16. Basal ganglia network dysfunctions and deep brain stimulation

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Abstract. Deep brain stimulation (DBS) is an effective treatment for motor symptoms of Parkinson's Disease and for a long list of other motor and non-motor disorders. The recent advent of adaptive deep brain stimulation (aDBS), in which local field potential signals are continuously recorded to decode the patient state and modulate the stimulation accordingly, improved the effectiveness of this therapy and allowed to continuously monitor basal ganglia dynamics in a variety of conditions. With standard DBS we had isolated pictures of pathological subcortical dynamics, now we have a live streaming. In this chapter we briefly summarize some results of the observations allowed by novel devices, and then we outline three lines of research going beyond the relationship between neural activity and behavior. The first one is integrating all the new results in computational models, to join the dots of diverse experimental observations and provide a unified framework. The second one is exploiting deep learning tools to improve the aDBS approach and design a stimulation algorithm that follows the evolution of the patients' condition over arbitrarily long periods of time. The third one is including in the picture of DBS tuning the genotype of the patients to move toward a really personalized stimulation.

Key words: Basal ganglia, Deep Brain Stimulation, adaptive Deep Brain Stimulation, Parkinson's disease, Computational neuroscience, Deep Learning, Genetics.

1. THE ROAD WE ARE TRAVELING

In the 2010's, after two decades of clinical use, Deep Brain Stimulation underwent a technological phase transition [1]. There were advancements in adaptive and on-demand stimulation, electrode design, stimulation paradigms, and sensing devices. The clinical implications of these advancements have been described in detail in the chapter "Deep Brain Stimulation for Locomotor Network Dysfunctions in Parkinson's Disease". However, the full extent of the possibilities open by these advancements has not been explored yet. We finally have a telescope, but we are still using it to look for islands at the horizon, rather than establishing our course looking at the stars.

The interplay between neurotechnologies and neurology is the key to most of the recent advancements in neuroengineering. Neurotechnologies improved the ability to

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diagnose and treat neural disorders, while enabling a deeper understanding of pathological and healthy dynamics of the implanted areas through stimulation and recordings [2]. In particular, DBS provided rich datasets on neural dysfunctions in the basal ganglia structures implanted such as the Subthalamic Nucleus (STN) [3]. Interestingly, while current algorithms of aDBS rely on exploiting the power of beta band [12 30] Hz oscillations in the STN as a marker of pathological dynamics [4], that very same range came under scrutiny and we found that, functionally, peak frequency shifts might be more efficient markers than power modulation [5], for instance relatively to gait initiation [6]. Even more relevant, high beta range (>20 Hz) and low beta range (<20 Hz) have been found to have distinct functional roles, both in reach and grasp [7] and speech tasks [8]: in both cases the low frequency beta range carried information about the task onset while high frequency beta range carried information about movement quality (respectively upper limb coordination and speech intelligibility). Regarding cognitive functions, analyses of explorative microelectrode recodings (MER) revealed that Parkinson's Disease (PD) patients with impulse control disorders (ICD), in drugs off condition, actually displayed less pronounced beta power than those without ICD [9], in particular in the ventral region of the STN [10] known to be functionally connected to the prefrontal cortex [11]. This suggests that while ICD and non-ICD PD patients display similar dysfunctions in the motor-related dorsal STN, the ventral STN might be actually less impaired in ICD PD patients. In this case, ICD would be likely a result of the effect of dopaminergic drugs acting on a non-pathological circuit.

The need to improve DBS localization, the associated volume of tissue activated, and to understand how these factor affect the reverberation of the stimulation effects on different areas of the cortex, led to the development of several localization toolboxes [12] and eventually to a series of studies in connectomic DBS [13]. Recent studies actually exploited the rich dataset provided by connectomic DBS across different movement disorders to draw an exhaustive atlas of basal ganglia connectivity [14]. In general, basal ganglia neuroscience, thanks to aDBS, stands now in the same position as genetics after the human genome was mapped, or as astronomy after Tycho Brahe's methodic observations of the stars: trying to understand what to do with this unprecedented amount of data, find patterns and schemes that can actually make the data meaningful and useful for translational applications.

Herein we briefly sketch three complementary approaches that could be followed to deal with experimental observations: the first one is to connect them and capture them in a complete computational model, the second one is to exploit them to develop explainable deep learning algorithms for clinical use, the third one is to account for their variability by correlating them to individual patients features, starting with their genetic profiles.

2. ROADS AHEAD: IN SILICO BASAL GANGLIA

The modeling of basal ganglia network evolved together with the amount of data available and also our perspective on the way DBS works, as a testament of the interplay between neuroengineering and basic neuroscience. Indeed, while in a first moment rate models were more than sufficient to capture the observed dynamics of the basal ganglia

[15], the field progressively moved toward detailed spiking network models [16]. In particular, when the beta oscillations acquired clinical prominence as biomarkers (as detailed above), computational studies investigated their origin and their relation with dopamine depletion. The two alternative hypothesis were that the pathological beta emerged, as a consequence of the dopamine depletion caused by PD, from the interplay between STN and the Globus Pallidus Pars externa (GPe) [17, 18] or from the interplay between the GPe and the striatum [19]. Interestingly, both hypothesis could display experimental evidences in support.

We recently developed an in-silico model reconciling the two hypotheses [20]. Briefly, we found that i) both the striatum-GPe loop (actually, the FSN-D2-GPe loop), and the STN-GPe loop display resonances in the beta loop, ii) when Dopamine depletion increases, the two loops synchronize leading to a strong increase in beta power.

While the work presented in [20] shed light on the endogenous beta oscillations, it did not take into account the interplay of the whole cortico-basal-thalamic-cerebellar loop. In a following work we developed then a broader multi area hierarchical network [21] in which the dynamics of basal ganglia [16] and cerebellum [22] were modeled with spiking neuron networks, while thalamus and cortex were modelled with mean field models [23]. Once the dynamics of beta oscillations in the broader network will be clarified, and possibly associated to movement dysfunctions, we could proceed to investigate in a more accurate way the effect of DBS parameters and aDBS algorithms in silico taking into account not only the well known local effects of the stimulation [24], but also the way they spread across functional circuits.

3. ROADS AHEAD: DEEP LEARNING AND ADBS

L. Wittgenstein, in his *Tractatus logico-philosophicus* [25] in 1922 argued that we do not really study language for its own sake, but because language reflects our thinking, i.e., the hidden patterns of our brain; and our thinking reflects the structure of the world. A century later, advances in science and technology have led to Natural Language Processing (NLP) and the development of Large Language Models (LLMs). Different systems implement different generative strategies, but we can summarise by saying that they all use contextual representations, or embeddings, to map words into a mathematical space. Words likely to appear together are positioned closely in this space; then a specific strategy is to generate text auto-regressively, i.e. the next word (or, more generally, token) in a sentence is chosen by calculating its probability on the basis of the immediately preceding words in the sequence.

Programming a DBS device that can adapt to the patient's needs in a closed-loop fashion requires a representation of these needs that is constantly updated in real time. To achieve this, a prediction of the long-term dynamics of this representation is required to close the loop. In aDBS, this representation is based on the beta power activity of the subthalamic nucleus (STN). Here we will discuss the possibility of using a *transformer-based framework* [26] to predict the daily STN beta power distribution. In other words, we are able to capture the hidden patterns of a patient's STN thanks to an architecture, the transformer, that today is at the core of the LLMs structure. Mapping brain evolution using the hidden properties of language is quite in line with the Wittgenstein's philosophy developed one hundred years ago.

3.1. The control system of aDBS

Adaptive DBS can be described as a system in which the system is perturbed, the system's output is then monitored and fed back into the controller to adjust the controlled input, allowing the system to dynamically respond to changes while maintaining the desired performance. In the current state of the aDBS workflow, the STN is the system, the STN LFPs are the system's output, and the aDBS device is the controller that works continuously in both directions by measuring the system's output and supplying stimulation current to the STN, which represents the controlled input [27]. The stimulation current, in the frame of [27], is linearly adapted according to the patient's STN beta power between two thresholds associated to minimal and maximal stimulation [28]. Crucially, to determine these two thresholds the expert needs to evaluate the LFP recordings based on specific device parameters (i.e., stimulation frequency and pulse width, two values for maximum stimulation current and two values for minimum stimulation current to address both hemispheres, and two thresholds for beta power) that are to be determined based on the patient's clinic [29]. While an efficient control of the stimulation in the *short-term* can be achieved through a linear control within the same set of device parameters, the *long-term* adaptation to the evolution of STN beta power activity requires non-linear analysis within and across multiple sets of device parameters.

3.2. Forecasting the long-term evolution of beta activity.

We collected extended data of chronic recording of a patient's STN beta activity, minute by minute, in adaptive mode [30]. Analyzing the patient's STN beta power activity over a long period of time, obtained from power oscillations retrieved within a patient-specific beta frequency band around the most prominent peak of the power spectrum [31], it is possible to see how the current effectively changes the beta power oscillations.

Specifically, for the *long-term evolution*, we examined the daily distributions of STN beta power activity (Fig. 1), characterized by strong temporal variability. Our aim is to

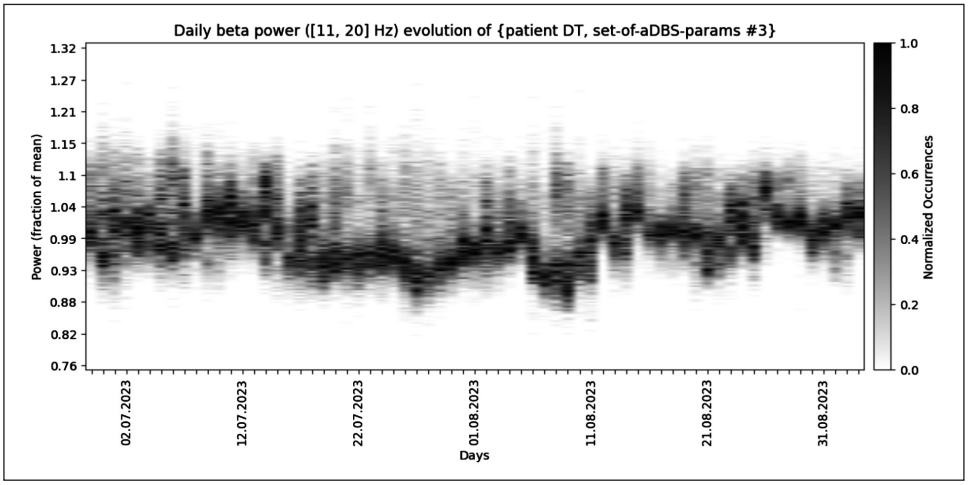

Fig. 1 - Daily distribution of power associated to patient-specific beta peak (reported in the title) over >60 days.

predict a certain daily distribution given the distributions of the previous days, dealing with a regression task. To capture the temporal patterns of the STN beta power evolution, generative stochastic models are of use, considering the complexity of the clinical data in the input, and the need to efficiently estimate both *one-step-ahead* and *multi-step-ahead* predictions. Indeed, several deep learning architectures have been developed to address time-series forecasting [32]. Among them we selected the aforementioned *Transformer* models, whose core is a new layer called *multi-head attention (MHA),* based on a general notion of sparsity of interactions within the sequence. The Transformer is an instance of the encoder-decoder architecture, though either the encoder or the decoder can be used individually in practice. Its strength is that scaling laws for Transformers are empirically better than for other models [33].

Considering a sequence of STN beta power distributions, each distribution would represent a token, for which we can perform the one-step-ahead and the multi-step-ahead prediction. This is where technical method and clinical need come together. To evaluate the results, we need to recall the clinical problem we are trying to solve: we need predictions that are good enough to determine a periodic tuning of the aDBS device parameters, which means that the predicted distributions must be evaluated on the basis of the previously mentioned parameters. Here we manage to fully understand how the definition of the control loop in the long-term treatment scenario has to be treated as a *personalized medicine task*, dealing with patients' own internal neurophysiological fluctuations, one by one. Crucially, drivers influencing DBS programming extend beyond beta fluctuations, preventing automatically programming of the device based solely on neural data. The *clinician-in-the-loop* approach is the winning strategy to make sense out of these predictions, enhancing the current long-term treatment strategy's efficacy for DBS-related brain disorders. However, our aim is the *autotuning strategy*. The real goal is to find the drivers for the DBS programming, and the way to do this is to make sense not only of neural data, but also of kinematic sensors and personal diaries maintained by patients themselves. We must translate neurophysiological results into clinical outcomes, and to do that we need to make sense of massive amounts of heterogeneous data. A *comprehensive, explainable deep learning framework* that can handle the complex, multimodal data we collect is our best shot at a deep understanding of the hidden patterns and visible outcomes implied in everyday life. Deep learning can take us beyond simple correlations and enable us to understand the causal mechanisms that can optimise DBS settings in real time, leading to more personalised and effective treatments for patients.

4. ROADS AHEAD: PATIENT SPECIFIC BASAL GANGLIA DYNAMICS

As we mentioned in the previous section, tuning DBS treatment based only on neural activity (e.g. beta level) is a limited strategy. A growing body of evidence suggests that the specific genetic profile could profoundly affect the efficacy of DBS [34]. Hereditary forms of movement disorders stem from pathogenic mutations in causative genes. Advances in next-generation sequencing (NGS) technologies and the improved availability and accuracy of genetic testing have linked many previously idiopathic cases to underlying genetic factors [35]. Currently, pathogenic variants in over 500 different genes are known to cause various movement disorders [36]. The clinical manifestations of these genetic

factors can exhibit distinct phenotypes in terms of age of onset, disease progression, body distribution of symptoms, morphological changes in various body parts, accompanying cognitive and psychiatric conditions, and response to pharmacological and deep brain stimulation treatments. Establishing a genetic diagnosis can guide the medical and surgical treatment of various movement disorders, potentially providing symptomatic relief and, in some cases, altering the disease course [36]. Therefore, understanding the pathological mechanisms of these disease-causing genes within the basal ganglia is crucial for treating drug-resistant forms of movement disorders with deep brain stimulation therapy.

4.1. Huntington's Disease

HD is an autosomal-dominant and progressive neurodegenerative disorder [37]. The disease originates from pathogenic CAG trinucleotide repetition in the first exon of the HTT gene which encodes huntingtin protein [38] and complete penetrance is observed for CAG repetition sizes of ≥ 42 [39]. Huntingtin protein is widely expressed in neural cells in the central nervous system [38], particularly in large striatal neurons in the basal ganglia and all corticostriatal neurons [40]. Altered neural activity due to the HTT gene mutations manifests differently within different basal ganglia structures. The single-unit activity of the globus pallidus nuclei is characterized by neural bursts [41], whereas subthalamic neurons exhibit weakly synchronized oscillations without significant bursting activity [42]. Regarding the efficacy of DBS, HD patients with predominant choreic symptoms are suggested as the best candidates for GPi-DBS treatment [43].

4.2. Dystonia

Over the past 10 years, an unprecedented increase has been observed in the number of genes associated with monogenic dystonias [44]. The hypothesis posits that dystonia results from abnormal sensorimotor integration within the basal ganglia thalamocortical circuit and is influenced by specific basal ganglia nuclei [45]. Consequently, translating the functional impacts of these pathogenic mutations into molecular, cellular, and brain circuitry changes is challenging for dystonia, despite the substantial progress made [46]. Research on genetic dystonia syndromes has investigated the biochemical mechanisms that are common across genes at various levels. Genes associated with DOPE-responsive dystonia syndromes have been demonstrated to play roles in dopamine synthesis and metabolism [47]. The identification of diverse genetic abnormalities converging on abnormal activation of the EIF2α pathway and disrupted cAMP metabolism in striatal neurons [46] emphasizes the significance of the convergence mechanism among dystonia genes at the molecular level [48]. The convergence paradigm is further observed at the cellular level by the functional convergence of various dystonia genes into specific neurons [49]. In addition to biological mechanisms, genetic dystonia syndromes can manifest distinct clinical phenotypes [50]. For instance, the majority of DYT-*GNAL* patients present cervical dystonia with an average onset age of 35.4 years [51]. The symptoms generally remain focal in the neck area or multifocal without significant cognitive and psychiatric issues [52]. Pallidal DBS is considered the most effective treatment for medically refractory dystonia [53]. Nevertheless, responses of genetic dystonia syndromes to GPi-DBS surgery exhibit considerable variability: mutations in *TOR1A*, *PANK2*, and *GNAL* genes show compelling evidence of benefiting from the procedure, whereas *THAP1* pathogenic

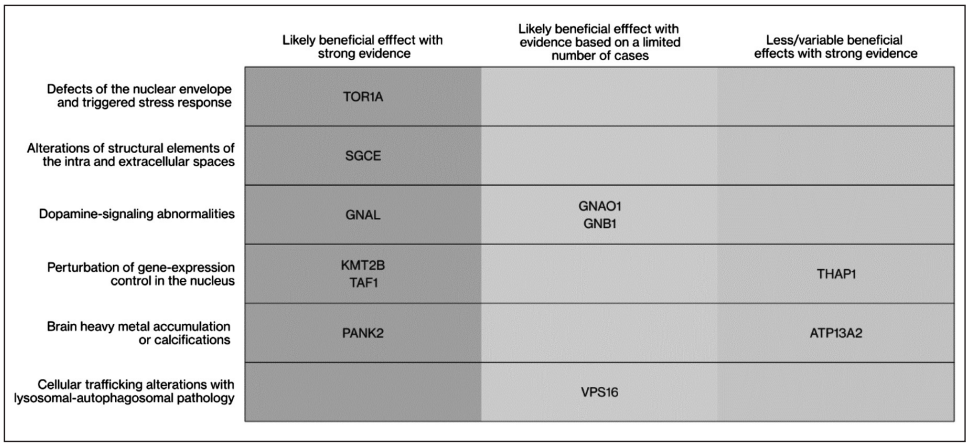

Fig. 2 - Major monogenic forms of dystonia are categorized based on their responses to deep brain stimulation [53], along with their respective biological pathway disruptions [56, 57].

mutations are less likely to benefit [53] (Fig. 2). Moreover, the literature is constrained by small cohort sizes or case reports, particularly for the rarer subtypes, and DBS may exert varying effects on distinct phenotypic manifestations of the same genetic factors [53]. Therefore, reports on the impact of GPi-DBS on novel mutations within the same gene [54] as well as long-term follow-up studies on rare mutations [55], are crucial for expanding our understanding and guiding patient selection for these surgical interventions.

4.3. Parkinson's Disease

Sporadic and monogenetic forms of PD represent a heterogeneous group of disorders with the pathophysiological shared end of a dopaminergic deficit [58]. The discovery of mutations in the gene that encodes alpha-synuclein, which is the major protein component of Lewy bodies [59], marked the beginning of understanding the genetic basis of PD [50]. Despite over 80 genes being potentially associated with monogenic forms of PD, the majority of these genes have been reported only once, frequently in isolated sporadic cases, and therefore require confirmation [60]. For the monogenic forms, several well-established genes exist, encompassing autosomal dominant (*SNCA*, *LRRK2*, and *VPS35*), autosomal recessive (*PRKN*, *PINK1*, *DJ1*), and X-linked inheritance (X-linked dystonia-parkinsonism), alongside atypical or complex parkinsonian phenotypes linked to mutations in *ATP13A2*, *DCTN1*, *DNAJC6*, *FBXO7*, *PLA2G6*, and *SYNJ1* genes [61].

Alpha-synuclein (aSyn) protein maintains neuronal membrane stability, affecting presynaptic signaling and membrane trafficking via vesicular transport [62]. The aSyn aggregates represent the main component of Lewy bodies (LB) which is considered a hallmark of PD [63]. Point mutations [64], duplications, and triplication [65] of *SNCA* gene cause PD [58]. Malfunction of the lysosomal-autophagy pathway can lead to the accumulation of dysfunctional proteins, contributing to the pathogenesis of several forms of PD, including those associated with genetic mutations in *SNCA*, *ATP13A2*, *VPS35*, *DNAJC6*, *SYNJ1*, *LRRK2*, and *RAB39B9* [66]. In addition, mutations in the *LRRK2* gene cause a toxic gain of function with increased kinase activity [67] and represent the most

common genetic cause of autosomal-dominant late-onset PD [61]. As can be seen, the genetic etiology of PD encompasses a wide range of molecular and biological pathways within neural cells. However, a recent study investigating subthalamic nucleus activity indicates that the genetic etiology of PD does alter neural functioning at the network level among these genes in the STN [68].

A genetic diagnosis can have profound implications for PD patients, influencing both the projected disease progression and the effectiveness of therapeutic interventions. Regarding levodopa-responsiveness, monogenetic forms of PD can be stratified into good response (i.e. *LRRK2*, *VPS35*, *PRKN*, etc.) and poor/variable response (i.e. *ATP13A2*, *PLA2G6, TAF1*, etc.) groups [61]. In cases where PD patients exhibit a poor response to levodopa treatment, they may be considered for subthalamic stimulation therapy. Similar to dystonia, genetic PD syndromes show varying responses to STN-DBS. Carriers of pathogenic mutations in genes such as *LRRK2*, *PRKN*, and *PINK1* benefit significantly from STN-DBS, whereas those with mutations in *PLA2G6* and *SYNJ1* show limited benefits [61]. Interestingly, carriers of different types of pathogenic variants (duplications vs missense mutations) in *SNCA* respond differently to subthalamic stimulation, highlighting the complexity of the pathogenesis.

In conclusion, the genetic landscape of movement disorders is intricate, and comprehending the effects of pathogenic mutations across causative genes on basal ganglia dysfunction at multiple anatomical scales presents a complex challenge that requires expertise from various disciplines. Our understanding of how these genes contribute to the pathomechanism of movement disorders is relatively recent. Therefore, further genetic, connectome, imaging, electrophysiological, and clinical studies are needed to elucidate the mechanisms underlying genotype-phenotype correlations.

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