Science AMA Series: Hi, I'm Warren Grill and we used computational evolution to design new patterns of deep brain stimulation to treat symptoms of Parkinson's disease. AMA!

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Abstract

Hi reddit! My name is Warren Grill and I've spent the past 15 years trying to understand how deep brain stimulation treats symptoms in persons with Parkinson's disease. This understanding will allow us to make the treatment better. A few years ago, we discovered that the effects of deep brain stimulation depend on the timing of the stimulation pulses. We then used a process based on the principles of evolution to design temporal patterns of stimulation that work better than traditional stimulation at a single high frequency. I've been trying to build on that discovery ever since. Our work recently earned a Javits Neuroscience Award from the National Institutes of Health, providing $4 million over the next seven years to fund my laboratory at Duke University. In our experimental work to test the theory that regularization of neural activity was required for deep brain stimulation (DBS) to relieve symptoms, we delivered different random patterns of DBS all at the same average high frequency. The results indeed showed that random patterns were not effective, and of importance to the current work, that the effects of DBS were dependent on the temporal pattern of stimulation. This inspired the idea of designing patterns of stimulation to be more effective and efficient. In one example, we developed a series of temporal patterns that were intended to act as probes for the potential mechanisms of DBS and found that specific patterns were more effective at relieving symptoms than conventional high frequency DBS. These patterns were also more effective at suppressing low frequency oscillatory neural activity. The current work demonstrates the design of patterns that are more efficient than conventional high frequency DBS. One critical aspect of our work is the novel paradigm that we developed to conduct studies during the surgical replacement of the implanted DBS pulse generator due to depleted batteries, as this enabled early translational studies in human subjects. A second key innovation was the design of an electronic system that enabled us to record very small amplitude brain signals in the presence of large artifacts generated by the application of DBS. I'll be back at 10:30 AM EST to answer your questions. AMA!

the WINNOWER

REDDIT

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WARREN_GRILL R/SCIENCE

Hi reddit!
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Hi Warren, and thank you for doing this AMA.

As I understand it, the premise for deep brain stimulation is that PD is a disease caused by the loss of dopamine producing cells in the brain. This lack of dopamine has second order effects on electrical discharge in cells within the subthalamic nucleus and the globus pallidus internus. The idea is that DBS can help to mitigate the abnormal firing of these cells by sending out electrical pulses.

With this in mind (and please correct me if I am wrong), I have two questions for you:

1. Under what conditions would DBS be preferable to conventional PD therapy: L-DOPA + anti-psychotic (i.e. Nuplazid)? It seems to me that the surgery must carry with it substantial risks (it is brain surgery after all). In trials of DBS, what fraction of patients see a benefit? What is the clinical meaningfulness of this benefit? And how does it weigh against the risks of the surgery and other

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treatment options?

2. The mechanism of DBS still seems pretty poorly defined. How exactly does constant frequency stimulation affect nearby brain cells?

Thanks!

SirT6

DBS is typically used after persons with PD are no longer deriving sufficient symptomatic benefit from their medications or when the use of medications is associated with significant dyskinesias. In most cases DBS is used in conjunction with medications, although, on average the dose is reduced by half. There are indeed risks of surgery including infection and bleeding in the brain, but at experienced centers these occur in fewer than 1% of cases. The relative benefit risk decision is a judgment best made by an individual patient, their family and their physician.

Yes, the mechanisms of DBS remain an open area of research. It is clear that DBS does stimulate the output from the neurons in the nucleus (eg, STN) where the electrode is implanted. This produces a regularized pattern of neuronal activity, which while different than normal brain activity, is clearly less deleterious than the parkinsonian neural activity that is there in the absence of DBS.

Could the results of this work also apply to the treatment of mental health conditions such as depression and bipolar disorder?

purpleintrepid

DBS is currently being studied clinically for treatment of treatment-resistant depression with promising results. The use of optimized patterns of stimulation in other applications of DBS is likely to result in increases in efficiency and efficacy, as we have shown in Parkinsons's disease, but we have not yet studied other disorders.

Please elaborate on "computational evolution". Do you mean what computer scientists refer to by the term of art "genetic algorithms"? What function do you use to evaluate the fitness of your evolved population? How do you generate new candidates in the population? If fitness is based on actual results with human subjects, what ethical concerns arise with testing your candidate solutions? Does an ethical requirement to discard poor candidates quickly tend to restrict you to a strict hill-climbing approach?

drsjsmith

Yes, computational evolution refers to the use of a genetic algorithm. This fitness function included a combination of the efficacy - predicted from the activity of model neurons in our model - and efficiency - defined as the average stimulation frequency. Thus there was no optimization done within the research participants.

Each new population of candidate solutions includes the best candidates from the prior generation, offspring created by single crossover with roulette wheel selection of the parents, including random mutations, a well as new random candidate solutions (immigrants).

Approximately 15 percent of people with Parkinson disease have a family history of this disorder. Has this small percentage been tested through your treatment and if so were there different results?

Holmes02

No, we have not segregated the participants in our studies by the genetic or other characteristics of their disease, as the relatively small number of participants, eight in this case, makes it hard to do such stratification.

Hi, surgical neurophysiologist here. I previously worked in DBS surgery guiding electrode implantation via CT targeting and live microelectrode recordings.

I read a paper- I believe the author's name was Park- which suggested that Parkinsonian symptoms may arise due to excessive neural synchrony in the basal ganglia, which made it difficult to initiate new movements by exiting a synchronous idling state. His idea was that DBS essentially desynchronized these neurons and lowered the threshold for initiating new movements. Just wondering whether you're familiar with such an idea, and what your thoughts are on it.

imVINCE

Yes, there are data of excessive synchronization and oscillation, especially in the beta band. Further, prior data show that both L-dopa and effective DBS reduce the elevated levels of beta-frequency oscillatory activity. We confirmed this is on current study, and found that, similarly, our optimized pattern of stimulation also suppressed beta-band activity.

I know there have been a lot of debates about the exact cause of Parkinson's disease. Does your research on using deep brain stimulation to treat patients shed any light on the most likely cause?

firedrops

No our results only impact the treatment of PD with DBS, and do not shed light on the potential causes of PD.

Can you explain your findings and what it means for ppl with the disease like im five years old? My mom has PD so im interested.

spartan1337

The important implication for people with PD, is that if they choose to have deep brain stimulation, then this innovation will make the batteries of their implantable stimulator last for ~ 10 years, while with current approaches they only last ~ 4 years. The surgery to replace the depleted battery is expensive and carries the risk of infection.

Can your work with DBS be applied to better treat other movement disorders such as cerebral palsy or dystonia?

wadss

DBS is currently being studied clinically for treatment of dystonia, as well as other movement disorders, with promising results. The use of optimized patterns of stimulation in other applications of DBS is likely to result in increases in efficiency and efficacy, as we have shown in Parkinsons's disease, but we have not yet studied other disorders.

What are the similarities between this treatment and the treatment for essential tremor?

Serenity-

The fundamental technologies are the same but the surgical targets - that is the location in the brain where stimulation is delivered - differ between ET and PD. In ET, the electrode is placed in the Vim nucleus of the thalamus, while in PD, the electrode is placed in the subthalamic nucleus (STN) or the internal segment of the globus pallidus (GPi).

Can you explain more what these waves/patterns are? Why does frequency matter?

ThirdWaveSutras

Previous data show that the pulse repetition frequency of DBS is critical to its effectiveness in relieving symptoms - low frequencies are ineffective or may increase symptoms and only frequencies greater than 100 pulse per second are effective at relieving symptoms. However, high frequencies also require a lot of electrical energy and the battery life of the implanted stimulator is limited to 3-5 years. Thus, we designed non-regular pattern that had a low average frequency (45 Hz) which will more than double the battery life while preserving the effectiveness in treating symptoms.

Hi Warren, my father has early onset Parkinson's Disease at 44, and was diagnosed a year and a half ago. He got worse quite quickly over a year period and has since plateaued on some decent medication, but it doesn't solve everything. So, we, of course, are very interested in the idea of deep brain stimulation as a way to manage the symptoms of the disease but I was informed through a few studies of what it is that it's a process to be performed sooner rather than later in the diseases progress which, as a daughter, made me worried - do you personally believe that the benefits of deep brain stimulation outweigh the costs and risks of the procedure? And also, I was wondering how do you feel the leaps in science will affect diseases such as Parkinson's Disease in the near future?

ateumi

For me personally, I do believe that the benefits outweigh the costs and risks of the procedure in well-selected patients. Whether to receive DBS is a decision to be made in consultation with your father's physician. There are ongoing studies of the potential benefits of earlier intervention - that is implanting DBS while patients are still deriving benefits from medication - but the outcomes of these studies are not yet known.

Evolutionary/genetic algorithms can be very effective at coming up with solutions people might not think of but they usually require a reasonably complete and accurate model of the system to ensure the results can translate into real life. I'd be interested to hear how complete you think the current computational models you're using are and how well the patterns evolved using this system performed in real testing. Do we have a good enough computational model of the neural structures involved and how the disease affects them, or is this an element that needs further research?

internetpillows

We employed a biophysically-based computational model of the effects of DBS of the STN on neural activity in the basal ganglia and cortex. Although the model reproduces a wide range of experimental data, and proved to be an effective tool for optimal design, it is clearly a crude approximation of the biology and would clearly benefit from further development. The optimized pattern that we designed using the model produced symptom relief that was comparable to that produced by conventional high

frequency DBS, but with only 1/4-1/3 the number of pulses.

What is the most rewarding part of your job?

ezzyrd

The opportunity to interact with and mentor students at all levels - undergraduate, graduate and post-doctoral - and then following their success when they leave Duke is the most rewarding part of my job.

Hi Warren, when you are doing DBS surgery, how do you know where to place the leads? are there abnormal patterns of electrical activity that you are able to detect or are you doing it solely off anatomy? Is this why patients are regularly awake?

yochana8

I am not a surgeon, I am a biomedical engineer, but I am familiar with the procedure. Preoperative planning using MRI is combed with stereotactic surgery to determine an initial target. Subsequently, microelectrode recording of neural activity is used to refine the target prior to placement of the stimulating electrode. Patients are typically awake during the procedure so that test stimulation can be delivered and its effects on symptoms and any potential side effects can be determined.

My great grandfather had PD, I've seen first hand the damage it can cause both to victims and to their families. As a musician, I'm terrified of getting it, myself. Thank you for the work you do and the hope you bring to those suffering from this disease.

My question is, is there hope for an actual cure, or do you believe that this is instead a long-term way to manage and live with the disease?

crimson_713

Currently, DBS is used only as a treatment for PD. There are no results indicating that it can be used to reverse or cure the disease.

There is some emerging evidence that the mechanism of DBS is actually not local to the stimulation site but rather due to antidromic propagation to M1. I've heard some suspicion in the community about the evidence in papers like Gradinaru et al. (2009) because of the way the optogenetics was used. Do you have an opinion about the likely location of the therapeutic action? Is there any way that you could use variations in the stimulation patterns your lab creates to try and determine the therapeutic location (rather than using the fitness functions you're currently using)? If you think it's cortical, do you see any hope for cortical implants that may be easier than deep implants?

BlueWreck

I think it is likely that DBS has important antidromic and orthodromic effects. I think that one result from Gradinaru that is suspect is the assertion that optogenetic stimulation of STN was ineffective, therefore the important symptom-relieving effects of DBS are mediated (only) by antidromic activation of the hyperdirect pathway. However, they used ChR2, which has a very limited bandwidth and cannot generate action potentials faithfully in response to high frequency (130 Hz) DBS (it can only follow up to ~ 40 Hz). Thus, optogenetic STN DBS was not producing STN stimulation at 130 Hz, as is required for the treatment of symptoms. It is not clear to me - maybe you have some ideas - about how to use

patterns to identify the relevant contributions of different neural elements. However, this might be accomplished with changes to the electrode geometry or stimulation waveform to produce element-selective stimulation. I think that there remains promise for cortical stimulation to treat PD and other movement disorders. The clinical results to date are mixed at best, but these were largely conducted non-systematically in the absence of understanding.

Hi! thanks for doing an AMA! My question is a bit... out there.

I read someplace that L-Dopa is used to help patience with Parkinson's.

There are some ADHD individuals who have damaged dopamine receptors due to prolonged use (15+ years) of drugs like adderall which oxidizes the synapse because the dopamine isn't removed by a vmat2 transporter. Some of these individuals are also seeing results from carefully administered/low-dose L-Dopa.

This seems like an off question, but if synapse damage or non-responsiveness is a similar issue in these two cases, do you believe that similar science could be used to help treat those whose dopamine receptors have been damaged? I'm not sure how much the scientific community contributes Dopamine interaction in the brain to the underlying cause of Parkinson's, so I apologize in advance if it's not a question you could even speculate on.

BloodyFreeze

Yes, L-dopa is used very successfully as the first line treatment for Parkinson's disease, and it is typically only after patients are no longer getting sufficient benefit or are experiencing significant side effects of L-dopa that DBS is used. In the case of PD, it is the neurons that make dopamine that die, rather than damage to the receptors, as you are describing.

My uncle was diagnosed two years ago and has been burdened by the fairly rapid onset of symptoms. Will this ever be an option for him, or is it far too early in trials? Is he able to volunteer for this or other PD studies?

mayaswellgiveup_vote

Deep brain stimulation is FDA-approved and available for the treatment of advanced PD. It is typically used in patients who are not getting benefits from their medications or are having too many side effects. I suggest that your uncle discuss this option with his neurologist.

[deleted]

[deleted]

Yes, computational evolution refers to the use of a genetic algorithm. This fitness function included a combination of the efficacy - predicted from the activity of model neurons in our model - and efficiency - defined as the average stimulation frequency. Thus there was no optimization done within the research participants. We typically run for 150-200 generations or until we see clear convergence. Each generation includes 20-25 organisms. Each new population of candidate solutions includes the best candidates from the prior generation, offspring created by single crossover with roulette wheel selection of the parents, including random mutations, a well as new random candidate solutions (immigrants). Convergence to a global minimum of course cannot be guaranteed, but when we repeat the process with new random initial patterns, we arrive at the same solution. For this particular study, we did not make an effort to localize the stimulating electrodes, but all participants were receiving

significant clinical benefit from their DBS, suggesting that the electrodes were positioned appropriately. It is likely that DBS is indeed activating fibers of passage, some of which might be involved in the mechanisms of symptoms reduction, as well as side effect generation.

I read a couple of years ago that deep brain stimulation was showing great promise in treating Alzheimer's, but I haven't seen anything since. Is this still being studied?

Heartofanother

Yes, studies of DBS to treat Alzheimer's disease are continuing. From the data so far, it appears that this can indeed be beneficial in properly selected patients, but further study is needed.

Could this treat other conditions under the Parkinson's "umbrella" such as early and severe forms of Dementia?

Ps. You're a rockstar.

cwittyprice

I am not aware of any data that indicate that DBS has beneficial effects on dementia. In most cases, persons with severe dementia are not considered good candidates for DBS, as there is a fear that the brain surgery may lead to further cognitive decline.

My father had Parkinson's. He passed away a few years ago. Thank you so much for dedicating your time to help people find relief.

I've never heard of DBS before and seems incredibly interesting. As you create patterns that are more efficient, are there any patterns you've noticed that could have a negative impact? Or areas to stay away from?

Meagasus

I am sorry for the loss of your father. Yes, we do identify patterns that could have a negative impact - that is make the symptoms worse. We are actually using these patterns to try to understand the relationship between the patterns of neural activity in the brain and the symptoms of PD, as we think this will give further insight into how to improve the therapy. I have an MD/PhD student here at Duke that is working on this right now!

Any relevance for tourettes

arutky

Yes, there are several centers that are implanting DBS as an experimental treatment for Tourettes Syndrome.

What are your thoughts on cannabis and Parkinson's, as displayed by this example? Is the endocannibinoid system something you study much or is it still mostly blocked from formal training?

godofallcows

I am not familiar with the data on cannabis as a treatment for PD.

Have you found any evidence to support the new theory that the CNS and immune systems are a lot more closely linked than anyone previously thought?

bitcheslovebutter

No our results only impact the treatment of PD with DBS, and do not shed light on the potential link with the immune system.

This looks promising! If Parkinson's disease and Schizophrenia are at opposite sides of the same spectrum, would it be possible to hope for a treatment via the same method for the latter?

projectgrey4specter

DBS is currently being studied clinically for treatment of a number of other diseases, but I am not aware of any studies in schizophrenia. The use of optimized patterns of stimulation in other applications of DBS is likely to result in increases in efficiency and efficacy, as we have shown in Parkinson's disease, but we have not yet studied other disorders.

Does DBS have any long term positive effects on the Parkinsonian brain, for example through BDNF-stimulation and/or plasticity in any form? Is it just the "desynchronization" of activity that's having an effect? Thanks for the AMA!

A_horse

There have been a couple of studies looking at whether there are any neuroprotective effects of DBS ... that is, might it slow the course of PD. However, thus far these studies have not provided support for this hypothesis. And, after 10 years of more or less continuous DBS, when the stimulator are turned off, the symptoms of the disease return.

What's the relationship between welders breathing manganese and Parkinson's disease?

rcrracer

I am aware of studies that show an elevated risk for PD in welders (and in agricultural workers), but I am not aware that the mechanism of this risk has been established.

Do we understand the effects of DBS on glial cells and Astrocytes? Thanks

TheDeakness

No, we know very little about the effects of DBS on glial cells or astrocytes and it is certainly possible that they play an important role in mediating the effects of DBS.

I'm unfamiliar with PD and DBS. So, can you explain what DBS is in a nutshell and how are DBS treatments conducted?

trollhunters123

DBS is a surgically-implanted brain pacemaker that is used to treat the symptoms of PD, typically after patients are no longer deriving sufficient benefit from their medications.

It sounds like computational evolution may have been a very natural choice for this work, but I'm curious whether you considered or tried other algorithms? What was the algorithm selection process like, if any? thanks!

miright

Computational evolution (genetic algorithm) is particularly well-suited to this problem where there is a highly non-linear relationship between input and output, the system cannot be described analytically, and the organisms (stimulation patterns) are binary strings.

Hi Warren, and thank you for doing this AMA.

Has your team ever worked on DBS for anything other than PD? Do you think the same type of treatment could by applied across other neural-based maladies, like severe RLS?

Darth_Draper

We have also worked on DBS for essential tremor, and DBS is very effective in that disease. DBS is being explored for other neurological diseases, but I am not familiar with any work in RLS.

What metric did you use to score your evolution algorithm?

arden13

The fitness function was a combination of therapeutic efficacy and efficiency. Efficacy was assessed using a proxy measure of neural activity in the computational model, which we showed previously was strongly correlated with symptoms. Efficiency was simply the average pulse rate of stimulation.

Hello! Does this treatment have the potential to treat/cure autism? In addition would this give more insight on how memories are stored?

Simpletactics

I am not aware of any basis to use DBS to treat autism. However, DBS is being explored as a treatment for Alzheimer's disease, and through this work is indeed providing insight into memory function. See the work by Andres Lozano at the University of Toronto.

No questions, but I want to thank you. My spouse has young onset Parkinsons (43 now, diagnosed 10 years ago), and has been considering DBS. It's likely going to be in her future.

Well, one question: What advice would you give us to ask the Dr. about, ahead of making the surgical decision? Meaning, what "gotchas" are out there that many patients/physicians might not consider or be aware of? What "heads up" could you perhaps provide to us? Thanks again!!!

FappDerpington

I suggest that in addition to talking to your physician, that you also talk to other patients who have had DBS to understand their experiences.

I saw a report recently that DBS via ultrasound is being tested with promising results. I'm interested in your perspective on these studies.

Parsleysage58

There are two potential applications of ultrasound in movement disorders. There are very promising studies of using high-intensity ultrasound to produce non-invasively ablative lesions in the brain, and these are effective in treating symptoms, especially in cases of tremor. Secondly, the feasibility of stimulating the nervous system with ultrasound has been demonstrated, but this is a very long way from a potential treatment or alternative to DBS.

Just wanted to say my dog, Warren G, is named after you. ;)

Cuda14

Lucky dog!

We are looking into dbs for my 8 year old daughter. She has althoid cerebral palsy with dystonia. Her brain damage was caused by high jaundice levels in her blood staining the basal ganglia. I am concerned her tone and mouments will make her extremely difficult to care for as she gets bigger. Do you have any experience or knowledge with this use for dbs? Thank you.

Ja58cK

There is now a growing experience using DBS in dystonia, and in well-selected patients that outcomes are quite good. This typically requires higher stimulation energy, so you may want to consider rechargeable implanted pulse generators to reduce the requirements for subsequent surgeries to replace the device.

Do you think that your research provides any insight into the functional role of oscillating activity in the brain? Does something go wrong in PD which makes it harder for the brain to sustain oscillating activity? Furthermore, why oscillations but not something else, perhaps something more irregular?

I know these are big questions and I don't expect you to answer them directly. Instead, I'm interested in whether you can draw any conclusions from your research towards answering them.

haffi112

There are data of excessive synchronization and oscillation, especially in the beta band, in the cortex and basal ganglia of persons with PD. Further, prior data show that both L-dopa and effective DBS reduce the elevated levels of beta-frequency oscillatory activity. We confirmed this is our current study, and found that, similarly, our optimized pattern of stimulation also suppressed beta-band activity.

Which parts of the brain does DBS target? Is the end result thalamic/cortical/basal ganglia inhibition or excitation?

Do we even understand why certain electromagnetic waves affect the human brain?

Why DBS, instead of transplantation? Reviews/work from Norway show(s) that transplantation has a similar story to DBS; amazing success stories, unintended side effects, varying outcomes.

Brundin and the VAI have, perhaps, the holy grail of PD treatment. If that pans out, why should we continue DBS research?

SextiusMaximus

In PD, the electrode is placed in the subthalamic nucleus (STN) or the internal segment of the globus pallidus (GPi). The effect is to stimulate both the afferent projections to (antidromic) and the efferent projections from (orthodromic) the stimulated nucleus. The effects of DBS are durable, with long-term studies for in excess of a decade, as well as adjustable through programming of the parameters and changes to medication. It is important to continue work on DBS to benefit patients now, and, as well, to extend to other diseases.

Have you heard about the success patients have had treating their Parkinson's with cannabis oil?

bishifterr

I am not familiar with the data on cannabis as a treatment for PD.

What is it like being a grill in computer science

maximumriskalways

I have the best job in the world! No boss, surrounded by young, creative and enthusiastic students, and I can work on any problem that interests me.

I saw the movie "The awakenings" a while back and they talked about the drug LDopa. I remember the issue was that not all drugs can pass the blood-brain barrier. My question is: how come drugs like opiates can enter the brain but not other drugs?

Cap_g

L-Dopa can indeed cross the blood brain barrier, and this is the reason that L-Dopa rather than dopamine is used to treat PD. The BBB is a barrier to diffusion of large molecules to protect the nervous system from potentially harmful substances. In the case of L-Dopa it actually crosses the BBB not by diffusion, but is "carried" across by a transporter molecule.

Have you tested the efficacy of treatment of Parkinson's with cannabis?

TXCentepede

I am not familiar with the data on cannabis as a treatment for PD.