



First-person constraints on dynamic-mechanistic explanations in neuroscience: The case of migraine and epilepsy models

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Abstract

According to recent discussion, cross-explanatory integration in cognitive science might proceed by constraints on mechanistic and dynamic-mechanistic models provided by different research fields. However, not much attention has been given to constraints that could be provided by the study of first-person experience, which in the case of multifaceted mental phenomena are of key importance. In this paper, we fill this gap and consider the question whether information about first-person experience can constrain dynamic-mechanistic models and what the character of this relation is. We discuss two cases of such explanatory models in neuroscience, namely that of migraine and of epilepsy. We argue that, in these cases, first-person insights about the target phenomena significantly contributed to explanatory models by shaping explanatory hypotheses and by indicating the dynamical properties that the explanatory models of these phenomena should account for, and thus directly constraining the space of possible explanations.

Keywords Mechanistic explanation · Dynamic explanation · Explanatory constraints · Epilepsy · Migraine · First-person experience

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1 Introduction

In the last two decades, a shift from cognitive science to cognitive neuroscience has taken place (e.g., Boone and Piccinini, 2016). The development of brain studies has changed the way we think about mental phenomena and their explanation. In particular, the neomechanistic model of explanation has become dominant and widely applied in cognitive neuroscience (e.g., Craver, 2007). According to the mechanistic framework, an explanation of a target phenomenon relies upon describing the causal mechanism which produces it (for an overview, see, e.g., Bechtel 2008, Craver 2007). To put it differently, mechanistic explanations are based on decomposition of the target system into one or more mechanisms, and further into their parts and operations, which are responsible for the system's behavior (explanandum phenomenon). Importantly, mechanistic explanations typically span multiple levels of organization. The involvement of all of these levels in an explanatory model of a mechanism necessitates the integration of multiple fields of research. Thus, according to Craver, "the goal of building a mechanistic explanation, rather than an explanation simpliciter, provides an abstract framework or scaffold that is elaborated as different fields add constraints on the explanation" (Craver, 2007, p. 231). The key notion here is that of constraints. The success of an explanation depends on various constraints provided by different research fields. Constraining relations can be conceived as limiting the space of possible mechanisms, which "contains all the mechanisms that could possibly explain a phenomenon" (Craver, 2007, p. 247). In other words, constraints provided by different fields of research limit the set of possibilities and thus contribute to the specification of the sought after mechanism.

Typically, in neuroscience, constraints concern the structural or functional properties of the mechanism responsible for the target phenomenon and are formulated in research fields in which third-person methods of investigation are utilized. Not much attention has been paid to the question of whether the mechanistic explanatory framework may take into account constraints formulated at the level of first-person experience, and if that is the case, then what the nature of such constraining relations might be. In this article, we fill this gap and claim that first-person descriptions of experiences can directly constrain mechanistic explanations of mental phenomena, in the sense that they limit the space of possible explanatory models. Furthermore, we argue that the nature of this constraining relation might go beyond the conceptual (i.e., providing descriptive categories for experiences) and that it concerns localization and dynamical properties of a mechanism underlying the target phenomenon. Our argumentation is based on two case studies of brain disorders. We chose migraine and epilepsy because they have a rich phenomenology that has been reported by patients and studied over an extended period of time. Another reason is that researchers have already proven able to propose dynamic-mechanistic explanatory models for them. We discuss these explanations and show how first-person insights are included and illustrate the character of first-person constraints.

In Sect. 2, after a brief sketch of the background, we discuss two case studies of research on brain disorders, namely migraine with aura and epilepsy. As we argue, in the case of migraine, first-person investigations have not only given us a description of the visual aura and a better understanding of migraine, but provided direct

constraints on explanatory mechanistic models. These constraints are related to the dynamic and structural properties of the underlying mechanism. Next, we discuss the dynamic-mechanistic models of the epileptic network, including a recently published model by Gentiletti and Suffczynski (Gentiletti et al., 2022). We argue that this model addresses the phenomenal properties of a seizure experience, namely it consists of specific phases of a seizure, i.e., the preictal, ictal, and postictal phase, which constrain possible explanations. Moreover, it differs from previous models in that it embodies the transition between phases of the epileptic seizure and provides a novel explanation of this phenomenon. In Sect. 3, we discuss the limitations of our approach as well as the prospects of future revision, for instance, by adding prodromal and postictal phases of seizures.

2 First-person constraints on dynamic-mechanistic models

Constraints on mechanistic explanations can come from research fields investigating the target system at different levels of organization. For example, neuronal behavior can be investigated in one research field focusing on the size and localization of neurons, whereas another field investigates the biophysical properties of neurons. Examples of interlevel constraints include epistemic or conceptual constraints, where one research field provides a conceptualization of a target phenomenon that informs research in another field. An important type of constraint are dynamical one, i.e., constraint that concerns a change of behavior of a target system or its components in time. Recent discussions about the relationship between the mechanistic and dynamical framework show that the opposition between them is only apparent and that, to some extent, these frameworks are complementary (e.g., Bechtel and Abrahamsen, 2010; Kaplan and Bechtel, 2011; Zednik, 2011). Thus, in this paper, we examine hybrid dynamic-mechanistic (DM) explanations. Specific examples of such dynamic-mechanistic explanations have been discussed in Bechtel and Abrahamsen (2010), Beer (2003), and Golonka and Wilson (2019). These examples, however, do not take into consideration first-person experience. Here, we discuss new examples of dynamic-mechanistic explanations in neuroscience, namely models of migraine aura (e.g., Dahlem & Müller, 2003) and of the epileptic neuronal network (Gentiletti et al., 2022). As we show, combining first-person reports with a DM approach allows researchers to develop models providing new insights into target phenomena.

The DM framework meets serious limitations when it faces complex and multifaceted mental phenomena. In such cases, explanations require addressing a first-person experiential dimension. By first-person, we understand the subjective access we have to our lived experiences that may provide descriptions and analyses of said experiences. This may be contrasted with the objective perspective obtained by third-person methods of investigation that are widespread in cognitive neuroscience, such as measurements, interventions, and observation of behavior. Indeed, neuroscientists tend to neglect the results of first-person investigations in research and modelling processes (e.g., Kandel, 2001; LeDoux, 2000). A similar trend of playing down the importance of first-person reports as less accurate as compared to behavioral and physiological measures may be noticed in psychiatry, where understanding of mental

disorders, such as schizophrenia and anxiety, is often limited to disfunctions of brain mechanisms (e.g., Andreasen, 1999; Fanselow and Pennington 2018). Things are no better in cognitive psychology, in which first-person reports of cognitive processes are often considered unreliable (e.g., Nisbett & Wilson, 1977) and thus explanatorily irrelevant. Other researchers see them as mere descriptions of an explanandum phenomenon in folk-psychological terms of beliefs, desires, and intentions (e.g., Murphy, 2017). On the other hand, after refinement, they can be utilized in the process of abstraction in functional-computational explanations (e.g., Newell & Simon, 1972) or in psychological-functional explanations (e.g., Cummins, 2000; Weiskopf, 2011).

It is worth noting that things have begun to change, and after years of neglect, there is a growing trend in appreciating first-person experience (e.g., Rigato et al., 2021) as well as new developments of first- and second-person methodologies, such as neurophenomenology (Varela, 1996), Descriptive Experience Sampling (Hurlburt et al., 2017), and phenomenological interviews (for an overview, see, e.g., Sholkhova et al., 2022). Growing interest in first-person experience can be noticed in such areas of study as, for example, consciousness (e.g., Chalmers, 2013; Seth, 2018), well-being (Alexandrova, 2017), psychopathology (e.g., Kyzar and Denfield, 2023), and is related to the general contention, which we share, that in cases of multifaceted mental phenomena, first-person information is crucial for formulating explanations. Important figures in neuroscience who in the past advocated for purely neurobiological and mechanistic explanations of mental disorders are changing their views. For instance, in a recent paper, LeDoux and colleagues (Taschereau-Dumouchel et al., 2022) argue that the marginalization of subjective experience in understanding mental disorders, such as anxiety disorder, is a dead-end and leads to ineffective treatments. Thus, they call for studying the subjective experience of anxiety in order to develop more effective approaches to treatment. Furthermore, in some cases, application of first-person investigations in psychiatry, describing the structure of subjective experience, is crucial for our understanding of the malady and inform our search for underlying neurobiological mechanisms (e.g., Colombo and Heinz, 2019; Kyzar and Denfield, 2023). It is important to consider, then, whether and how exactly first-person reports can constrain DM explanatory models.

The “mutual constraints” between first-person reports and neuroscientific data were already discussed in the context of naturalizing phenomenology (e.g., Gallagher, 1997; Varela, 1996). Our approach is different and novel. First, the notion of constraints used in the naturalization of phenomenology debate was notoriously ambiguous (for an extended discussion, see, Pokropski 2021). For example, Thompson et al. (1999) defended the view that such constraints are isomorphic relations between the phenomenological and neural level. On the contrary, Varela (1996) and Lutz (2002) criticized the conception of isomorphism and introduced a constraining relation that they called “generative passages,” and Petitmengin et al. (2007) in the study of the epileptic prodromal experience argues for a homeomorphic relation, i.e., topological equivalence, between phenomenal dynamics and neural dynamic processes. In this paper, we adopt Craver’s (2007) notion of constraints understood in accordance with the mechanistic integrative framework; i.e., the role of constraints is to limit the space of possible explanatory mechanisms, and we argue that first-person reports can directly constrain explanatory models in neuroscience. The second prob-

lem with the “mutual constraints” discussed across conceptions of naturalized phenomenology is that they are postulated rather than supported by scientific evidence. Although Lutz (2002) and Petitmengin et al. (2007) conducted original research, including first- and second-person methods of investigation, the discussion about the constraining relation between the experiential and neuronal levels that accompanies this research is purely speculative. Finally, in these neurophenomenological studies, we do not find any explanatory models whatsoever. We approach the subject differently and defend first-person constraints on explanatory models, analyzing selected studies of migraine and epilepsy, and show how first-person reports have contributed to DM explanatory models.

2.1 Migraine with visual aura

Migraine headaches with auras are a common condition which occurs in 8% of the general population (Kirchmann, 2006). The aura is a subjective phenomenon which often accompanies headaches in migraine onsets. Although the phenomenology of aura experiences is diverse, including sensory feelings progressing through the body and aphasic symptoms (language disturbance), the most common type of aura is visual (see, e.g., Russell and Olesen, 1996).

The visual aura experience had been illustrated by migraineurs over the years, and these drawings were key in finding an explanation of what mechanism is responsible for the aura phenomenon (Schott, 2007). The typical method for drawing the aura was fixing one’s eyes on a point in the center of the visual field and sketching the aura in relation to this point. These illustrations show that migraine auras have a uniform structure that usually consists of a characteristic zig-zag pattern, which, by some, is called a fortification figure because of its resemblance to fortifications of medieval city walls. Usually, the zig-zag pattern is accompanied by an inner, bean-shaped scotoma (flickering blind spots). Some migraineurs also drew a progression of the aura. A typical migraine visual hallucination appears in the center of the visual field and gradually moves towards the periphery, although there are cases in which the aura moves in the opposite direction (Hansen et al., 2013). The progression of an average visual aura lasts less than 30 min. Lashley (1941) was first to measure aura propagation velocity. He drew his own aura experiences (see, Fig. 1) focusing on a given shape and its localization in the visual field every few minutes. This method allowed him to estimate the propagation speed of the aura in the primary visual cortex as constant and approximately 3 mm/min.

The estimation of aura propagation based on first-person experience was critical in formulating a hypothesis concerning a mechanism responsible for the aura phenomenon. Milner (1958) noticed that there is a striking similarity between the speed of propagation of auras in the cortex and the velocity of another neural phenomenon, namely the cortical spreading depression (CSD), which was described earlier by Leão (1944) in animal models. CSD is a wave of depolarization of neurons that moves across the cortex and consists of a short period of increased activity and cerebral blood flow followed by a longer phase of depressed activity and hypoperfusion. Recent studies in humans using functional MRI (e.g., Hadjikhani et al., 2001) or implanted electrode strips (Strong et al., 2002) firmly established that CSD is the

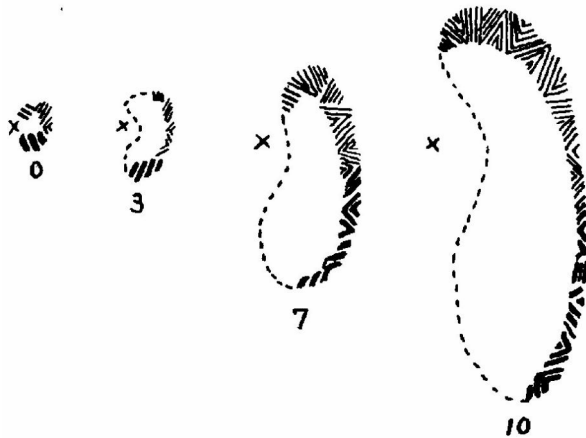


Fig. 1 Drawings of spatiotemporal progression of migraine visual aura. Symbol “X” represents the fixation point; numbers represent the time of the aura experience in minutes. The migraine aura gradually enlarges across the visual field and consists of zig-zag lines on a leading edge and an inner bean-shaped scotoma. From “Patterns of Cerebral Integration Indicated by the Scotomas of Migraine,” by K. S. Lashley, 1941, *Archives of Neurology and Psychiatry*, 46(2), pp. 333–334. Copyright 1941 by the American Medical Association
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mechanism responsible for the migraine aura experience. The specific relationship between subjectively described visual aura symptoms and corresponding neural processes was hypothesized by Dahlem and Müller (2003). They proposed that passage of a CSD wave through the visual cortex causes neuronal hyper-excitation experienced as zig-zag lines followed by suppression of neuronal activity after the passage of the depolarization wave, experienced as scotoma.

2.1.1 CSD and the explanatory model of migraine

As is known, neurons communicate by passing short electrical impulses, i.e., action potentials, to each other. During each action potential, sodium ions flow into the cell and increase its electrical potential, and potassium ions outflow from the cell decreasing the cell’s membrane potential back to the resting level. Ionic concentrations are maintained by energy-fueled sodium-potassium pumps and additionally by supporting glial cells, blood vessels and by diffusion. Grafstein’s influential hypothesis linking potassium and CSD states that potassium released during intense neuronal firing accumulates in the space around neurons and leads to strong excitation (Grafstein, 1956). As potassium continues to increase due to hyperactivity, the cells eventually reach nearly complete depolarization, which causes the depression in neuronal firing that comes after a spreading excitation wave. Excess potassium diffuses to neighboring cells, propagating the excitation wave.

Models of migraine usually focus either on the pathophysiology of CSD initiation or investigate CSD propagation leading to visual migraine aura symptoms. CSD initiation was tested in a computer model of a single neuron incorporating realistic physiological parameters, extracellular space and glia-vasculature potassium uptake

(Kager et al., 2000). When sodium-potassium pump rate and potassium uptake were in normal range, the cell generated a physiological response to external stimulation. However, weakening of either the sodium-potassium pump or glial potassium uptake led to pathological behavior consisting of increased activity followed by sustained neuron depolarization and activity suppression accompanied by a strong rise in extracellular potassium. These results were expanded in a more recent single cell model, which incorporated oxygen dependent sodium-potassium pumps (Wei et al., 2014). Simulations showed that elevating extracellular potassium and lowering oxygen level in a biophysical model produced a broad range of phenomena including seizures and spreading depression. In this way the model demonstrated that these two seemingly unrelated phenomena belong to a continuum from the perspective of neuronal membrane dynamics. Although this finding was based on a single cell model, it provides a plausible explanation of the association between seizures and CSD (Fabricius et al., 2008) and of the migraine headache often experienced by epileptic patients after a seizure (Ekstein and Schachter, 2010).

Single cell models could provide a mechanistic explanation of CSD initiation, but a spatially extended network is necessary to account for the spatial properties of CSD and visual hallucination patterns. Spatio-temporal models of CSD are generally based on chemical reaction–diffusion systems. These models incorporate fluxes of ions across neuronal membranes and simulate diffusion of ions in the extracellular space to account for propagation of excitation waves through a cortical surface (e.g., Tuckwell and Miura, 1978; Shapiro et al., 2001). Often, rather than modeling a detailed biophysical reaction-diffusion system, a simplified approach based on a kinematic theory of wave propagation is applied. One such simple dynamical model simulating spatio-temporal pattern of excitation waves in a visual cortex was developed by Dahlem and Müller (2003). In order to estimate excitability parameter values, the authors analyzed 207 patients' reports of auras (Wilkinson and Robinson, 1985) and noted that auras typically lasted about 30 min and that no reports of multiple visual aura symptoms within the same attack were reported. Based on these first-person reports, they proposed that the functional excitability of the cortex leading to CSD is most likely within the so-called weak excitability regime. In this regime no reentrant waves (spirals) exist and the propagating wave self-terminates due to change (decrease) in its curvature. To recreate the visual percept, the authors applied an inverse mapping of the visual cortex onto the retina. Model simulations predicted that the overall visual disturbance is initially C-shaped, propagates radially, elongates, changing its curvature, and then disappears near the periphery. These simulated aura symptoms match the typical spatiotemporal progression of visual migraine aura drawn by patients (Fig. 1). To further account for the subjects' experience of the characteristic fortification pattern at the edge of the scotoma, the authors included functional organization of the primary visual cortex, i.e., V1 area. Neurons in V1 respond to lines of particular orientation within their receptive field, and neurons with preferred orientations are grouped together in so-called orientation columns (Hubel and Wiesel, 1962). Accordingly, each cortical location is associated with a preferred stimulus orientation in a certain location of the visual field. By adding the retinotopic and orientation map features into the model, the authors were able to reproduce the visual disturbance perceived subjectively. Their simulations showed a typical zig-zag

pattern corresponding to the moving front of the propagating CSD wave. The animated fortification pattern from the model was found strikingly realistic by migraine patients (Dahlem & Chronicle, 2004), as can be also observed in comments to a publicly available video showing visual aura simulations (Markus Dahlem, 2015). The authors envisaged that consulting patients having different aura patterns, e.g., blobs and dots, may help to further improve the match between the model simulations and patients' experiences (Dahlem & Chronicle, 2004).

It should be noted that other computational models were also able to recreate the fortification pattern, even without cortical orientation selectivity features. A reaction-diffusion model representing potassium diffusion through the cortex showed that the leading edge of the potassium wave associated with high activity could form concentric rings or irregular pattern of multiple dots and lines (Reggia and Montgomery, 1996). The model predicted that due to mapping of visual cortical surface onto visual field, the perceived speed of visual hallucinations passing from the center to the periphery should be exponentially increasing. Although this prediction was confirmed in the self-observation of a single patient (Hare, 1966), the authors noted that more testing is needed to verify or falsify the model. They also suggested that model-generated visual aura patterns should be evaluated by the migraine patients to further improve and validate the model, leading to better understanding of the migraine aura phenomenon.

To sum up, taking into account the history of the development of migraine explanations, first-person insights about visual aura propagation in the visual field and the shape of aura percepts were essential contributions to the CSD hypothesis which underlies current explanatory models. The first-person information delivered direct dynamical and structural constraints on explanatory models. First, the reported aura experience was used to define a relevant parameter window of cortical excitability. Low excitability corresponds to normal healthy conditions that don't support CSD propagation. High excitability leads to spiral waves that would propagate endlessly, generating repetitive visual field disturbances within the same attack, which were never reported. The confined shape and duration of the aura commonly described by the patients suggested that the excitability of the cortex may be within the weak excitability regime leading to CSD propagation and self-termination. Second, the percept's zig-zag pattern followed by a scotoma indicated neuronal structures in the visual cortex, such as orientation columns in the V1 cortical area. These reports are the only functional confirmation of visual orientation columns in humans (Dahlem & Chronicle, 2004).

2.2 Epilepsy and dynamics of experience

Epilepsy has been affecting people through millennia and was commonly attributed to supernatural causes until it gradually became recognized as a brain disorder in the 17th century (e.g., Kaculini et al., 2021). Currently, people are diagnosed with epilepsy if they have had two or more unprovoked seizures (Fisher, 2015). Seizures are defined as "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" (Fisher et al., 2005) and are typically classified into focal onset or generalized onset seizures (Fisher et al., 2017). A

seizure has focal onset when it starts in one side of the brain, while the onset is said to be generalized when it starts in both sides. Often, a seizure may start focally and then spreads to involve both brain hemispheres, e.g., as in focal to bilateral tonic-clonic seizures. Importantly, electroencephalographic (EEG) recordings of brain electrical activity with implanted electrodes show that focal seizures typically consist of distinct phases or dynamic states. They start with low amplitude fast oscillations in the recorded signal, evolve into high amplitude irregular activity (tonic phase), which is followed by regular oscillation (clonic phase) that slows down and stops suddenly. Some seizures are followed by short, lasting seconds to minutes, suppression of electrographic brain activity called postictal EEG suppression (PES). It may be followed by a longer, lasting days to weeks, postictal state affecting patients' cognitive functions and well-being.

In some epileptic patients, two additional phases may be distinguished, namely the prodromal phase and aura. The prodromal phase is a subjective feeling that a seizure is on its way. The typical symptoms include irritability, anxiety, mood changes, and cognitive disturbances, which may start hours to days before the actual seizure. This phase may be used as an early indication that a seizure is approaching. The epileptic aura lasts from seconds to minutes. Although traditionally it had been thought of as a warning sign of an impending seizure, currently it is considered an early part of a seizure (Commission on Classification and Terminology of the International League against Epilepsy, 1981). It is experienced by about 56% of patients (Lennox & Cobb, 1933) and, as described below, its symptoms may help to localize the region of the brain initiating the seizure.

Seizures may have specific behavioral, autonomic, cognitive, emotional, sensory, or motor manifestations, which depend on seizure type. During focal seizure a person may be aware of his or her self and environment or awareness may be impaired. Currently, epilepsy diagnosis relies on an interview by a physician and is accompanied by an EEG recording of brain activity and magnetic resonance imaging (MRI) brain scan. It is worth noting that, during an interview, the subjective experience described by a patient or witnessed by an observer greatly contributes to accurate medical evaluation. In the revised classification of epileptic seizures (Commission on Classification and Terminology of the International League against Epilepsy, 1981) the impairment of consciousness reported by the patients has been essential to the classification system. Subsequently, Lüders and colleagues (1998) proposed a practical seizure classification system that was solely based on seizure signs and symptoms. In that framework, seizures with subjectively experienced sensory or psychological symptoms without loss of consciousness were called auras. Depending on the sensory brain area affected by a focal seizure, an aura could be somatosensory, auditory, olfactory, visual, autonomic, psychic, or gustatory. If cognitive functions are affected, the epileptic event is considered a dyscognitive seizure. Dyscognitive seizures could lead to loss of consciousness, confusion, or emotional changes. Seizures with autonomic manifestations are known as autonomic seizures. They affect functions controlled by the autonomic nervous system and may lead, e.g., to altered respiration, sweating, or epigastric sensations. Seizures with abnormal movements are called motor seizures. Motor seizures involve involuntary motor movements with or without loss of consciousness. All these signs and symptoms may be experienced

by a patient before or during initial stages of a focal seizure as defined in time using EEG signal. They provide important information regarding the brain area initiating epileptic discharge (Palmini and Gloor, 1992; Foldvary-Schaefer and Unnwongse, 2011). E.g., analysis of 491 patients with focal epilepsies showed that specific symptoms, such as progression of an abdominal aura into unaware execution of simple or complex movements, suggested that seizures originate in the temporal lobe with a probability of 98.3% (Henkel et al., 2002). Furthermore, subjective reports of temporal sequence of aura progression, e.g., from anxiety and epigastric sensations to a disorder of thoughts and finally to *deja vu* and language disturbances may reveal dynamic links between different functional brain areas (Kanemoto and Janz, 1989).

During generalized seizures, awareness is typically not maintained. For example, in the absence epilepsy, seizures are characterized by transient loss of consciousness lasting typically less than 10 s and are not accompanied by motor manifestations. A patient may stop his/her activity during an attack and resume it after a seizure, often not being aware of having had a seizure. To diagnose absence epilepsy, an EEG test is most commonly used as the attacks have clear electrographic manifestations of high amplitude oscillations that start and stop suddenly.

Different seizure types with diverse accompanying manifestations show that epilepsy has a rich phenomenology. First-person and witness reports together with brain imaging techniques are commonly used to make an accurate diagnosis. On the other hand, development of new clinical treatments is limited by an incomplete understanding of the pathophysiology of epilepsy. In accelerating the advances in epilepsy treatment, the basic mechanisms of seizure initiation, evolution and termination still need to be better understood.

2.2.1 The DM model of focal epilepsy

Nearly all models of seizures assume constant model parameters and simulate the evolution of a seizure through different stages by manipulating some parameters externally, e.g., strength of synaptic connections (e.g., Wendling et al., 2002). Such models can hardly explain dynamic processes governing seizure initiation, progression, and termination. Besides, most models rely on the conventional view that the hyperexcitable state is related to an imbalance between excitatory and inhibitory synaptic communication in the brain. However, some striking experimental results incompatible with this traditional approach have begun to accumulate. For example, it has been demonstrated that seizure discharges may emerge after blocking synaptic transmission (Jefferys and Haas, 1982), showing that seizures don't require synaptic communication. It was confirmed in another experiment, in which a seizure was induced in an *in vitro* brain slice. When two parts of the slice were separated by a cut made using a scalpel, high synchrony was preserved between activities generated in the two disconnected parts (Lian et al., 2001). Recently, a paradoxical increase in inhibitory neuron firing and a decrease in excitatory cell activity at the time of seizure onset was observed in an animal seizure model (Gnatkovsky et al., 2008) as well as in human patients (Elahian et al., 2018). These experimental results point out that the current paradigm based on excitatory and inhibitory imbalance needs to be revised. Novel conceptual approaches as well as recent experimental investigations aimed to

explain the above-mentioned results by showing the importance of other levels of neuronal organization, such as ionic dynamics.

As has been mentioned above, action potential firing leads to a flow of sodium ions into the cell, and potassium ions outflow from the cell. During normal, physiological activity, these membrane currents are compensated by sodium-potassium pumps, which restore original ionic balance. However, when action potentials are fired at a high rate, sodium accumulates inside cells and potassium accumulates in the space around neurons. Elevated extracellular potassium increases neurons' membrane potential leading to their increased excitability. Accordingly, the 'potassium accumulation hypothesis' was set forth by Fetzinger and Ranck (1970). It proposed that a rise in extracellular potassium increases excitability and neuronal firing that in turn promotes further potassium accumulation. Once such a self-reinforcing process starts off, it may result in hyperexcitability leading to the initiation and maintenance of a seizure. This hypothesis has been since rejected, as its predictions couldn't be experimentally verified due to limitations of experimental methods.

Recent experimental advances allowed Gentiletti and Suffczynski (Gentiletti et al., 2022) to develop a dynamical-mechanistic seizure model that led to reconsideration and expansion of the potassium hypothesis. This biophysically realistic computational model complemented mathematical equations describing neuronal firing (Hodgkin and Huxley, 1952) with physical laws of ion diffusion, osmosis, and accumulation. The model consists of 5 neurons (4 excitatory and 1 inhibitory) synaptically connected. All of the neurons are endowed with intracellular and extracellular space, in which the accumulation and movement of ions takes place. All of the cells are embedded in a common external environment representing the surrounding neural tissue and vasculature. Additionally, each neuron has a supporting glial cell that buffers excess potassium from its immediate surroundings. A number of physiological mechanisms have been included, such as passive and active membrane currents, ion pumps, and transporters as well as cell swelling due to osmotic imbalance.

Importantly, a seizure in the model, once initiated, follows spontaneous transitions through different dynamical states as seen in implanted electrode recordings during typical human focal seizures. The simulated seizure activity starts with low voltage fast oscillations (LVF), evolves into irregular activity during tonic phase, is followed by a regular bursting during clonic phase, terminates spontaneously, and enters a period of reduced excitability, resembling postictal EEG suppression. These changes are mediated by shifts in various ionic concentrations, including an increase in extracellular potassium. Different dynamical states arising during the simulated seizure are shown in Fig. 2.

This model accurately reproduces the electrographic seizure pattern of human seizures. Notably, it offers a dynamical-mechanistic explanation of seizure pathophysiology and also provides a hypothesis for a mechanism responsible for the seizure termination. As has been already mentioned, strong neuronal discharges during seizures lead to potassium accumulation in the space around neurons and sodium accumulation inside cells. These changes lead to increased activity of the sodium-potassium pumps, which work at a higher rate to restore ionic balance. The pump moves two potassium ions into the cell and three sodium ions out of the cell in each pump cycle. This process results in one positive ion being removed from the cell per

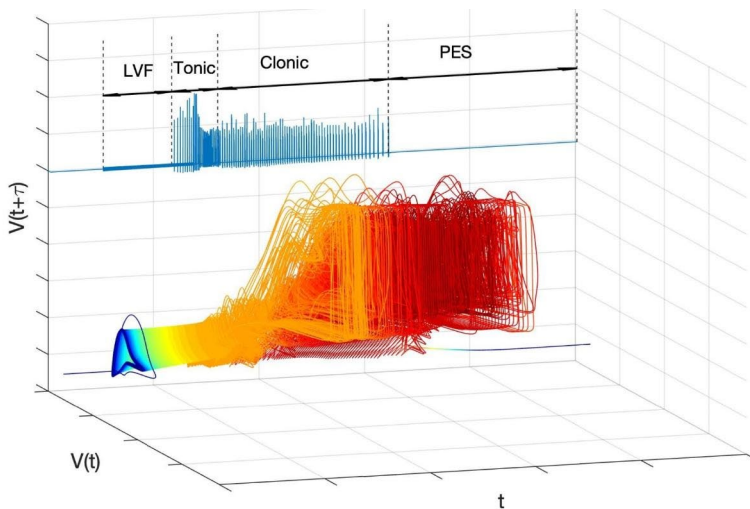


Fig. 2 Simulated seizure in the model. The simulated EEG signal is shown by a dark blue line with different seizure stages, i.e., LVF (low voltage fast), Tonic, Clonic, and PES (postictal EEG suppression) marked by the arrows. The colored 3D plot shows seizure evolution in a phase space, which represents all possible states of the system. V represents the sum of the membrane potential of all of the cells; τ represents delay time used for phase space reconstruction; line color corresponds to extracellular potassium concentration (blue - low, red - high). The figure shows that a rise in potassium concentration (marked by line color change from blue to red) is associated with progression of seizure activity through a series of transitions between different oscillatory states (i.e., limit cycles) in the system's phase space. After spontaneous seizure termination and during postictal EEG suppression state, extracellular potassium declines to its resting, pre-seizure value

cycle and leads to lowering of the cell's electrical potential. Increased pump rate creates appreciable negative shift in the cell membrane potential that ultimately prevents action potential firing and leads to seizure arrest. This hypothesis is corroborated by the observation that inhibition of the sodium-potassium pump in vitro prolonged seizure discharges in hippocampal slices (Haas and Jefferys, 1984).

This model illustrates that adding ionic dynamics to neuronal models allows one to simulate a sequence of transitions between different seizure stages, which match phases visible in EEG signals recorded with implanted electrodes during focal epileptic seizures. Importantly, initial and postictal seizure phases may be experienced and retrospectively described by the patients. The low amplitude fast oscillations phase may correspond to the early seizure stage at which awareness is preserved. At this stage a seizure is already present in the seizure focus and involves only local brain networks. The abnormal neural activity in a localized brain area may contribute to epileptic aura experiences. During an aura, scalp EEG recordings appear generally normal (Devinsky et al., 1989), which might lead to the notion that an epileptic aura precedes an attack. Nevertheless, in clinical practice, an aura is considered evidence of focal seizure onset and its symptoms depend on the affected brain region (Perven & So, 2015).

During the tonic and clonic stages of focal to bilateral tonic-clonic seizures, clinical manifestations such as body stiffening (tonic phase) and rhythmic jerking of muscles (clonic phase) may be observed by an eyewitness, but awareness is usually lost (Blumenfeld and Taylor, 2003). If awareness is partly preserved, metaphors used by the patients to describe the seizure state often refer to the brain being switched off (Kılınç et al., 2018), change in perception (light and darkness), natural phenomena (storm, waves), and struggle (e.g., a battle “at a higher mental level”) (Bronnec et al., 2023). The postictal phase occurring after seizure termination is characterized by a flattening of the EEG signal and slowing of brain rhythms (So and Blume, 2010). Postictal symptoms include changes in consciousness and disturbances in cognition, memory, motor function, and mood as well as headache and fatigue (Pottkämper et al., 2020). Models that realistically reproduce seizure activity but do not represent the postictal state (e.g., Liou et al., 2020) may be deemed unrealistic as they contradict first-person experience.

The model of focal seizure discussed above (Gentiletti et al., 2022) is a perfect example of dynamical-mechanistic explanation in neuroscience. On the one hand, the model is able to reproduce distinct phases of a seizure; on the other, it describes details about the underlying mechanisms. By taking into account ion dynamics, the model has increased explanatory power, as it is able to explain spontaneous transitions between states with only a few assumptions based on physical laws. Additionally, the states and their characteristics at the neuronal level have their manifestation at the subjective level. The initial low amplitude fast oscillations phase may correspond to the experience of auras, whereas the flattening of the EEG and the subsequent phase may correspond to postictal cognitive and emotional impairments. First-person information about seizure phases, including preictal and postictal phases, informed the search for responsible mechanisms. Furthermore, such dynamic first-person constraints allow one to limit the set of possible models by excluding those which do not account for seizure phases, as they present insufficient or incomplete explanations.

3 Discussion and conclusions

Research on migraine and epilepsy shows the gravity of first-person reports in formulating explanatory hypotheses and building models of underlying mechanisms. It is worth noting that first-person reports about the seizures as well as depictions of the visual aura should not be seen as mere subjective descriptions of target phenomena that are explanatorily irrelevant, but rather as descriptions providing direct constraints on explanatory models. These constraints come from dynamic properties of the target phenomena and have contributed considerably to our understanding of the underlying physiological mechanisms. Accurate reports of the speed of the peripheral spread of the aura pattern allowed for suggesting a link between this experience and an electrophysiological phenomenon called cortical spreading depression. This contribution is a clear example of dynamical constraints shaping an explanatory hypothesis. Subsequently it was suggested that consistently reported structural properties of migraine auras, i.e., scintillating zig-zag patterns spreading towards the periphery followed by an inner bean-shaped scotoma, may correspond to a passing wave of

hyperactivity followed by suppression of neuronal firing. Computational models of migraine auras used first-person reports to guide model structure (e.g., cortical orientation columns), select a range of model parameters (e.g., weak excitability regime excluding spiral waves), and to validate model predictions (increasing speed of aura spread in the visual field).

Descriptions of the first-person experiences of epileptic patients are an essential part of epilepsy diagnosis and contribute to the refinement of explanations of the phenomenon. The nature of sensations during the initial stage of a focal seizure, i.e., an aura, may provide valuable clinical information regarding the localization of the mechanism responsible for the seizure focus. Major seizure discharges often interrupt consciousness resulting in loss of aura symptoms. This limits to some extent subjective information that could provide insight into the mechanisms underlying a seizure. On the other hand, it has been argued (Gloor, 1986) that consciousness and its loss is difficult to define and that subjective reports in epileptology, especially in terms of impairment of consciousness, are not reliable. In his critical review, Gloor (1986) also pointed out that language disfunction (aphasia) or inability to remember a past event (amnesia) associated with a seizure may be often misinterpreted as “loss of consciousness.” Consequently, he recommended careful observation of and interaction with the patient during and after a seizure to distinguish between various impaired components of consciousness. Since then, there has been a growing interest in approaches to epilepsy that take into account patients’ experiences (Gloor, 1990; Johanson et al., 2008; Bronnec et al., 2023), including consciousness (Blumenfeld and Meador, 2014). E.g., Monaco et al. (2005) introduced the concept of epileptic qualia, which refer to subjective experiential states associated with seizures. They argue that epilepsy offers a privileged window into consciousness and that analysis of neural correlates of seizure-induced qualia can reveal valuable insights into neurobiological mechanisms of consciousness.

In terms of seizure models, analysis of first-person experience of an epileptic attack, i.e., an aura followed by impaired awareness which gradually returns during the postictal phase, provides important clues regarding seizure dynamics. Namely, it suggests that seizures follow a characteristic temporal pattern and their evolution is governed by processes with a time scale slower than fast electrical discharges, and thus we should look for the underlying mechanism on the lower biophysical level. It puts a constraint on realistic seizure models, such that they ought to include a mechanism (e.g., ion accumulation) which governs distinct seizure phases and spontaneous transitions between them. This allows one to exclude models which do not account for the dynamic pattern.

It should be noted that epileptic auras and migraine auras share similarities and differences. They are comparable in terms of both representing warning symptoms of impending episodes (seizure or headache), but their duration and phenomenology are different. Epileptic aura durations range from seconds to minutes with a mean value of about 60 s (Liu et al., 2017), while migraine auras typically last from 5 to 60 min (Headache Classification Committee of the International Headache Society, 2018). In migraine aura phenomenology, visual symptoms prevail (99% of the migraine auras) with less common sensory (31%), language (18%), and motor (6%) symptoms (Russell and Olesen, 1996). Epileptic auras have a much richer phenomenology that

includes sensory sensations but also emotional, autonomic, memory, motor, and psychic (e.g., dreamy state) disturbances (Perven & So, 2015). The rich phenomenology of migraine aura and epileptic seizures makes it impossible to create universal models of these phenomena. In our study, we restricted our analysis to cases where patient reports are consistent, i.e., classic visual aura and typical focal seizure. But it is likely that the same modeling principles can be used to extend the models to account for distinct first-person reports (Dahlem & Chronicle, 2004).

Despite the multiple advantages of the discussed models of migraine and epilepsy, they have certain limitations. One limitation, is the lack of a prodromal period which could be considered a separate phase. It was reported that in 87% of patients premonitory symptoms of migraine were present hours or even days before onset (Becker, 2013). Similarly in epilepsy, prodromal experiences were reported up to hours to days before the seizure (e.g., Petitmengin et al., 2007; Scaramelli et al., 2009) which corroborates intracranial EEG studies showing that in epileptic focus the number of bursts of high-voltage electrical EEG activity increases up to 10 h before a clinical seizure (Litt et al., 2001). First-person studies could shed a new light on this period preceding the seizure ictal phase and supplement existing models. Furthermore, in the case of epileptic auras progressing in a sequence, the subjective timing of sensations could provide constraints on models simulating spatial seizure spread. Such reports have proved very useful in the context of migraine.

Another limitation concerns the epileptic postictal phase as well as the postictal phase in migraine. The great majority of existing models do not include the period after the seizure in which cognitive impairments and altered EEG signals are still present. The model proposed by Gentiletti and Suffczynski (Gentiletti et al., 2022) partly fills this gap by reproducing an early postictal state of reduced neuronal excitability and by providing a plausible mechanistic explanation. In this state the sodium-potassium pump keeps working at an increased rate in order to restore ionic imbalance disturbed by seizure activity. Increased pump rate contributes to negative shift in the cells' membrane potential and limits their activity for about 100 s, in agreement with the duration of the postictal EEG suppression described in literature (Bauer et al., 2017). However, the postictal symptoms occurring after a seizure are far more complex phenomena that may extend to days or even weeks (Pottkämper et al., 2020). Clearly, more modeling work supported by first-person reports is needed to account for this state on both short and long time scales.

In our view, first-person constraints play a crucial role in finding explanations of multifaceted mental phenomena. That being said, we consider this process to be iterative; i.e., explanatory models informed by first-person constraints should be validated by the subjects, as was the case in the noted simulations of migraine aura (Dahlem & Chronicle, 2004). Subsequently, patients' evaluations may guide researchers to advance created models towards a better match between simulated behavior and patients' own experiences. This kind of iterative process may lead to further refinements of existing models, providing new insights into brain pathophysiology leading to disfunction. In this way, integration of first-person constraints with realistic models of neurological disorders facilitates progress in understanding the disfunction that may ultimately lead to improved therapeutic approaches.

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Declarations

Conflict of interest The authors declare that there is no conflict of interest.

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