Optogenetics: A quantum leap in neuroscience

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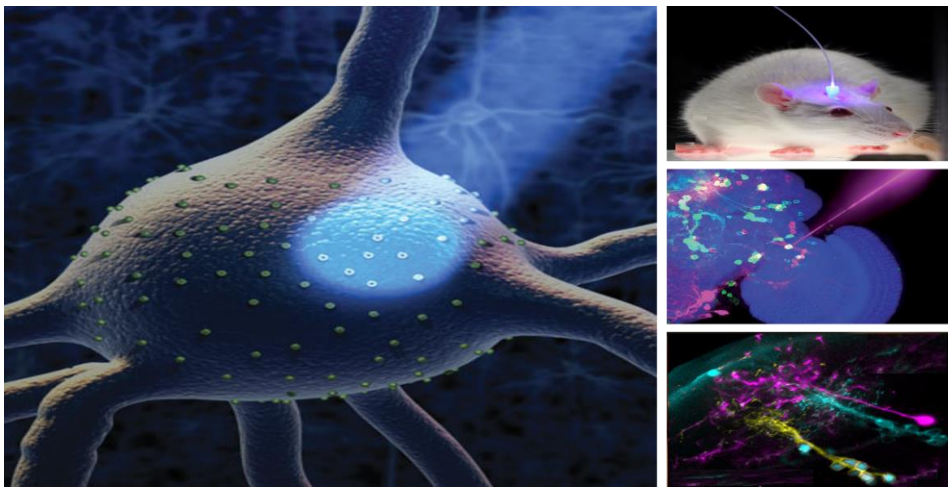
Optogenetics

From Theory to Neurological Applications



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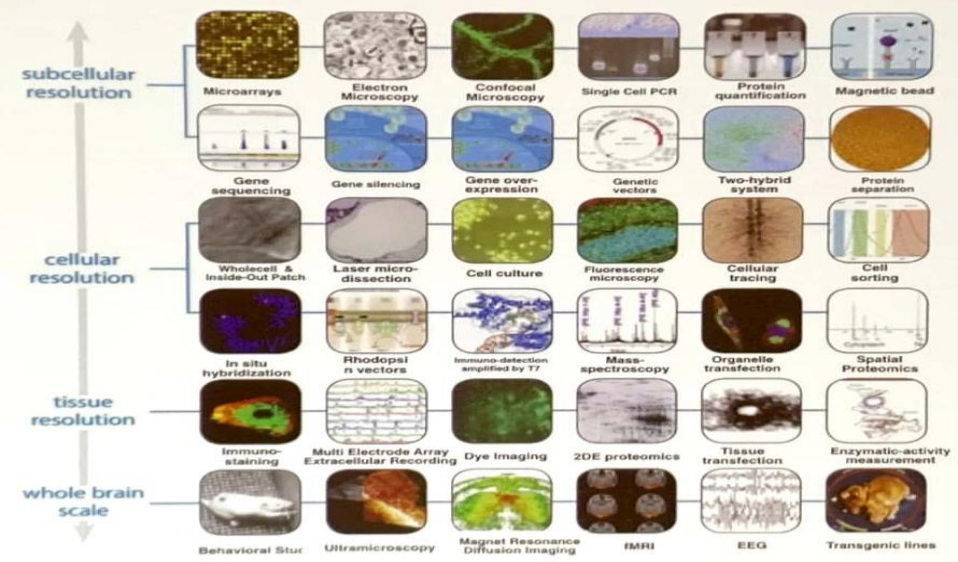
Neuroscience Challenges

◘ Background:

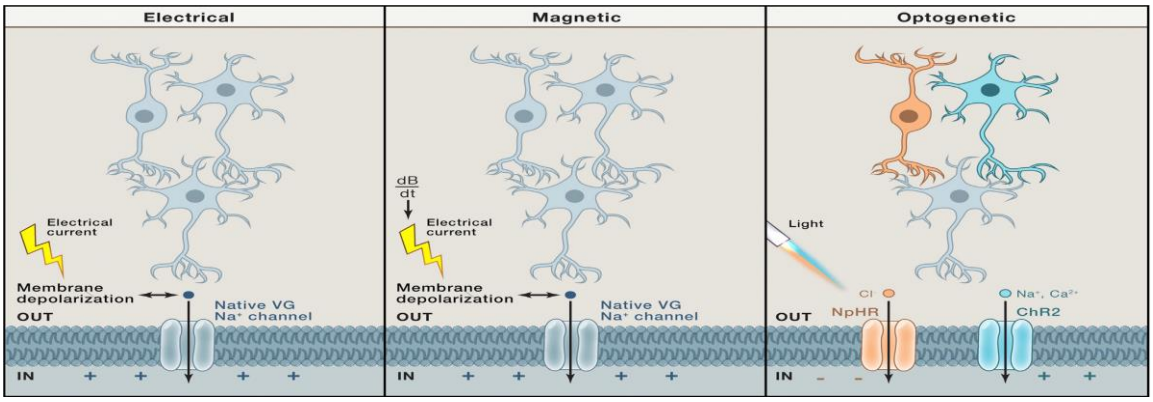
Neuroscience is the branch of the life sciences that deals with the anatomy, physiology, biochemistry and/or molecular biology of the nervous system. It spans a multi-model and a multi-scale assessment of the nervous system through manipulation of the neuronal activities by pharmacological approaches and/or neurostimulation (electrical / magnetic). Unfortunately, these traditional maneuvers have limited spatiotemporal precision with consecutive restricted abilities to study the complex microcircuits especially when exhibiting fast spiking neurons e.g. pharmacological approaches do not act on particular subset of cells (possible stimulation of unintended neurons) and have weak temporal precision (the induced cellular changes may remain altered hours after administration of the pharmacological agent) ***(Sanders, 2017).***



Figure–1: Multi-model and multi-scale neuroscience data.

Regarding conventional electric deep brain stimulation (DBS), the electrode tip does not only excite surrounding cell bodies but also the axons that happen to pass in its vicinity, even if their cell bodies reside far outside the stimulation zone. This weak spatial precision results in simultaneous pro-kinetic and anti–kinetic actions e.g. up to present time, it is not ascertained whether the improvement in PD manifestations using electrical subthalamic (STN) DBS is due

to direct stimulation of STN neurons themselves or axons from other brain areas traversing the STN ***(Barnett et al., 2018; Deubner et al., 2019).***



Figure–2: Neuronal probing by electrical current (left), TMS (middle) and optical stimulation or inhibition (right) of neurons expressing light-sensitive channels ***(Rajasethupathy et al., 2016).***

Thus, the major obstacle facing neuroscientists is the introduction of a maneuver permitting selective control of a specific type of brain cells in certain locations and leaving other types unaltered with real-time precision. This prospect has encouraged neuroscientists to introduce optogenetic and chemogenetic technologies (DREADDs; Designer Receptors Exclusively Activated by Designer Drugs) ***(Spangler and Bruchas, 2017).***

Optogenetics

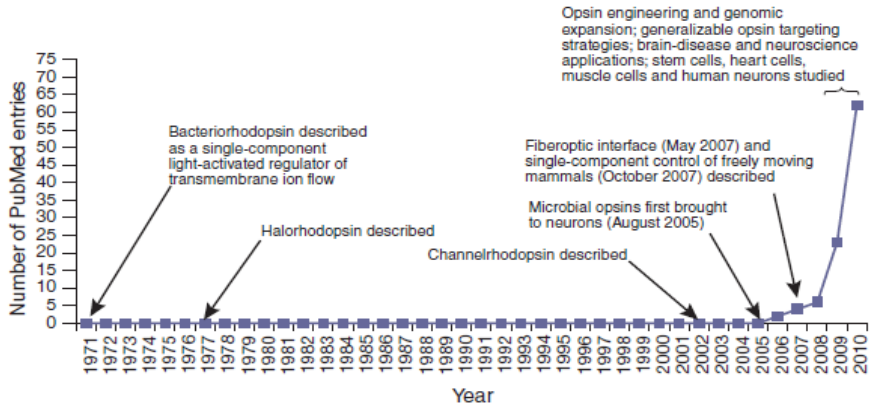
Optogenetic is a light-based technology which incorporate optical manipulation of the activities of type-specific cells after promoting their expression of a non-native light-sensitive transmembrane ion channel (opsin) either for diagnostic (fiber-photometry) or therapeutic (optogenetic activation) approaches.

Concisely, how to control the electrical activities of specific neurons by light.

▫ Historical Review:

In 1971, Oesterhelt and Stoeckenius described a transmembrane receptor in the archaeon Halobacterium salinarum pumping protons out of cells in response to green light exposure and named it bacteriorhodopsin. At that time, neuroscientists believed that, photoreceptors expression in the fragile mammalian cells is invaluable as they will be toxic and the response elicited by their stimulation will not be enough to alter the cellular excitability ***(Deisseroth, 2010).***

In 2005, Boyden and colleagues had incorporated genes for microbial opsins to cultured neurons which became light responsive. In 2006, Zhang and colleagues succeeded to control freely moving mammals using microbial opsins and fiberoptic neural interface. After that date, the technology had expanded to comprise opsin genomic engineering, opsin targeting strategies and advanced light delivery actuators ***(Kim et al., 2017).***



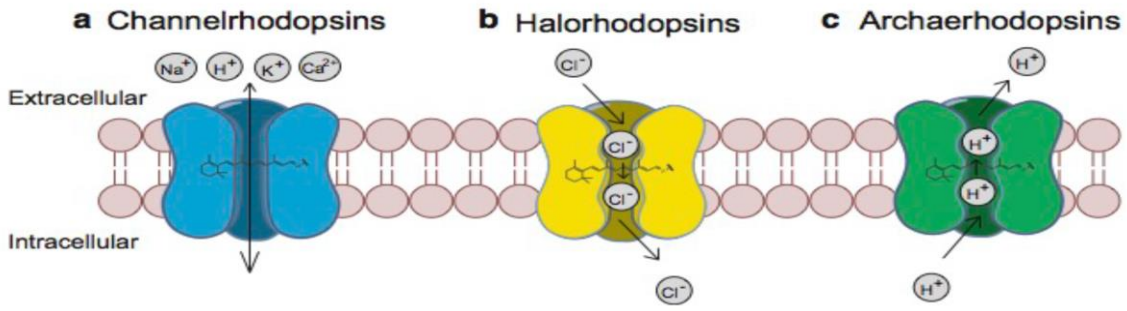
Figure–3: Optogenetic emergence in scientific literatures ***(Deisseroth, 2010).***

◘ Optogenetic Basics:

Opsins are either microbial or mammalian; the former is present in microorganisms like bacteria, archaea, algae, or fungi and are usually ion channels while the mammalian opsins are largely present in the retina and are G-protein coupled receptors ***(El-Shamayleh et al., 2016).***

Delivery of the photosensitive proteins to the brain could be accomplished by stereotactic convection-enhanced delivery (CED) injection of a recombinant replication-defective viral vector (lentivirus or adeno-associated virus) inoculated with the gene expressing optogenetic protein (after removal of its native genome) ***(Sizemore, et al., 2016).***

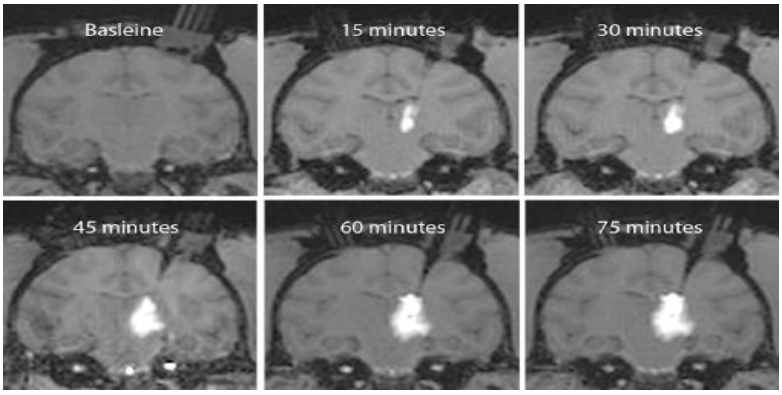
Three major rhodopsins are used in most of neuroscience researches; ***(a) channelrhodopsins (ChR)*** which are non-selective cation channels that open when exposed to blue light leading to neuronal depolarization and initiation of action potentials synchronous with light pulses, ***(b) halorhodopsins (HR)*** respond to yellow light producing hyperpolarization with inhibition of neuronal firing, ***(c) archaerhodopsins (Arch)*** respond to green light causing hyperpolarization and neural silencing.



Figure–4: ***(a) channelrhodopsins*** depolarize neurons through passive transport of Na+, K+, H+, Ca2+ down their electrochemical gradients, ***(b) halorhodopsins*** hyperpolarize neurons by active pump of Cl- into the cells, ***(c) archaerhodopsins*** hyperpolarize neurons by active pump of H+ out of the cells ***(Han, 2012).***

Selective expression of these genes in specific cell phenotypes is achieved by co-inoculation of a specific cell type promotor system (Cre recombinase / loxP enzyme) which is related to bacteriophage recombination system and improve the spatial resolution by affording cell-type specificity where opsin gene expression will be limited to the targeted brain cells within the injection site. Long lists of promoters have been developed with continuous

expansion of their toolbox e.g. synapsin promoter globally targets neurons, GFAP is astrocyte-specific, GAD67 targets GABAergic neurons and CaMKII targets glutamatergic neurons ***(Kim et al., 2017).***



Figure–5: Coronal MRI sections showing stereotactic convection-enhanced delivery injection of the viral optogenetic vector during medial thalamic infusion in rhesus macaques ***(Yazdan-Shahmorad, 2018).***

The brain is a non-transparent organ while the nontoxic levels of light (3 mW/mm2) illuminate only about 1–1.5 mm of tissue immediately surrounding the optical fiber tip. These evidences necessitate highly precise implantation of the illumination source beside the areas needed to be handled. In experimental studies, insertion of the optical fibers is done at the time of stereotactic opsin inoculation where optogenetic expression is often adequate 4–weeks post-injection ***(Boros et al., 2018).***

◘ Technological Advances in Optogenetics:

Since discovery, a fast progress is going on optogenetics including expansion of the opsins toolbox, improvement of light delivery systems and recently concurrent inoculation of different types of opsins to simultaneously or consecutively manipulate the activities of one or multiple cells populations ***(Erofeev et al., 2015).***

(a) Introduction of new opsins:

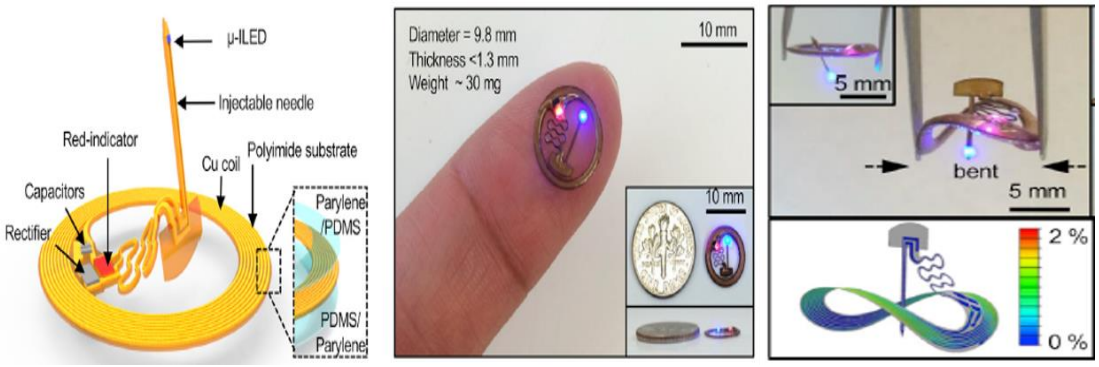
- ***Fast and ultra-fast firing ChR*** (ChETA family and ChIEF) with channel closure time <4–ms and spike rate at >40–Hz light stimulation.
- ***Bi-stable opsins*** permitting sustained activation or inhibition with brief light pulses.
- ***Red–shifted opsins*** activated by near-infrared light (to which brain tissue is relatively transparent) which can reach deep tissue from a sub-dermally implanted probe but carries the disadvantage of tissue heating.

- ***Topologically inverted opsins*** within the membrane e.g. inverted ChR will change it from a potent activator into a fast-acting inhibitor.
- ***Bioengineered opsins*** act beyond ion channel activities to initiate G-protein-coupled receptor downstream signaling (these opsins do not only operate the neuronal electrical activities but also the biochemical ones) ***(Brown et al., 2018; Gagliardi and Pertz, 2019).***

(b) Light delivery:

Development of fiber-optic instruments delivering optical beams into any brain area of the freely moving animal is a necessity for optogenetics' practical application. Progress in the light delivery systems includes the introduction of high–power output lasers, flexible light emitting diode (LED) arrays, waveguides and beam splitting probes as well as diffusing fibers which assure large volume tissue activation, minimal heating and lower power consumption ***(Masseck, 2019).***

The light actuators (current source and train generator) control the light intensity, wavelength, duration of illumination, frequency and stimulus train characteristics. At the same time, wireless systems controlling illumination onset and offset in freely moving animals are developing ***(Deisseroth and Hegemann, 2017).***



Figure–6: Fully implantable wireless device ***(Shin et al., 2017).***

(c) Intracellular delivery of optogenetic protein:

Recently, direct micro/nano injection, microfluidic shearing or ultrasound-based methods are tried for direct optically expressing gene inoculation into the cytoplasm or nucleus of the targeted cells. Injections of genetically modified opto-stem cells into the anatomically

targeted tissue are also tried with some degree of experimental success ***(Hsieh et al., 2018; Luchkina and Bolshakov, 2018).***

◘ Optogenetics Disadvantages:

(1) Invasiveness of the technique.

(2) Direct neuronal photodamage by the generated oxidative radicals and tissue heating. This risk could be avoided by using illumination < 10–20 mW/mm^2 and trials to enhance efficacy without increasing illumination intensity.

(3) Excess ion movement and pH shifts.

(4) Uncontrolled opsins actions including receptor overexpression, dissociation between neuronal firing and transmitter release as well as rebound firing after light offset.

(6) Fading of illumination intensity over time which needs regular assessment and readjustment ***(Masseck, 2019).***

Neurological Applications of Optogenetics

Optogenetics is a fast-developing neuroscience which speedy evolution in the last decade put this technology in a close proximity to diagnostic and therapeutic neurological applications.

- Amenable brain nuclei:

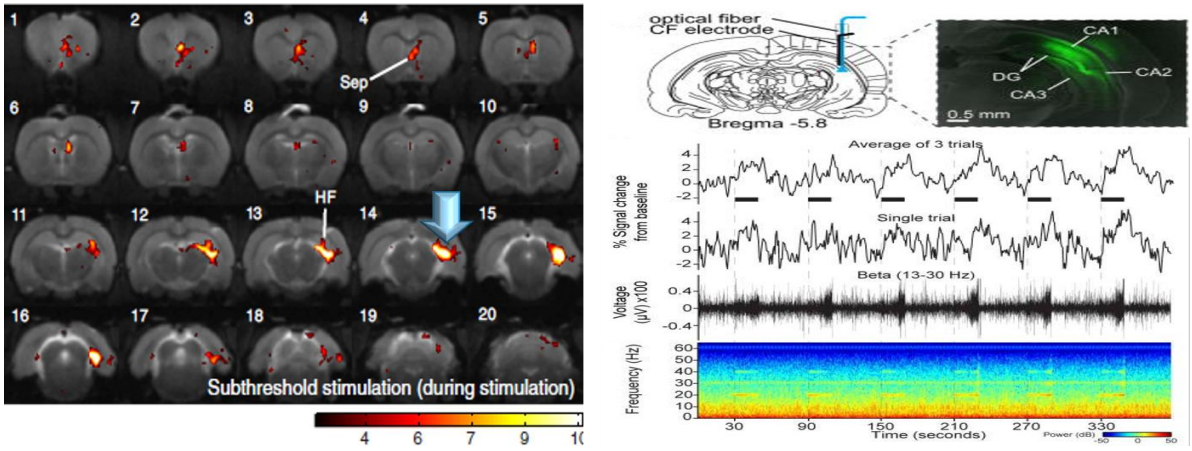
The opto-fiber can illuminate a small brain area close to its tip (1–1.5 mm) which necessitates a highly targeted applications to specific nuclei which handling could modulate the brain functions in some neurological disorders. These amenable nuclei include; the subthalamic nucleus (treatment of PD), basal forebrain (improving level of arousal and attention), nucleus accumbens (for OCD and addictions), amygdala sub-nuclei (for anxiety), superior colliculus (for seizure suppression) and thalamic sub-nuclei (for potential seizure termination, indirect cortical modulation and tremor) ***(Pedersen and Gross, 2018).***

▫ Optogenetic Brain Mapping:

The human brain is the most complex network in the real word composed of 100 billion (10^{11}) neurons connected by about 100 trillion (10^{14}) synapses. Mapping of these complex matrixes could be described at 3 levels; anatomical connectivity (white matter tracts), functional connectivity (statistical dependencies among remote neurophysiological events) and effective connectivity (how activity in one part of brain affects function elsewhere i.e. causal interactions) (***Snyder and Bauer, 2018).*** The core functions of neurons are electrical spiking and synaptic transmission with nonlinear interactions of multiple ion channels within cells and of multiple cell types within circuits. Such complex functions need highly meticulous spatiotemporal techniques capable of dissecting and decoding the dynamic connections information ***(Crimi et al., 2019).***

When combined with other techniques, optogenetics have a great potential to enhance our study and analysis of the complex brain networks. For example, optogenetic integration with fMRI (opto-fMRI) allow temporally precise probing of cell-type specific activities with simultaneous imaging of the whole-brain and subsequent highly precise computation of micro- and macro-brain circuity e.g. studying the cortical layers functional connectivity, functional sleep–wake circuits and cerebellar as well as striatal input/output connections. Other optogenetic

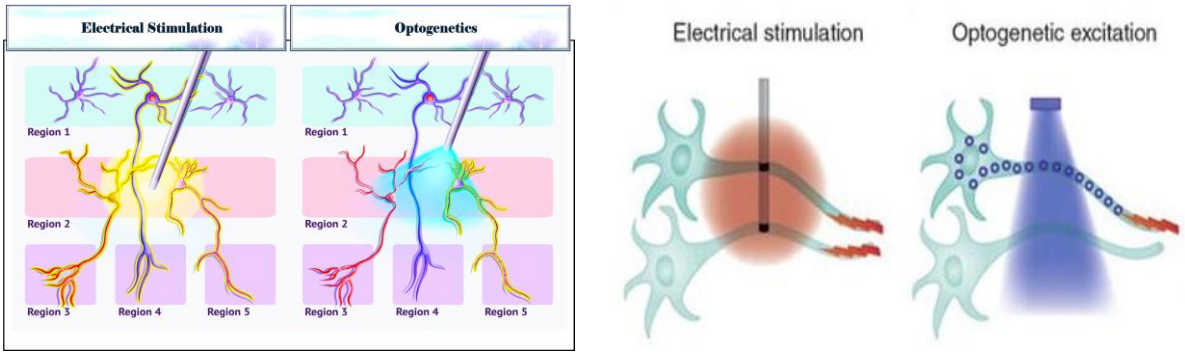
tool for dissecting functional networks include optical intrinsic signal imaging (OISI) which enables simultaneous optical stimulation of a substantial cell–type and electrical recording of activities changes in the remainder of the circuity ***(Bernal-Casas et al., 2017; Choe et al., 2018).***



Figure–7: Optogenetic–fMRI during subthreshold stimulation of the hippocampus and simultaneously recorded EEG in an experimental mouse ***(Duffy et al., 2015).***

◘ Optogenetic Deep Brain Stimulation:

Electrical DBS (electro-DBS) represents a revolutionary brain-region specific neuromodulation therapy that gained FDA approval for treating essential tremor, Parkinson's disease (PD) and dystonia. The DBS electrode designs consist of 4 – 8 contact sites separated by 0.5 – 1.5 mm inter-contact spaces where the electrical currents are integrated by trial and error using different electrode pairs to achieve the optimal clinical efficacy ***(Kondabolu et al., 2015).***



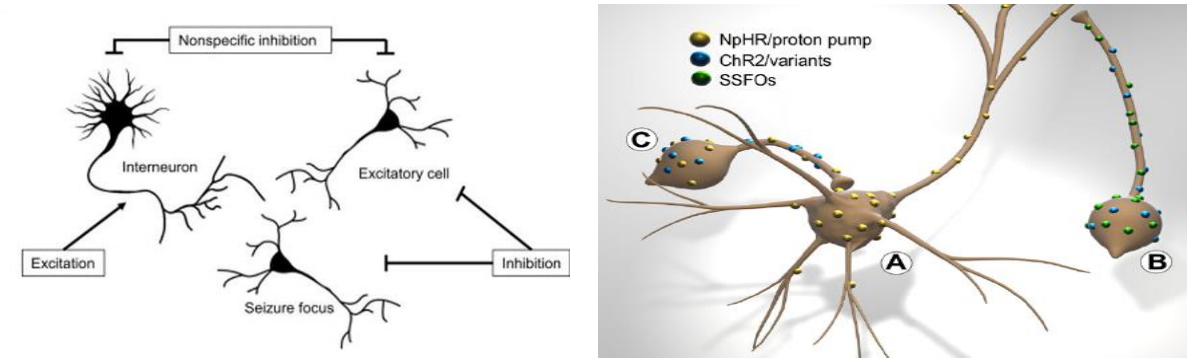
Figure–8: Target specificity of electrical and optogenetic deep brain stimulation ***(Gittis and Yttri, 2018).***

Continuing efforts are spent to use optogenetic DBS (opto-DBS) with expected efficacy outweighing the electrical ones due to its potential of cell-type specific manipulations and avoidance of stimulation of axons beside the optical-fiber tip. This refined DBS technique allows further insight about the pathogenesis of many movement disorders and to explore new circuit-inspired applications of DBS achieving maximal therapeutic benefits ***(Gittis and Yttri, 2018).***

To highlight the value of cell-type specific opto-DBS, experimental studies showed that stimulation of D1 spiny projection neurons (SPNs) in the striatum activated the direct pathway with consecutive improvement of bradykinesia as happening with L-dopa treatment. On the other hand, opto-DBS stimulation of a subset of D1-SPNs by ChR2 resulted in induction of dyskinesia while their inhibition using HR alleviated the dopa induced dyskinesia. This discovery opens new avenues of research into the mechanism of L-dopa induced dyskinesia and the dosing regimens that will be more selective for the therapeutic population of D1-SPNs, but not the dyskinetic sub-population ***(Girasole et al., 2018; Picconi et al., 2018).***

◘ Optogenetic Modulation of Epileptogenic Networks:

Optogenetics have been applied to understand the relevant role of certain types of cells like astrocytes, entorhinal principal cells and cerebellar parvalbumin-expressing neurons in the process of epileptogenesis. At the same time, optogenetic brain mapping allows more accurate localization of the seizure onset zone with subsequent more precise implantation of the neurostimulation probe ***(Zhang et al., 2018).***



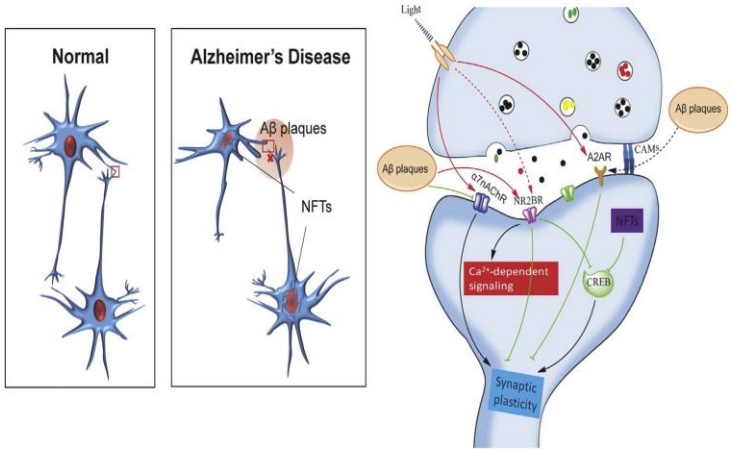
Figure–9: Optogenetic approaches for seizure control ***(Tung et al., 2016).***

Optogenetic neurostimulation has been tried for seizure suppression in animal models of epilepsy with greater success in dissecting and modulating circuitry involved in seizure generation compared to electrical stimulation alone. Three optogenetic approaches had been used in clinical researches based on the type of opsin and cell types targeted; nonspecific inhibition of neurons by high frequency subthreshold optogenetic stimulation (kindling), inhibition of excitatory (e.g. glutamatergic) neurons and excitation of inhibitory (e.g. GABAergic) neurons ***(Lin et al., 2019).*** Moreover, optogenetic activation of 5-HT neurons in the dorsal raphe had been tried to suppress seizure-induced respiratory arrest and produces anticonvulsant effect in mouse SUDEP model ***(Pedersen and Gross, 2018; Zhang et al., 2018).***

◘ Optogenetic Memory Enhancement:

The detailed mechanisms of neural circuit disruption in Alzheimer's disease (AD) still poorly understood. Optogenetics permit time-linked recording of certain brain regions in relation to specific memory stages (encoding, storing and retrieving) which could distinguish the exact stage of memory malfunctions ***(Roy et al., 2016; El-Heneedy and Elbahnasy, 2019).***

The earliest changes in AD is hippocampal neuronal hyperactivity with consecutive place and engram cells dysfunctions. A large body of researches had studied the use of optogenetic approaches to modulate neurotransmitter and synaptic dysfunctions as well as unbalanced microcircuits in AD. Optogenetic stimulation of the entorhinal cortex, anterior and medio-dorsal thalamic nuclei as well as dentate gyrus have been tried to improve spatial learning and memory retrieval in mouse models of MCI and AD ***(Yang et al., 2017; Perusini* et al.*, 2017).***



Figure–10: Optogenetics ameliorate synapses functions, which are degenerated by A β plaques and neurofibrillary tangles in Alzheimer's Disease ***(Yang et al., 2017).***

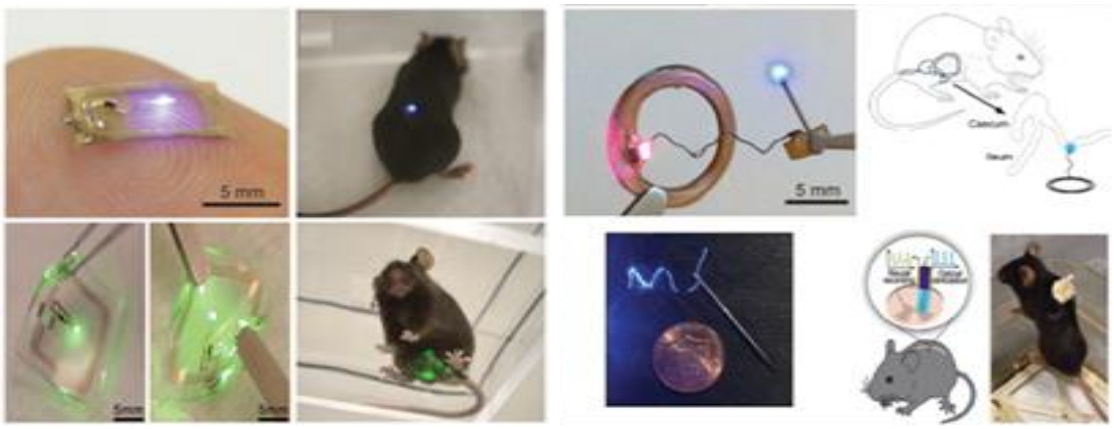
◘ Optogenetics and Stroke:

Optogenetic stimulation of the vascular endothelium has been tried to control the release of the vasoactive substances and slow down the process of atherosclerosis in experimental studies which will be of great value in primary stroke prevention in high risk patients ***(Zhang et al., 2015).***

Regarding stroke rehabilitation, optogenetics have been used in stroke mouse models to stimulate the undamaged circuits in layer V of the ischemic motor cortex with a resultant restoration of the disrupted interhemispheric interactions and better functional recovery as well as improved stimulus induced cerebral blood flow to the ischemic areas. In another domain, optogenetic stimulation of the striatal glutamatergic activity triggered neuroblasts mediated neurogenesis in the subventricular zone and encouraged their migration into the peri-infarct cortex ***(Cheng et al., 2014; Song et al., 2017).***

◘ Optogenetic Pain Modulation:

Intractable pain is the single most common cause of disability worldwide. The high spatiotemporal precision of optogenetics provides unique opportunities to study and modulate circuits involved in nociceptive pathways at spinal, subcortical and cortical networks. Optogenetic viral vector transduction with specific promotors to dorsal root ganglia has been tried to control visceral and somatic pain as well as pain related anxiety ***(Spencer et al., 2018; Xie et al., 2018).***



Figure–11: Peripheral light delivery technology for optogenetics ***(Mickle and Gereau, 2018).***

◘ Optogenetic Management of Sleep Disorders:

Optogenetic technologies allow deeper understanding the complex neural circuits controlling sleep and arousal as well as transitions between sleeping and waking states e.g. understanding how the brain modulates between REM, NREM, quiet waking, active waking and hyper-arousal states as well as sleep related memory consolidation ***(Tyree and de Lecea, 2017).***

Optogenetic handling of GABA-ergic and cholinergic neurons of the basal forebrain, hypocretin-expressing neurons of the lateral hypothalamus, serotoninergic dorsal raphe nuclei, noradrenergic locus coeruleus and peri-optic area had been applied in sleep studies and management of certain sleep disorders including excessive daytime sleepiness, insomnia, sleep apnea and narcolepsy ***(Drew et al., 2018).***

◘ Optogenetics in Spinal Cord Injury:

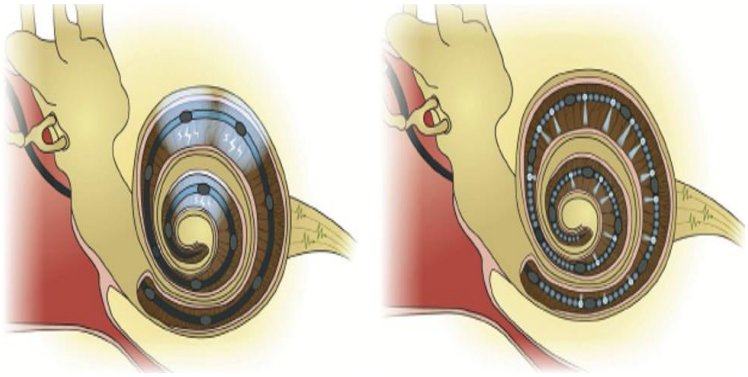
Optogenetics can play a vital role in reconstruction of broken neuronal circuits in traumatic spinal cord injury. In this condition, ChR can be expressed in motor neurons and they can be activated to develop connections with other neurons on the other side of injury. In addition, transduced stem cells in spinal cord injury could be handled after promoting their opsin expression which increase their potential to reduce the functional disability ***(Ahmad et al., 2018).***

◘ Optogenetic Visual and Hearing Restoration:

Optogenetic visual restoration in inherited retinal diseases (cone or rod dystrophy) as Leber's congenital amaurosis offered promising results with superior kinetics than electronic retinal implants. The optogenetic strategy is based on restoration of the dysfunctional photoreceptors and bypassing the damaged ones to provides direct stimulation to the surviving retinal ganglion cells and drives them to send visual signals to the brain ***(Yan et al., 2016; Simunovic et al., 2019).***

Regarding auditory neuroscience, electrical cochlear implants are by far the most successful neuro-prostheses worldwide enabling open speech comprehension but are limited in providing music discrimination as well as speech understanding in noisy environments due to low frequency resolution and the wide current spread from stimulation contacts. As light can be conveniently focused, optical stimulation might provide an alternative approach to cochlear

implants with increased number of independent stimulation channels ***(Jeschke and Moser, 2015).***



Figure–12: Schematic overview of electrical (left) versus optical (right) cochlear implants ***(Jeschke and Moser, 2015).***

◘ Extra-neurological Applications of Optogenetics:

In the field of psychiatric disorders, optogenetic tools have been used to study and modulate circuits sponsored for anxiety, phobia, depression, aggression and drug/alcohol abuse disorders ***(Luchkina and Bolshakov, 2018; Tritschler et al., 2018).***

Outside neurons and brain matrices, many tissues are potential targets of optogenetics, and large amounts of researches had tried optically guided pacemakers for rhythm control in cardiomyocytes ex vivo heart preparations, optical pancreatic β-islet cells regulator for better diabetic control and opto-immuno-engineering in cancer immunotherapies as well as anticancer drug discovery ***(Eickelbeck et al., 2019)***.

- Optogenetic Closed Loop Control:

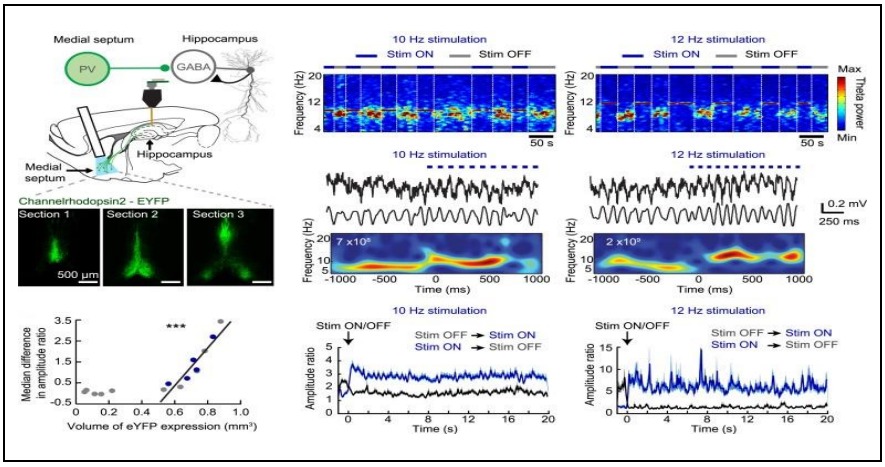
In most optogenetic experiments, the stimulus is open-loop delivering phasic bursts of light chosen prospectively to evoke the predicted best response without recourse to feedback. Closed-loop control refers to the use of an error signal (the difference between the measured and the desired output) to guide changes in input systems and makes real-time decisions (how and when) to stimulate the optogenetic input ***(Grosenick et al., 2015).***

◘ Applications of Optogenetic Closed-loop Control:

(a) Brain network studies:

Optogenetics closed-loop control using ultrafast opsins (evoke frequencies > 200 Hz) allowed studying the highly complex small world neural circuitry exhibiting fast-spiking

neurons with a very high spatiotemporal precision e.g. gamma oscillations mediated by interactions between fast-spiking inhibitory parvalbumin neurons and pyramidal cells, causal role of theta oscillations in information encoding and retrieval as well as genetically targeted cell types in high-frequency ripple oscillations in the hippocampus ***(Siegle and Wilson, 2014; Pedersen and Gross, 2018).***



Figure–13: Optogenetic rhythmic stimulation of medial septal parvalbumin CH2 expressing neurons controls the frequency of theta oscillations in freely behaving mice ***(Zutshi et al., 2018).***

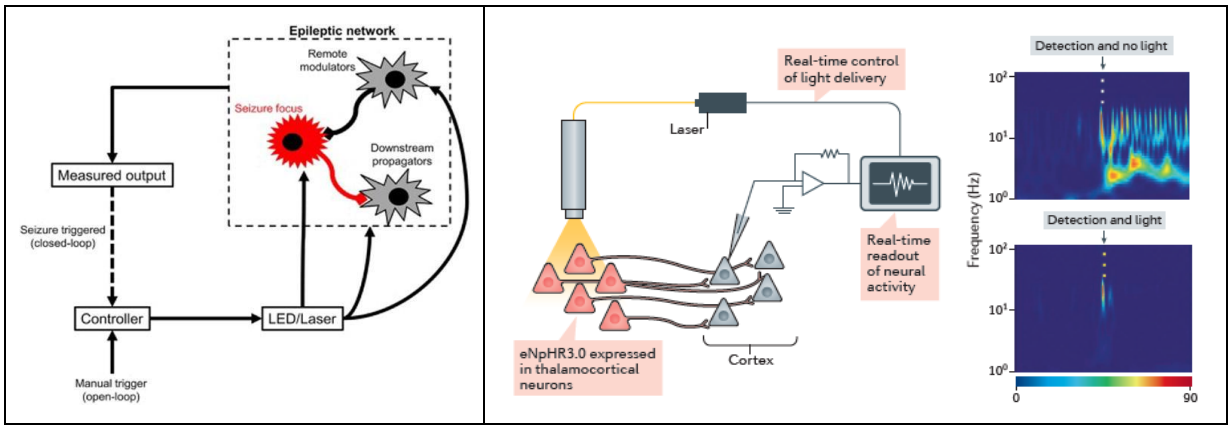
(b) Parkinson disease:

Closed loop opto-DBS has the potential of better improvement of PD motor manifestations with a superadded neuro-modulatory action through enhancing neural plasticity and consecutive partial repair of disrupted circuits. This action had proven through the lasting improvement of bradykinesia after illumination stopped in relation to electro-DBS which displayed rapid return of PD motor manifestations when the battery is switched off. The opto-DBS neuro-modulatory action is also beneficial in management of poorly understood symptoms as PD-related dementia ***(Moon et al., 2018).***

(b) Epilepsy Management:

Most of the currently used AEDs do not alter the underlying epileptogenic pathology but only provide symptomatic seizures control ***(Clossen and Reddy, 2017).*** Closed-loop optical control had been used in several types of epilepsy syndromes including thalamo-cortical neurostimulation in a poststroke epilepsy mouse model as well as closed-loop control of cerebellar parvalbumin-expressing neurons or dentate gyrus granule cells hyperpolarization in temporal lobe seizures. Surprisingly, the closed-loop optogenetic epilepsy control exerts a long-lasting neuro-modulatory effect due to the induced synaptic plasticity changes which changes

our prospects from symptomatic seizure control to optogenetic induced antiepileptogenic action ***(Zhang and Cohen; 2017).***



Figure–14: Real-time closed-loop optogenetic inhibition of thalamocortical neurons is triggered when seizure activity is detected in the cortex by EEG ***(Grosenick et al., 2015).***

- Conclusion:

Optogenetic technologies permit cell-type and circuit specific milliseconds–scale control which have revolutionized our understanding of the complex neural networks in health and disease as well as changing our prospective from passive observers to active manipulators of brain matrixes functions with a prospected more effective, sustainable neuro-modulatory effects of distorted circuits in a wide array of neurological disorders.

- References:

- Ahmad A, et al. Asian Spine J. 2015. doi: 10.4184/asj.215.9.2.299
- Barnett SC, et al. Hippocampus. 2018. doi: 10.1002/hipo.22960
- Bernal-Casas D, et al. Neuron, 2017. doi: 10.1016/j.neuron.2016.12.035
- Boros ÖC, et al. Appl Opt, 2018. doi: 10.1364/AO.57.006952
- Brown, et al. Cell. 2018. doi: 10.1016/j.cell.2018.09.026
- Cheng MY, et al. ACS Chem. Neurosci. 2014. doi: 10.1021/cn500216f
- Choe KY, et al. NeuroImage. 2018. doi: 10.1016/j.neuroimage.2018.02.047
- Clossen BL, Reddy DS. Biochim Biophys Acta Mol Basis Dis. 2017. doi: 10.1016/j.bbadis.2017.02.003
- Crimi A, et al. Sci Rep. 2019. doi: 10.1038/s41598-018-37300-4
- Deisseroth K. Nature Methods. 2010. doi: 10.1038/NMETH.F.324
- Deisseroth K, Hegemann P. Science, 2017. doi: 10.1126/science.aan5544
- Deubner J, et al. Current Opinion in Structural Biology, 2019. doi: 10.1016/j.sbi.2019.04.003
- Drew VJ, et al. Sleep Med Res. 2018. doi: 10.17241/smr.2018.00178
- Duffy BA, et al. NeuroImage. 2015. doi: 10.1016/j.neuroimage.2015.07.038

- Eickelbeck et al. Handbook of Neural Plasticity Techniques. 2019. doi: 10.1016/B978-0-12-812028-6.00016-1
- El-Heneedy Y and Elbahnasy W. Researchgate. 2019. doi: 10.13140/RG.2.2.31427.96806
- El-Shamayleh Y, et al. J Neurophysiol, 2016. doi: 10.1152/jn.00087.2016
- Erofeev AI, et al. St. Petersburg Polytechnical University Journal. 2015. doi: 10.1016/j.spjpm.2015.12.001
- Gagliardi PA, Pertz O. Developmental Cell. 2019. doi: 10.1016/j.devcel.2019.01.022
- Girasole AE, et al. Neuron. 2018. doi: 10.1016/j.neuron.2018.01.017
- Gittis AH, Yttri, EA. Current Opinion in Biomedical Engineering. 2018. doi: 10.1016/j.cobme.2018.08.008
- Grosenick L, et al. Neuron. 2015. doi: 10.1016/j.neuron.2015.03.034
- Han X. ACS Chem Neurosci, 2012. doi: 10.1021/cn300065j
- Hsieh FY et al. Biomaterials. 2018. doi: 10.1016/j.biomaterials.2018.05.014
- Jeschke M, Moser T. Hearing Research. 2015. doi: 10.1016/j.heares.2015.01.005
- Kondabolu et al. Handbook of experimental pharmacology. 2015. doi: 10.1007/978-3-319-16522-6_15
- Kim CK et al. Nat Rev Neurosci. 2017. doi: 10.1038/nrn.2017.15
- Lin BH, et al., Biomedical Signal Processing and Control. 2019. doi: 10.1016/j.bspc.2019.03.006
- Luchkina NV, Bolshakov VY. Pharmacology and Behavior. 2018. doi: 10.1016/j.pbb.2017.05.005
- Masseck OA. Handbook of Neural Plasticity Techniques. 2019. doi: 10.1016/B978-0-12-812028-6.00015-X
- Mickle AD, Gereau RW. Pain. 2018. doi: 10.1097/j.pain.0000000000001329
- Moon HC, et al. Neuroscience Letters. 2018. doi: 10.1016/j.neulet.2017.10.019
- Pedersen NP, Gross RE. Neuromodulation, 2018. doi: 10.1016/B978-0-12-805353-9.00035-8
- Perusini JN, et al. Hippocampus. 2017. doi: 10.1002/hipo.22756
- Picconi B, et al. J Neural Transm. 2018. doi: 10.1007/s00702-018-1864-6
- Rajasethupathy P, et al. Cell. 2016. doi: 10.1016/j.cell.2016.03.047
- Roy DS, et al. Nature. 2016. doi: 10.1038/nature17172
- Sanders TH. Front. Integr. Neurosci. 2017. doi: 10.3389/fnint.2017.00024
- Shin G, et al. Neuron. 2017. doi: 10.1016/j.neuron.2016.12.031
- Siegle JH, Wilson MA. Elife. 2014. doi: 10.7554/eLife.03061
- Simunovic MP, et al. Experimental Eye Research. 2019. doi: 10.1016/j.exer.2018.09.003
- Sizemore RJ, et al. Journal of Neurophysiology. 2016. doi: 10.1152/jn.01131.2015
- Snyder AZ, Bauer AQ. Biological Psychiatry. 2018. doi: 10.1016/j.bpsc.2018.10.005
- Spangler SM, Bruchas MR. Curr Opin Pharmacol. 2017. doi: 10.1016/j.coph.2016.11.001
- Spencer NJ, et al. Brain Research. 2018. doi: 10.1016/j.brainres.2018.02.002
- Song M, et al. Neurobiology of Disease. 2017. doi: 10.1016/j.nbd.2016.11.005
- Tritschler L, et al. Neuroscience Research. 2018. doi: 10.1016/j.neures.2017.12.002
- Tung JK, et al. Brain Stimul. 2016. doi: 10.1016/j.brs.2016.06.055
- Tyree SM, de Lecea L. Int J Mol Sci. 2017. doi: 10.3390/ijms18081773
- Xie YF, et al. Experimental Neurology. 2018. doi: 10.1016/j.expneurol.2018.05.003
- Yan B, et al. Vision Research. 2016. doi: 10.1016/j.visres.2016.01.006
- Yang O, et al. Neuroscience and Biobehavioral Reviews. 2017. doi: 10.1016/j.neubiorev.2017.05.015
- Yazdan-Shahmorad A, et al. Journal of Neuroscience Methods. 2018. doi: 10.1016/j.jneumeth.2017.10.009
- Zhang H, Cohen AE. Trends in Biotechnology. 2017. doi: 10.1016/j.tibtech.2017.04.002
- Zhang H, et al. Neurobiology of Disease. 2018. doi: 10.1016/j.nbd.2017.11.003
- Zhang S, et al. Vascular Pharmacology. 2015. doi: 10.1016/j.vph.2015.05.009

- Zutshi I, et al. Current Biology. 2018. doi: 10.1016/j.cub.2018.02.061