Future Perspectives of Investigation

Pre-prints

2023	Neural and behavioral dynamics of temporal processing in basal ganglia and cerebellar lesion patients A Criscuolo, M Schwartze, S Nozaradan & SA Kotz *bioRxiv*
2023	Challenging age-related decline in brain function: Evidence from fast neuroimaging of musical sequence recognition L Bonetti, G Fernandez-Rubio, A. Criscuolo, et al. *bioRxiv*

Pre-registrations

2023	B-Waves: a holistic bio-feedback training program based upon Body-Brain Waves A Criscuolo, SA Kotz *OSF*
2022	Sampling the environment with body-brain rhythms A Criscuolo, M Schwartze, SA Kotz *OSF*

In preparation

	Body and brain waves in health and pathology A Criscuolo, A Czepiel, M Schwartze, SA Kotz
	Dynamical interactions of partners' genitals in arousing scenarios A Pawlowska, A Criscuolo, et al
	Attentional fluctuations influence the processing of temporal regularities A Criscuolo, M Henry, M Schwartze, SA Kotz
	Ageing deteriorates the capacities to encode and predict temporal regularities in auditory streams A Criscuolo, L Bonetti, M Schwartze, SA Kotz
	Body-Brain Waves explain inter-individual variabilities in rhythmic behavior A Criscuolo, M Schwartze, SA Kotz

Talks and Conference contributions

Conference talks

2023	"Basic neural oscillatory mechanisms of rhythm processing". Timing Research Forum conference, Lisbon.
2023	"A dynamic Body-Brain Functional Connectome from Rest to Cognition". Body-Brain Waves conference, Salerno.
2023	"Sampling the environment with body-brain rhythms". NeutoTech Leuven, University of KU Leuven.
2023	"A cross-species and translational perspective on basic neural oscillatory mechanisms to encode and predict temporal regularities". Rhythm Perception and Production Workshop (RPPW), Nottingham University.
2022	"The body-brain dynamic system for neurocognitive profiling". Italian Association of Cognitive Sciences (AISC22), University of Rovereto-Trento.
2022	"On the phylogenesis of rhythm cognition and the causal involvement of cortico-subcortical structures". Advances and Perspectives in Auditory Neuroscience (APAN), San Diego.

Conference posters

2022	"On the phylogenesis of rhythm cognition and the causal involvement of cortico-subcortical structures". Society for Neuroscience, San Diego.
2022	"Modelling temporal predictions in human's rhythm and beat processing". NVP, Dutch Society for Brain and Cognition.
2022	"An individualized and comparative approach to the neurophysiology of beat and rhythm processing". International Cognitive Neuroscience Conference (ICON), Helsinki University.
2022	"An individualized and comparative approach to the neurophysiology of beat and rhythm processing". Social Bridges, Munchen University

2021	“Does attention influence temporal predictions in sound sequences?”. Locumus consortium
2021	“Towards individual fingerprinting: neurophysiological signatures of Rhythm and beat processing - Part I”. CuttingEEG, Aix-Marseille University
2021	“The Neuroanatomy of Musical Expertise: A systematic review and meta-analysis of neuroimaging studies”. NeuroMusic VII, Aarhus University

Invited talks

2023	“Sampling the environment with body-brain rhythms”. European Biomedical Research Institute, Salerno.
2023	“Sampling the environment with body-brain rhythms”. Timing Research Forum, Journal Club
2022	“On the phylogenesis of rhythm cognition and the potential role of body-brain interactions”. Ghent University.
2022	Invited talk: ‘Sampling the environment with body-brain rhythms’. Music Dynamics Lab at the University of Connecticut.
2022	“Temporal predictions in rhythm and beat processing”. Max Planck Institute (MPI) for Human Cognitive and Brain Sciences, Frankfurt.
2022	“Modelling temporal predictions in rhythm and beat processing”. Center for Music in the Brain (MIB), Aarhus University.

Public outreach talks

2023	“Il ruolo fondamentale del ritmo nelle funzioni cognitive”. Istituto Comprensivo ad Indirizzo Musicale, Salerno.
2023	“Oscillazioni ritmiche nel corpo e nel cervello” Università Aldo Moro, Bari.

Talks within Maastricht University

2023	“Timing cognition with Body & Brain Waves”. UM Colloquia
2023	“Timing in dynamic environments”. Auditory Cognition and Perception Lab.
2022	“Timing in dynamic environments”. FPN Research Day

2022	“Timing in dynamic environments”. NP&PP Research Day
2022	“Neural oscillations in rhythm processing”. Research Master’s cohort
2022	“A dynamic body-brain system: from physiology to its influence on cognition”. Lunch talk, NP&PP Department
2021	“Temporal predictions in rhythm and beat processing”. Lunch talk, NP&PP Department
2021	“Temporal predictions in rhythm and beat processing”. Research Master’s cohort

Other initiatives

2024	Founder and Organizer: Body-Brain Waves, Summer School Salerno, Italy
2023	Co-organizer: Public outreach event “Neuroscienze della Musica nello sviluppo cognitivo ed in riabilitazione” Salerno, Italy
2023	Symposium Organizer: “Rhythmic synchronization in and out of the brain: a cross-species and translational perspective spanning single interval estimations to interpersonal interactions”. Timing Research Forum conference, Lisbon.
2023	Founder and Organizer: Body-Brain Waves, International Conference Salerno, Italy
2021-23	BAND-lab Journal Clubs with external guests

Acknowledgements

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