abnormal brain dynamics in schizophrenia, and (iii) improve treatment outcomes by assessing the effectiveness of two antipsychotics, amisulpride and clozapine using synthetic and empirical functional MRI (fMRI) data.
VBTs are digital copies of patients' brains modeled as a network. The activity of each brain area is described by a neural mass model from [4], extended to include dopamine's concentration and effects through Michaelis-Menten kinetics and a dose-response curve. Using dynamical systems theory, we explore how dopamine interacts with GABA-ergic and glutamatergic synapses, with and without antipsychotic intervention. Each patient's brain is parcellated using T1-weighted MRI. Structural features, such as gray matter volume or receptor density, are mapped onto the neural mass for each brain region. These latter are connected based on diffusion-weighted MRI data, with connections being glutamatergic, GABA-ergic, or dopaminergic. Simulating whole-brain fMRI dynamics across varying parameter levels allows us to generate predictions about brain activity. We then use seed-based analysis of the blood oxygenation level-dependent (BOLD) signal from empirical fMRI data of our patients, collected before and after antipsychotic treatment, to analyze brain dynamics and identify key data features. To fine-tune the model, we apply Bayesian inference with a Markov chain Monte Carlo algorithm, integrating the model predictions with the empirical data features to infer clinically relevant values of the parameters. This approach allows us to evaluate how antipsychotics modify dopamine dynamics and, in turn, brain function.
We identified significant parameters related to glutamatergic synaptic density, dopamine connectivity weight, receptor density, and kinetics. Varying these parameters with and without the effect of medications in the VBT simulations reveals altered brain dynamics consistent with the literature. These include hypofrontality, impaired default mode network connectivity, and changes in low-frequency fluctuations. After training the model with empirical data, we expect it to predict individual fMRI responses to antipsychotics leveraging the inferred pharmacodynamic parameters.
This work wants to show how dynamical systems and Bayesian inference can be employed to create personalized virtual brain models, providing a valuable tool for understanding schizophrenia and advancing precision medicine.
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FOCUSED NEUROPROTECTION IN PARKINSON'S DISEASE: EFFECTS OF N-ACETYLCYSTEINE AND MRI-GUIDED ULTRASOUND NEUROMODULATION

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Parkinson's Disease (PD) is characterized by a progressive degeneration of dopaminergic neurons (DAn) in the brain, leading to severe symptomatology. Current treatments mainly address motor symptoms rather than preventing DAn damage or degeneration. Hence, there is an urgent need for novel strategies, particularly those that can combine neuroprotective and neuroregenerative approaches [1]. **Drug repurposing** is a powerful method for identifying new applications for approved drugs outside the scope of the original medical indication [2]. Under this concept, **N-acetylcysteine** (NAC), a potent antioxidant, has shown therapeutic abilities in modulating oxidative stress and preventing dopamine-induced cell death [3], suggesting potential disease-modifying actions in PD. Notably, recent data from our team revealed that NAC could restore dopamine transporter (DAT) levels in the dorsal striatum of PD animals [4].
Nonetheless, the precise mechanisms through which NAC provides disease-modifying properties still require clarification. Additionally, NAC's low bioavailability (9.1%) and limited accessibility to PD-affected brain areas represent a significant problem posed by the blood-brain barrier (BBB). As a method of overcoming such challenges, magnetic resonance imaging **(MRI)-guided focused ultrasound (FUS)** is currently being investigated, as it can induce transient openings in the BBB, enabling precise and brain-localized therapy delivery [5]. Therefore, using an established striatal 6-hydroxydopamine (6-OHDA) rat model of PD, we implemented two distinct therapeutic strategies: **1)** a 7-day consecutive NAC treatment regimen and **2)** a novel approach combining NAC treatment with MRI-guided FUS-BBB transient openings. This dual methodology allowed us to directly compare the efficacy of these treatments in mitigating PD pathology.
After 6-OHDA PD model validation, **as a first approach**, NAC was administered once a day for seven consecutive days (oral gavage, 12000 mg/kg [3]). One and four weeks after treatment, motor and non-motor behaviour, basal ganglia circuit functionality, and microglia responses were addressed to evaluate the therapeutic relevance of NAC. **As a second approach**, leveraging the same 6-OHDA model, NAC was injected intravenously (2 weeks, 50mg/kg [3]), followed by MRI-guided FUS at the striatum level. Motor and non-motor functions were assessed. Moreover, structural, functional, and metabolite quantifications were evaluated using fMRI and MR spectroscopy protocols to observe changes in the rat brain. Statistical analyses were used to compare treatment outcomes, including t-tests, two-way ANOVA analysis, and mixed-design factorial ANOVA. Considering the first experiment, NAC monotherapy displayed intriguing results. Initial observations suggest that a 7-day treatment with NAC may not effectively modulate PD motor and non-motor symptomatology, as anticipated. Notwithstanding, at the histological and molecular level, NAC produced neurorescue effects in specific midbrain circuits, significantly affecting regions such as substantia nigra, ventral striatum, olfactory tubercle, and striatum-like amygdala nuclei ($p<0.0001$). Modulation of glutamatergic projections on the striatum, thalamus, and subthalamic nucleus was also observed ($p<0.05$). Regarding MRI-guided FUS procedures, NAC biodistribution was enhanced, allowing a brain-specific delivery with alterations of behaviour symptomatology ($p<0.05$) and insights into multiple structural, functional, and metabolic changes.
These findings highlight a potential milestone for NAC's therapeutic application in PD. Understanding its complex interaction with PD's mechanisms could inform future therapeutic strategies focused on disease modification and neuron repair.
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