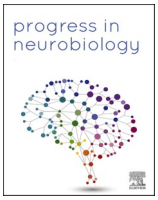
Progress in Neurobiology 226 (2023) 102465

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio



Perspective article

Cytoelectric coupling: Electric fields sculpt neural activity and "tune" the brain's infrastructure

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ARTICLE INFO

Keywords:
Memory engrams
Bioelectric field
Ephaptic coupling
Cytoskeleton
Mechanotransduction
Electrodiffusion

ABSTRACT

We propose and present converging evidence for the Cytoelectric Coupling Hypothesis: Electric fields generated by neurons are causal down to the level of the cytoskeleton. This could be achieved via electrodiffusion and mechanotransduction and exchanges between electrical, potential and chemical energy. Ephaptic coupling organizes neural activity, forming neural ensembles at the macroscale level. This information propagates to the neuron level, affecting spiking, and down to molecular level to stabilize the cytoskeleton, "tuning" it to process information more efficiently.

1. Electric fields, ephaptic coupling and LFPs

Ephaptic coupling describes direct influences of the brain's electric fields to individual neurons. It is different from the influence of one neuron to the other through synapses (Anastassiou et al., 2011). The activity of populations of neurons generates electric fields near each neuron and in extracellular space as currents flow in their dendrites, somata and axons. In turn, these electric fields influence the activity of individual neurons and their parts.

Detailed imaging of brain anatomy and structure at the microscopic level allows us to understand the currents and electric fields. Advances in super resolution imaging (Novak et al., 2013; Hochbaum et al., 2014), multiphoton brain imaging (Denk and Svoboda, 1997) and computational studies have revealed the contribution of different electric and geometric properties of individual neurons to the electric fields. Besides synaptic and intrinsic currents, the fields depend on microscopic processes like gap-junction activity and neuron-glia interactions. They also depend on large scale properties, like the inhomogeneity of extracellular tissue and the anatomy of grey matter (Kotnik et al., 1997; Gimsa and Wachner, 2001; Jeong et al., 2016; Jia et al., 2016). In brief, knowing the brain's anatomy, it is possible to understand properties of emerging electric fields.

Here, we aim to understand the reverse: How the fields influence individual neurons. Whether electric fields are an epiphenomenon of neural activity or not is unknown. Some studies suggest that fields are coupled to neural activity (Anastassiou et al., 2011; Anastassiou and Koch, 2015). They are thought to have very small amplitudes (about 0.5 mV) (Faber, 2010). Spikes from individual neurons are unlikely to affect firing of nearby neurons unless a large number of neurons are firing synchronously (Anastassiou and Koch, 2015; Fröhlich and McCormick, 2010). Also, isolating fields is difficult: ephaptic coupling co-occurs with electrochemical processes. But they can be studied using the theory of electrodiffusion from chemical physics. This examines how electric fields and concentration gradients change the flow of ions in electrolytes and conductors (Savtchenko et al., 2017).

Electric fields change the flow of currents and information transfer at the local circuit level. One way to study ephaptic coupling is via computational modelling. Models have described field effects on synapses and changes in the flow of neurotransmitters (Savtchenko et al., 2004). Electrodiffusion studies have used the Nernst Planck (NP) equations (Planck, 1890; Lu, 2013) to study ephaptic effects on local field potential (LFP) waveforms (Pods et al., 2013), the voltage distribution in spines (Cartailler et al., 2018) and membrane bound aqueous compartments known as Ranvier nodes (Lopreore et al., 2008). Input currents to bipolar neurons can feed back to membrane potentials (Gardner et al., 2015). Diffusive currents in extracellular space generate electric field gradients that alter the soma potential (Perram and Stiles, 2006; Sokalski and Lewenstam, 2001), an effect known as liquid

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https://doi.org/10.1016/j.pneurobio.2023.102465
Received 15 March 2023; Received in revised form 9 May 2023; Accepted 17 May 2023
Available online 18 May 2023

junction potential (Velumian et al., 1993).

Direct evidence of ephaptic coupling has been found in slices (Anastassiou and Koch, 2015; Chiang et al., 2019; Jefferys et al., 2012). Ephaptic coupling has been shown to change spike response latencies (Schmidt et al., 2021), increase spike synchronization, and affect synaptic interactions (Anastassiou and Koch, 2015; Traub et al., 1985). Eccles and Jaeger (1958) showed ephaptic effects on ion currents in synaptic cleft. Externally applied fields were found to regulate network dynamics (Deans et al., 2007). Endogenous fields can form a feedback loop that modulates the very activity that generates them (Fröhlich and McCormick, 2010). Changes in the average membrane potential of the population influenced synaptic currents and the ionic flux in the synapse, along with its plasticity and conductance (Vöröslakos et al., 2018; Kronberg et al., 2017; Ye and Steiger, 2015). Experimental evidence for ephaptic coupling is reviewed in (Anastassiou and Koch, 2015).

In vivo ephaptic effects are difficult to isolate. But evidence is consistent with ephaptic coupling in the intact, functioning brain. This is found in local field potentials (LFPs). LFPs capture spatially distributed activity over patches covering a few square millimetres of cortical surface (Buzsáki et al., 2012). Experiments have shown that LFP signals coordinate individual neuron spiking (Fröhlich and McCormick, 2010). They also contain oscillations thought to be produced by coordinated activity of groups of neurons. Application of external electric fields resulted in membrane potentials oscillating at the same frequency as the drive (Anastassiou et al., 2011). LFP oscillations during epilepsy affect structure and contribute to pathogenesis and maladaptive myelination (Knowles et al., 2022).

In brief, properties of LFPs oscillations are consistent with ephaptic effects. We will come back to this later. Before this, we discuss the neural sources (ensembles) that generate LFPs.

2. Mesoscale organization and neural ensembles

Ephaptic coupling to the LFP oscillations suggests large-scale organization of neural activity on the level of millions of neurons. Is mesoscale organization useful for brain function? The short answer is yes. The idea has a long history going back to the work of Semon (Semon et al., 2018), Hebb (Hebb, 1949) and Hopfield (Hopfield, 1982). Studies by us (Miller et al., 2018; Antzoulatos and Miller, 2016; Buschman et al., 2012; Kornblith et al., 2015; Pinotsis and Miller, 2020; Pinotsis et al., 2018, 2017a) and others (Fujisawa et al., 2008; Benchenane et al., 2010; Obien et al., 2014) exploiting multielectrode arrays support the conclusion that oscillations can form neural ensembles via synchronous activity at the LFP level. They seem to mediate the processing of incoming stimuli (Gray, 1999), attention (Desimone and Duncan, 1995; Fries, 2009), encoding of rules, memory encoding and recall (Buschman et al., 2012) or the binding of sensory inputs to representations (Singer and Gray, 1995).

This can be connected to the neuron level. With the advent of super resolution imaging (Tønnesen et al., 2014) and modern engram imaging techniques (Tonegawa et al., 2015a), including immediate early gene labelling (Reijmers et al., 2007) (IEG) and optogenetics (Deisseroth, 2011), neurons participating in ensembles can be identified and their activity can be recorded. Their dendrites, spines, organelles and other biophysical details can be mapped (Liu and Tao, 2022) along with their electrical activity. Transgenes allow the activity of a target neuron to be visualized during production of proteins needed to perform cognitive functions. Optogenetics allows for control of neural firing during various functions, including memory storage and recall.

LFPs seem to play a role in selecting neurons representing memories (neural ensembles). Using ensemble (engram) imaging, the authors of (Tonegawa et al., 2015b) suggested a dissociation between memory storage and recall that indicates a role for LFPs. Storage relies on long term potentiation (LTP) that includes a late phase of protein synthesis for consolidation aided by NMDA receptors. During learning, neural ensembles are formed. Neurons participating in ensembles have increased spine density and higher synaptic strength. Increased strength seems to be required only for memory recall, not storage. Under drug-induced amnesia, direct activation of ensemble neurons is sufficient to overcome impaired synaptic potentiation and leads to memory recall (Ryan et al., 2015).

Importantly, memory storage seems to depend on connectivity patterns (which neurons are connected to which), not how strong the connection is. Ephaptic coupling via LFPs could produce detailed connectivity patterns that allow specific memory content to be stored. This is also consistent with a wide variety of work showing that not only memory but cognition in general depends on the mesoscale organization of neural activity. Studies in monkey and rat IT (Gross et al., 1972), PFC (Miller and Cohen, 2001) and hippocampus (Opris et al., 2015) have found cognitive maps (Behrens et al., 2018) with multidimensional representations (Fusi et al., 2016). Increased mesoscale activity has also been recorded in vivo in humans with PET (Cabeza et al., 1997) and fMRI (Nolde et al., 1998) during memory tasks.

Neural oscillations are a natural way to organize activity on the mesoscale. Oscillations underlie many cognitive functions (Buzsáki et al., 2012; Kahana, 2006), including working memory (Miller et al., 2018; Pinotsis et al., 2018), attention (Fiebelkorn and Kastner, 2019; Buschman and Miller, 2007; Lakatos et al., 2008; Pinotsis et al., 2014; Fries et al., 2001; Gregoriou et al., 2009), and predictive coding (Bastos et al., 2020; Pinotsis et al., 2017b). Waves of LFP activity across cortex serve many functions (Muller et al., 2018) including regulating spike-timing dependent plasticity (Muller et al., 2016). Gamma LFP oscillations organize spiking activity to odours in the olfactory bulb (Kay et al., 2009). Rhythms in the cortex entrain to the rhythms of the outside world (Schroeder et al., 2010; Fries, 2015), which are exploited for focusing attention. In cortex, oscillations can bind together networks (Singer, 1993). They organize activity to produce computation (Lundqvist et al., 2023). In short, mesoscale organization of neural activity underlies many brain functions. Ephaptic coupling seems like a good way for the brain to produce this organization.

3. The cytoelectric coupling hypothesis

The brain infrastructure that connects neurons is collectively referred to as the cytoskeleton. It includes proteins, neurotransmitters, filaments, microtubules etc. Above, we saw how electric fields generated by neurons and other parts of the cytoskeleton carry information being used for behavior. Here, we propose the Cytoelectric Coupling Hypothesis: Electric fields help organize components of the cytoskeleton in order to "tune" it to process information efficiently.

Direct tests of this hypothesis would require linking LFP recordings to molecular level imaging. Still, many components of cytoskeleton themselves support information processing, learning and memory (Lee et al., 2000; Queenan et al., 2017; Nikolić, 2023). Microtubules form electric circuits that are stabilized during memory formation (Craddock et al., 2010, 2012). Cytoskeletal proteins regulate neuronal inputs and outputs and are remodelled with learning (Priel et al., 2010). Proteins at synapses enable spike timing dependent plasticity (STDP) (Caporale and Dan, 2008) along with long term potentiation and depression (Teyler and DiScenna, 1987). Proteins in the extracellular space also play a role in learning. They form the extracellular matrix (ECM). The ECM is a network of macromolecules that holds neurons together (Yue, 2014). Proteins anchor the neuron-ECM junctions and allow neurons to communicate (Herrmann et al., 2007). The ECM allows for cell adhesion and communication and maintains the links between them, despite protein changes within each neuron and extracellular space (Brockman, 2006; Tsien, 2013). Both synapses and ECM are built from scaffold proteins. These form sites to which neurotransmitter receptors are inserted. They are important for synaptic functions like the trafficking and clustering of glutamate receptors and adhesion molecules (Kim and Sheng, 2004). They hop in and out of the ECM and synapses similarly to the way that electrons move within semiconductors (Queenan et al.,

2017).

This flexibility endows the neurons and extracellular space with homeostatic stability. Stimulation perturbs the ECM via mechanical forces in neurons, other cells, and ECM proteins. Filaments and microtubules are subject to them—and use them to interact with other cytoskeleton structures through a process known as mechanotransduction (Iskratsch et al., 2014). A well-known example is sound perception in inner ear hair cells. The cytoskeleton is subject to similar forces generated by motor proteins (Sweeney and Holzbaur, 2018). At the same time, mechanosensitive proteins convert these forces back to chemical energy. An important example of an ECM protein is talin. It is known to underlie neuron adhesion and cytoskeleton stabilization (Goult et al., 2018). Besides ECM, ion channels in neurons also change as a result of mechanotransduction (Gu and Gu, 2014). In response to these perturbations, the cytoskeleton seeks to return to a stable configuration. Protein filaments and microtubules in the ECM are only a few nm long. But homeostasis requires organization on a much larger scale, i.e. meso- and macroscale (Ingber, 2003).

One contributor to cytoskeleton organization is tensegrity (tensional integrity). Tensegrity enables mechanotransduction. It shows that multicomponent structures achieve organized stability via a pre-existing stress (some strings shorten, others lengthen to achieve isometric tension) rather than continuous deformation. It has been proposed as a principle for cytoskeleton self-organization and hierarchical integration (Ingber, 2003). This principle also endows the cytoskeleton with structural flexibility despite continuous protein changes and new stimuli. However, tensegrity is not directly linked to information processing and memory storage in the brain. It cannot, by itself, configure the cytoskeletal structure to support information processing and neural ensemble (engram) formation. In other words, structural flexibility is not sufficient to achieve cognitive flexibility. The latter depends on information processing.

Here, we propose Cytoelectric Coupling. Electric fields are the link between the information the brain is processing (Pinotsis and Miller, 2022) and a stable, organized cytoskeleton. The goal of homeostasis is efficient information processing and memory storage. It provides stability necessary for cognitive flexibility. Above, we showed that mesoscale electric fields and LFPs help form ensembles of memories being used, see also (Pinotsis and Miller, 2022, 2023). These ensembles can form, break apart and re-form on the fly to enable thoughts (Pinotsis et al., 2017a) and cognitive control (Puig et al., 2014; Buschman et al., 2011). This needs to happen fast, at the timescale of neuronal activity. Thus, it stands to reason that electric activity and fields could play a direct role by configuring and stabilizing cytoskeleton proteins. Importantly, the electrical fields carry information that the brain is processing, information that can organize the brain's infrastructure to support efficient storage and information processing needed for cognitive flexibility. Thus, Cytoelectric Coupling connects information at the meso- and macroscopic level down to the microscopic level of proteins that are the molecular basis of memory (Gallistel, 2017; Langille and Gallistel, 2020). Maybe even further. Electric fields have been linked to consciousness (Fingelkurts et al., 2012; John, 2005; McFadden, 2020; Pockett, 2000; McFadden, 2006). Penrose and Hameroff, following the pioneering work by Sherrington (Sherrington, 1951), suggested microtubules might be related to efficient information processing by exploiting quantum superposition (Hameroff, 1994; Hameroff and Penrose, 2014).

Above we discussed evidence for ephaptic coupling and the importance of LFPs and mesoscale organization of brain activity for cognition. Besides this, other support for Cytoelectric Coupling comes from results from developmental biology and known effects of electric fields on components of the ECM. Electric fields play a role in the development of multicellular organisms and invertebrates by regulating anatomy (Krüger and Bohrmann, 2015; Levin, 2021), allowing for limb and spinal cord regeneration (Durant et al., 2019; Beane et al., 2011) using electrical stimulation (Leppik et al., 2015; Murugan et al., 2022). They guide morphogenesis (Adams et al., 2016) and can control tumorigenesis (Chernet and Levin, 2014). Fields also control neuronal migration (Bertucci et al., 2019) and sculpt neurodevelopment (Luhmann et al., 2018). Spatiotemporal patterns of transmembrane potentials during development regulate organogenesis of the brain itself (Pai et al., 2015). Cytoskeletal dynamics regulate bioelectric properties and mesoscale electric fields and result in an asymmetry of the left-right body axis (Vandenberg et al., 2013). Conversely, electric fields alter the cytoskeletal structure (Weiß and Bohrmann, 2019). All in all, there seems to be a strong influence of electric fields on the anatomy and structure of multicellular organisms.

On the level of primates, many components of the brain's ECM are affected by electric fields. This includes proteins like microtubules, actin and filaments, and scaffold proteins at synapses that allow information transmission and form the post synaptic density (PSD) (Fernández--Busnadiego et al., 2011). Microtubules form bundles that are parallel to axons and dendrites (Yamada et al., 1970). There are ions in mitochondria (Santo-Domingo and Demaurex, 2010). All these proteins are affected by electric fields. Microtubules align with external electric fields (Kim et al., 2007) and change dendrite configuration and neuronal polarization (Baas et al., 2016). They also interact with actin, which changes the microtubule shape and elongation (Dent and Gertler, 2003) and modulates their electric activity (del Rocío Cantero et al., 2020). Actin has also been linked to neurotransmitter release and changes in synaptic architecture (Doussau and Augustine, 2000). Other protein filaments in PSD can form and dissolve fast and interact with neurons by responding to mechanical stimuli (mechanosensing) (Gauthier and Roca-Cusachs, 2018). We saw above that electric signals result from stimuli (mechanotransduction). Thus, stimuli change the environment around proteins and the forces they are subjected to. Ion channel probabilities change in response to different mechanical stimuli, calcium ions that diffuse through the mitochondria membrane (Jasielec et al., 2016) which, in turn, alters the ECM electric field.

This could be exploited for clinical purposes (Widge and Miller, 2019). In Brain-Computer Interface (BCI) systems, neural read-outs are used to control motor prosthetics (Hochberg et al., 2006) and employ decoding algorithms trained on LFPs and spikes (Waldert et al., 2009). The application of external electric fields (e.g., in conjunction with behavioral training) could move the cytoskeleton into stable states that support normal cognitive function. Transcranial direct current stimulation (tDCS) has been shown to affect memory storage and improve cognitive function in human subjects (Tedla et al., 2022; Widge et al., 2019). In-vitro slice experiments using tDCS have shown that entrainment, even only 5 mV (Bikson et al., 2004), affected speed of spike propagation (Chakraborty et al., 2018), the size of excitatory postsynaptic potentials (Rahman et al., 2013), and contributed to long term potentiation (Kronberg et al., 2017). New technology allows modulation on the scale of LFPs using an implantable device. Using an analogue of separated interface nerve electrode (Ackermann et al., 2011) in conjunction with the implantable freeform stimulator, it can deliver undulating and electric fields (Aplin and Fridman, 2019). Closed-loop electrical stimulation can be used to modulate endogenous oscillatory power, rather than impose outside rhythms on the brain (Widge et al., 2018). It has been shown to alter reward guided learning in the orbitofrontal cortex (Knudsen and Wallis, 2020) of animals. Closed-loop electrical stimulation has also been used to improve cognitive function in human surgical patients (Widge et al., 2019).

In sum, ECM proteins, neurons and other cells in cytoskeleton generate heterogeneous electric fields that feed back to them. To achieve homeostasis, different cytoskeleton parts should work synergistically. This includes exchanges between electrical, potential and chemical energy as a result of electrodiffusion and mechanotransduction. Electric fields can organize neural activity to form neural ensembles (engrams) used for memory and cognition. This information transmitted to the molecular level via electric fields can "tune" the cytoskeleton for efficiency, stability and enable cognitive flexibility.

Declaration of Competing Interest

The authors declare no competing interests.

Data availability

No data was used for the research described in the article.

Acknowledgements

This work is supported by UKRI ES/T01279X/1, Office of Naval Research N00014-22-1-2453, The JPB Foundation and The Picower Institute for Learning and Memory. The authors are grateful to the anonymous reviewers for providing useful comments and references.

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