The Future of Personalized Brain Stimulation for the Treatment of Neuropsychiatric Disorders

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Abstract

Over a billion individuals worldwide suffer from neuropsychiatric disorders, many of which are resistant to traditional medications and therapy. Both invasive and non-invasive electrical stimulation have emerged as promising treatment options in recent years since they have been shown to attenuate neuropsychiatric symptoms by modulating the underlying abnormal brain network activity. However, neurological disorders manifest differently across individuals and the way brain activity and patient symptoms respond to stimulation is highly individualized. In addition, brain activity is not constant over an individual's lifetime. Changes due to development, aging, and the progression of chronic conditions need to be taken into account. All of this reveals the need for personalized treatments that can adapt to brain activity dynamics.

Research into the use of personalized brain stimulation to treat neuropsychiatric disorders has already proven promising. Recent studies have successfully applied personalized stimulation to treat depression, obsessive-compulsive disorder, and epilepsy using invasive techniques like deep brain stimulation (DBS) and stereo-EEG, as well as non-invasive techniques like transcranial alternating-current stimulation (tACS).

While these studies demonstrate success in using personalized brain stimulation to treat neuropsychiatric disorders, these approaches lack the ability to adapt stimulation to brain activity dynamics. In order to achieve this kind of adaptivity, there is a need for more comprehensive models of large-scale, multi-regional brain network dynamics. Recent work in this area has proven promising so far and shows that the field is moving in this direction. While this effort will aid in more personalized and adaptive treatment of neuropsychiatric disorders, it also brings with it ethical concerns on the use of AI and closed-loop systems.

This paper will first review how personalized brain stimulation has been successfully used to treat neuropsychiatric disorders in recent years and then look at the future of the field, which involves developing computational models of brain response dynamics. Lastly, the ethical concerns associated with using adaptive, closed-loop neurostimulation to treat neuropsychiatric disorders will be discussed.

Background

Globally, neurological disorders make up the leading cause of disability and are the second leading cause of death [3]. Of these, neuropsychiatric disorders have the highest global burden of disease, with depression taking the lead [10]. This is expected to increase as populations grow and age in the coming years. While medication and therapy-based treatment options currently exist, clearly more effective treatments are needed, especially for patients who are resistant to available forms of treatment.

Electrical stimulation of the brain has historically been used to treat neurological disorders and has become a promising treatment option for neuropsychiatric disorders in recent years with the emergence of deep brain stimulation (DBS) and transcranial stimulation methods [9]. Both invasive and non-invasive stimulation attenuate neuropsychiatric symptoms by modulating the activity of associated brain networks. Stimulation has traditionally been applied in an open-loop manner, meaning its parameters are set in advance and are not responsive to changes in symptoms [12]. Likewise, target sites are chosen based on established disorder pathways and previous work. While this approach has had limited success in early trials, clinical trials have failed to show significant attenuation of neuropsychiatric symptoms [8]. In a recent example, two randomized controlled studies using DBS to treat treatment-resistant depression have failed to significantly decrease depressive symptoms [6, 2]. This reflects a major limitation to this approach which is the lack of personalization. Neuropsychiatric disorders manifest uniquely which means the optimal target(s) for stimulation may vary across patients [4, 12]. The manner in which brain activity and patient symptoms respond to stimulation is also highly individualized [8, 12] which highlights the need for custom stimulation patterns.

However, while open-loop stimulation with personalized parameters and targets is a significant step forward and has shown promise in recent work, it is not enough [8]. Brain activity is not constant over an individual's lifetime which means that changes due to development, aging, and the progression of chronic conditions need to be taken into account when applying this treatment long-term. Thus, the future of personalized brain stimulation for the treatment of neuropsychiatric disorders is adaptive, closed-loop neuromodulation systems.

Current Use of Personalized Brain Stimulation to Treat Neuropsychiatric Disorders

Research into the use of personalized brain stimulation to treat neuropsychiatric disorders has already proven promising.

Depression

In a recent study by Scangos et al. [11], researchers showed that personalized electrocortical stimulation was able to improve symptoms of depression and anxiety in a patient with severe, treatment-resistant depression. In this ten-day, proof-of-concept study, they bilaterally implanted ten stereo-EEG electrodes across the orbitofrontal cortex, amygdala, ventral capsule, ventral striatum, subgenual cingulate, and hippocampus (six regions implicated in depression) in order to observe the relationships between target selection, stimulation parameters, and the patient's clinical response (Figure 1).

The researchers began by systematically assessing the patient's clinical response to a set of focal stimulations applied to different targets for 90-second intervals. They then tested the stimulation paradigms that resulted in positive responses for 3-min periods. Three paradigms reliably improved the patient's symptoms and interestingly, targeted different dimensions of depression. When each of these stimulation paradigms were applied for 10-minute intervals in a test of prolonged stimulation, the researchers observed that the patient's response and stimulation preferences were dependent on her current state and these responses could be reliably reproduced if the context and state were matched. For example, whenever the patient was in an aroused state, stimulation to the orbitofrontal cortex resulted in a positive and calming effect. However, when the patient was in a low-arousal state, the patient became drowsy and reported a worse mood.

These findings suggest that different stimulation targets are mapped to certain clinical effects while being influenced by the patient's unique symptom profile. The results of this study not only highlight the importance of personalizing treatment, but also motivate the development of a closed-loop approach in which the patient's internal state drives the delivery of stimulation, tailoring treatment to the patient's brain dynamics and applying it only as needed.

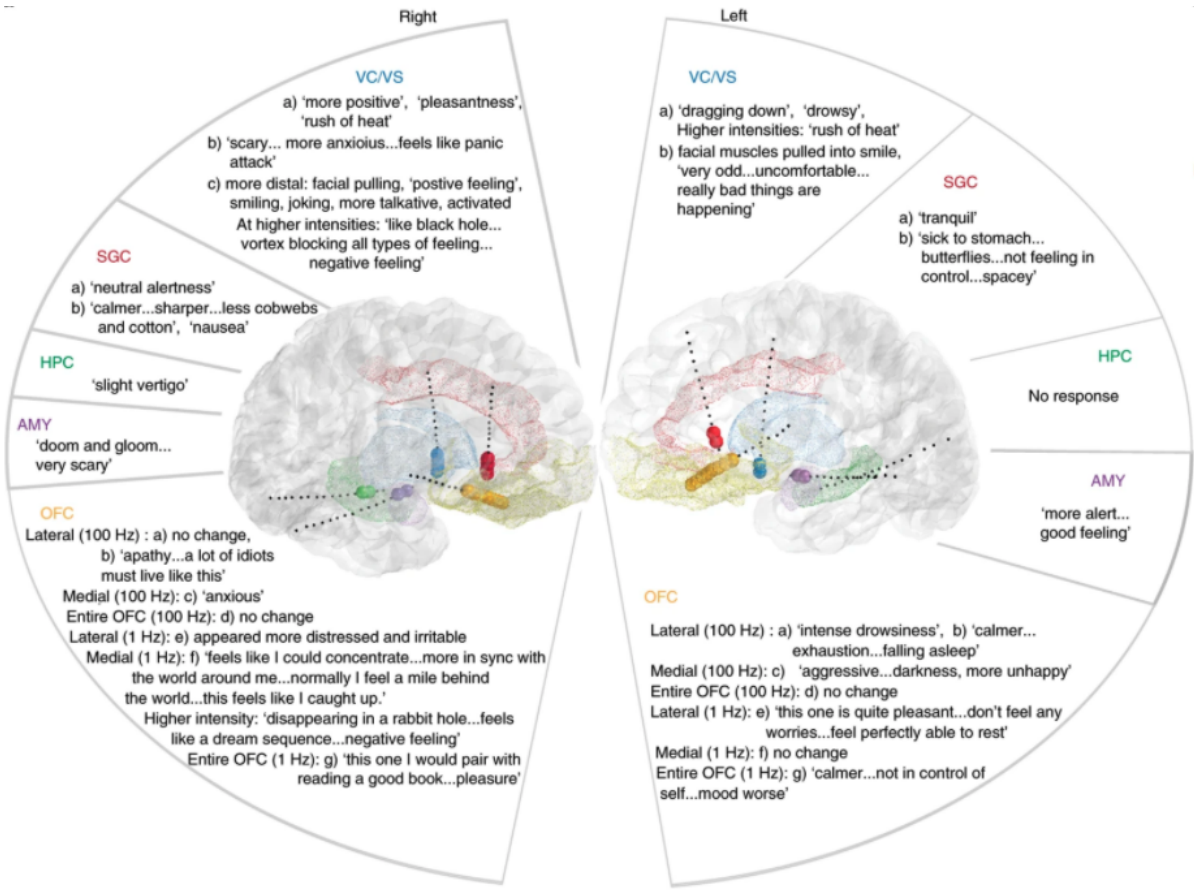

Figure 1. Display of the relationships between stimulation targets and parameters, and the patient's clinical responses in Scangos et al. [11]

Obsessive-Compulsive Disorder (OCD)

In Grover et al. [5], researchers demonstrated that personalized, non-invasive cortical stimulation was able to reduce symptoms of obsessive-compulsive disorder (OCD) in a group of 128 non-clinical study participants. The researchers based their experiments on the theory that obsessive-compulsive behavior stems from abnormal beta-gamma oscillations between the medial orbitofrontal cortex and the ventral striatum which abnormally associates a sense of reward with a preceding event (Figure 2).

In the first part of the study which involved 60 participants, researchers used scalp EEGs to create personalized maps of each participant's reward-related beta-gamma frequency peak across the medial orbitofrontal cortex. These maps were then used to direct non-invasive stimulation using transcranial alternating-current stimulation (tACS) which resulted in a significant reduction in abnormal oscillations and the associated reward-learning.

In the second part of the study which involved the remaining 68 participants, researchers examined the effects of applying personalized cortical stimulation over the course of five days (specifically, for 30 mins each day). They again observed a significant decrease in the severity of OCD-related symptoms. Interestingly, this reduction in symptoms lasted for three months, indicating evidence of neuroplasticity. These findings demonstrate the effectiveness of personalized treatment in modulating brain networks associated with OCD. Further benefit may be achieved by using a closed-loop system to monitor changes in neuroplasticity over the course of long-term treatment and re-apply stimulation at optimal time points to maintain the reduction in symptoms.

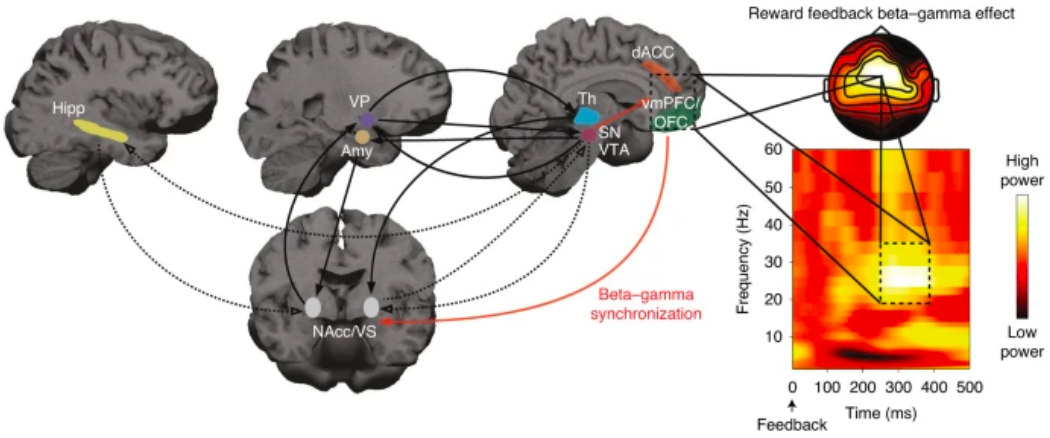

Figure 2. Anatomical and functional depictions of the reward feedback beta-gamma effect used as the ground-truth cause of obsessive-compulsive behavior in Grover et al. [5]

Epilepsy

The use of personalized stimulation in treating epilepsy is much more advanced than what has been discussed so far. The current state-of-the-art is the NeuroPace RNS System, a closed-loop stimulation device that is the first to be approved by the FDA for drug-resistant epilepsy (Figure 3). In clinical studies, it has shown a median reduction in seizure frequency of 53% after two years, with a 72% decrease in frequency at six years [14]. The device consists of an onboard processor with four recording channels and two bi-directional leads which are able to both record and stimulate. It is also capable of capturing and storing neural data for offline analysis.

While closed-loop stimulation methods are inherently personalized, setting the parameters for detection and stimulation in a closed-loop device determines the level of personalization. For

example, if a standard threshold for detecting abnormal activity is used, regardless of patient response, then this would represent a low level of personalization. Otherwise, if the detection and stimulation parameters are tuned to optimize patient clinical response, this would demonstrate a high level of personalization. Sisterson et al. [14] proposed a method for optimally fine-tuning these parameter settings in the RNS system using machine learning and brute-force combinatorics on the neural data collected by the device. According to the authors, detection and stimulation parameters for the RNS system are currently adjusted based on guidance from NeuroPace (the device manufacturer), data from the clinical trials, and anecdotal experience. Therefore the current use of the device represents a low level of personalization. Since the detection and stimulation parameters on the device are numerous with complex combinations, they can be difficult to tune, which is why the authors suggest using a bottom-up, informatics-based approach for increased personalization. To facilitate this, the authors created a platform called BRAINStim which takes in hardware and ECoG data from the device and performs spectral and statistical analysis using machine learning algorithms. This analysis can then be used to develop an algorithm which can optimize the RNS detection and stimulation parameters and reduce seizure frequency more efficiently.

The success of the RNS system already demonstrates the benefit of using personalized stimulation to treat epilepsy. However, the approach proposed by the authors in this paper reflects the direction the field is moving in, where advanced modeling techniques are becoming necessary to reach the next step of adaptive neuromodulation.

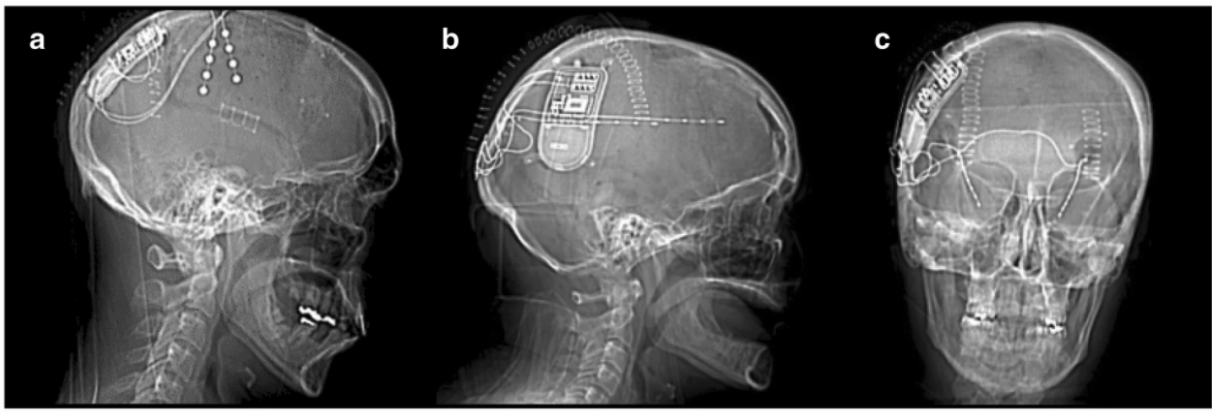

Figure 3. CT scans of three patients after implantation with RNS System [14]

The Path to Adaptive Closed-loop Neuromodulation: Developing Computational Models of Brain Response Dynamics

Because brain activity is not constant over time, stimulation needs to be adaptive in order to be truly personalized. In adaptive, closed-loop systems, the stimulation pattern needs to change in real time and respond to activity from multiple regions. Computational models of brain activity can provide the means to predict how stimulation affects brain dynamics of large-scale multi-regional brain networks, which makes them essential to developing such systems. These models can also be used to better understand the interactions between electrical stimulation and neural circuits since they can be utilized as a virtual experimental platform, and because their development requires a deep dive into these mechanics. According to Capogrosso et al. [1], this aforementioned lack of understanding is a major roadblock to actually applying neurostimulation treatment in clinical settings and receiving regulatory approval. Thus, the development of these comprehensive models is crucial on multiple levels.

One approach to creating a computational model of brain activity comes from Singh et al. [13]. In this paper, researchers noted that previous modeling attempts have either created mechanistic (biologically-based) models that are not able to characterize individual brain activity, or data-driven models that capture individual brain activity but are not mechanistic/biological. Their approach, Mesoscale Individualized Neurodynamic (MINDy) modeling, sought to bridge this gap. This proposed framework involves fitting dynamical models of brain networks for thousands of interacting regions to fMRI data on a per-subject basis. The result is a personalized model for each subject that can predict the individual's resting-state brain dynamics. Each dynamical model is similar to a neural mass model in that it describes brain activity dynamics at each distinct region. However, unlike in traditional neural mass modeling, the researchers used an fMRI timescale.

Each model contains three components: a weight matrix which contains causal pathways between neural populations; a parameterized sigmoidal transfer function which captures the relationship between a neural population's local activity and its output; and a diagonal decay matrix which describes how soon a population will return to baseline activity after excitation. In order to make the models robust and ensure validity, their approach utilized three features. First, they included a scalar parameter in the transfer function which was allowed to vary with each brain region and is fit for each subject. Then, they used a robust optimization technique during fitting, known as NADAM which gave their approach the speed of stochastic gradient descent without overfitting or underfitting the models. Finally, they split the large weight matrix into two smaller components: a sparse weight matrix which represents the communication between different connectivity hubs, and a low-dimensional weight matrix which represents the communication between connectivity hubs and their associated subnetworks. This change in the

weight matrix allowed the models to represent the interactions within and across brain networks more concisely and flexibly.

The researchers fit MINDy models on a per-subject basis on data extracted from resting state scans of 53 subjects (taken from the Human Connectome Project). After conducting analysis on the behavior of each model, they found that the models were able to capture individual connectivity, were reliable and valid, and showed anatomical variation. Thus, the models were able to predict individual functional brain dynamics. However, there are some major limitations to using this modeling framework. Most notably, because the dynamical models are fit to fMRI data, they carry the same limitations as fMRI (ex: low temporal resolution). Because of this, each model is naturally more sensitive to slower interactions that cover large spatial scales, making this approach less useful for developing adaptive, closed-loop neuromodulation systems. This work also focused on modeling resting-state dynamics, while closed-loop neuromodulation devices would need to respond to a variety of states since they would be used during daily activity.

In a more recent approach by Yang et al. [16], researchers developed input-output (I/O) models of brain dynamics that are able to predict response strength across multiple brain regions when fed temporally varying stimulation as input. To do this, they first gathered I/O data from experiments with two awake rhesus macaque monkeys. They created a new stimulation waveform that changes its amplitude and frequency randomly in time, which allowed the data to represent a wide range of possible stimulation patterns. In each experiment, researchers applied this new stimulation waveform to a target site (orbitofrontal cortex, anterior cingulate cortex, amygdala, or superior parietal lobule) and recorded the resulting local field potential (LFP) across multiple brain regions. From this data, they curated 16 I/O datasets, consisting of frequency-amplitude pairs as inputs and computed LFP power feature time series as outputs. The I/O models were constructed using a dynamic linear state-space model (LSSM) structure. The researchers then trained and evaluated I/O models across all 16 I/O datasets using machine learning techniques. The resulting models were able to accurately predict input-driven dynamics of target regions as well as the overall brain network dynamics in each monkey (Figure 4). When the researchers tested the I/O models on different days, over the course of seven months, the models were still able to accurately predict the brain network responses for both monkeys in 100% of experiments, demonstrating that the I/O models were robust to natural changes in brain state. These findings demonstrate that the I/O models developed by the researchers were comprehensive and capable of modeling large-scale, multi-regional brain network dynamics. This latest advancement is a promising step toward developing adaptive, closed-loop neuromodulation systems.

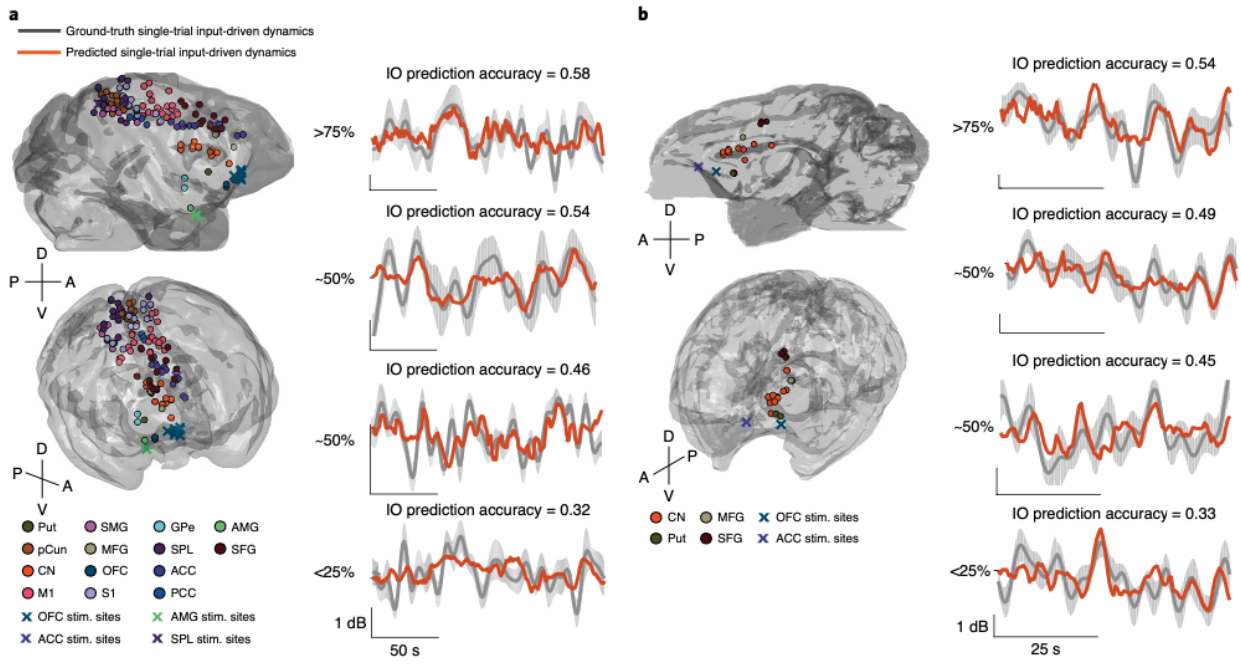

Figure 4. 3D-reconstructed monkey brains showing all the predictable channels. The graphs depict single-trial, input-driven dynamics across multiple brain regions, with the gray lines representing the ground-truth and the orange lines showing the model predictions. [16]

Ethics to Consider When Moving to Adaptive Closed-loop Neuromodulation Systems

While the development of personalized, adaptive closed-loop neuromodulation systems has great potential to transform the treatment of neuropsychiatric disorders, there are non-technical issues that will need to be addressed as the field advances and the technology is more widely used.

One of the main ethical concerns when applying any data-driven technology to the health care setting is data privacy and security. Large amounts of neural data are needed to develop the comprehensive models necessary for adaptive, closed-loop systems. Even after the system has been created and patients are using the device, neural data will continue to be collected for monitoring by the patient and clinician. Thus, the data will need to be stored in a secure manner, with the patient's privacy protected. Applying cybersecurity methods to data collection and storage is crucial during the developmental stages of this technology and during its application going forward [7].

Another issue that must be addressed is the automatic nature of the device. Since the stimulation is meant to be applied automatically in response to changes in brain network activity (in real time), this abstraction can potentially take away patient autonomy over their own mind since there may be no opportunity for choice. In addition, because the technology is still quite new, the stimulation recommended by the device may be incorrect. Since the stimulation is automatically applied, there would be no opportunity for a clinician to approve the stimulation before deleterious effects are caused [7]. Going forward, there will be a need to include an error checking mechanism and provide opportunities for patients and clinicians to both monitor the activity of the device, and intervene when appropriate.

A final ethical issue to consider is the effect of these devices on a patient's personality and sense of identity [15]. While symptoms stemming from a neuropsychiatric disorder can have serious, negative effects on a patient's life, at the scale of brain networks how can we accurately delineate activity belonging to the disorder from activity integral to the patient's personality. More specifically, how much should these devices alter brain network activity, and how do we decide what the baseline for "normal" activity is -- given the main premise behind personalized, adaptive devices is inter-individual variation. Computational error (especially if left unchecked) may also cause serious, long-term changes to the patient's mind/personality. While these questions cannot be easily answered and come down to a matter of philosophy, it is important when developing this technology to allow regular monitoring and checks, to receive consistent feedback from the patient, and to provide the means for the patient to maintain their autonomy by including a level of subjective oversight.

Most importantly, as this technology continues to advance, solving these ethical concerns will need to be held to the same level of importance as developing the algorithms behind it.

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